ECTRIMS 2022 – Poster

Poster Session I

Clinical aspects of MS - Diagnosis and differential diagnosis

P001

Autoimmune screening panel in patients with multiple sclerosis – a Vienna MS database study

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Introduction: Autoimmune screening panel (ASP) is routinely ordered as a part of diagnostic work-up in people with suspected multiple sclerosis (MS). However, data on prevalence and significance of ASP seropositivity in MS is scarce.
Methods: In this retrospective study, we investigated patients who were diagnosed with MS (pwMS) between 2014 and 2021 and had a blood sample drawn for ASP.Autoantibody titers were defined as either negative, or mildly (1:640) and strongly (1:1280) positive.
Results: We analyzed 212 pwMS (median age 29 [IQR 25–36] years, 67.0% female). Ten (4.7%) patients had red flags for presence of systemic autoimmune disease (joint pain [n=4], dermatitis [n=3], sicca syndrome, bronchial asthma/rheumatic fever in childhood [n=1, each]). Antinuclear antibodies (ANA) were positive in 24/210 (11.4%) with 18 (8.6%), 5 (2.4%), and 1 (0.5%) having mildly, moderately, and strongly positive ANA titers, respectively. Positive autoantibodies were found as follows: anti-Ro (5/211; 2.4%), IgM against cardiolipin (4/205; 2.0%), anti-centromere B (2/211; 0.9%), anti-dsDNA (1/208; 0.5%) and anti-La (1/211; 0.5%). Antibodies against smooth muscles were mildly positive in 11/166 (6.6%) patients. None of pwMS was positive for other autoantibodies (anti-SCL70, anti-SM, anti-u1RNP, anti-Jo1, c-ANCA, p-ANCA). Further evaluation following positive results led to diagnosis of rheumatoid arthritis (n=2) and Sjögren's syndrome (n=1), all of them presenting with red flags (ASP PPV 8.8%, NPV 96.1%).
Conclusions: Rate of ASP seropositivity in pwMS is low and within the range expected in the general population. Performance of ASP without clinical suspicion of systemic autoimmune disease seems unwarranted.

Disclosure
has nothing to disclose.

P002

Are MRI findings enough to differentiate, susac syndrome from multiple sclerosis, and primary angiitis of the central nervous system?

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Introduction: Differential diagnosis between white matter lesions affecting the central nervous system (CNS) may be difficult. Multiple Sclerosis (MS), Susac Syndrome (SuS) and Primary Angiitis of the CNS (PACNS) may represent differential diagnoses to consider. These disorders have different underlying pathophysiological mechanisms, which can be enlightened by ancillary methods (such as brain biopsy or retinofluorescein angiography) but, in most of the cases, those are not easily available.
Objectives: To explore which MRI findings are more specific and useful to distinguish between MS, SuS and PACNS
Methods: Retrospective cohort of patients with SuS from a national multicentric registry, was compared against randomly selected MS and PACNS patients followed in a referral neurological center in Buenos Aires from 2007 to 2021. Results were reported as median and interquartile range (IQR) or absolute frequency. A bivariate logistics regression analysis was carried out to explore the association of MRI findings with SuS. Sensitivity and specificity of the MRI findings was calculated assuming as Gold Standard the presence of 2 or more diagnostic criteria for SuS, and the level of agreement was compared through a Kappa coefficient.
Results: 92 patients (55 women) with a median age at clinical presentation of 34 years old (IQR1-3 27-43) were evaluated. 37

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had MS, 36 SuS, and 19 PACNS. No differences were found in demographic and clinical data between different groups.
In the bivariate analysis, association between SuS and the following lesions were found: Corpus Callosum: snowball lesions (OR 160, CI 95% 20-1317, p<0.001), spokes (OR 16, CI 95% 5-49, p<0.001), icicles (OR 7.4, CI 95% 2.5-21.7, p<0.001), absence of Dawson's fingers (OR 23.6 CI 95% 3-186, p 0.003) the presence of more than 5 lesions (OR 4 CI 95% 2-10, p 0.002) and in the Internal Capsule multiple lesions in a string of beads pattern (OR 12, CI 95% 3-45, p<0.001).
The level of agreement between the diagnosis of SuS and the presence of snowball and spoke lesions were moderate (kappa coef 0.6 CI 95% 0.41-0.75)
The sensitivity and specificity, of the presence of snowballs and spokes for SuS final diagnosis, were 58.3% (CI 95% 40.8-74.5) and 96.4 (CI 95% 87.7-99.6%). The PPV was 91% and NPV 78%.
Conclusion: A thorough MRI analysis could be enough for an initial differentiation between SuS from MS and PACNS. The presence of snowball and spoke lesions in the corpus callosum presented high specificity for SuS diagnosis.

Disclosure
All authors: nothing to disclose.

P003
Neurological Involvement in IgG4-related disease

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Introduction: IgG4-related disease (IgG4-RD) is a fibroinflammatory disease that may affect any organ or system. Neurological involvement is rare, and data is limited.
Objectives: To evaluate characteristics of neurological involvement. Methods: Patients diagnosed with IgG4-RD were included. All clinic, radiologic and therapeutic parameters were examined.
Results: 76 out of 99 patients with IgG4-RD were included. Female to male ratio was 1:1, the mean age at diagnosis was 47,38 ± 14,9 SD, the mean serum IgG4 level was 171.6 mg/dl and the median follow-up duration was 25,5 months. 21% (n: 16) of the patients had neurological involvement (neuro-IgG4-RD); orbital disease (n:10), pachymeningitis (n:5), hypophysitis (n:1). In neuro-IgG4-RD, serum IgG4 levels tended to be lower (p=0,06) and co-existing malignancy tended to be higher (p=0,09). 60% of patients who had orbital disease were male and the most common symptoms were headache, visual loss, and proptosis. Mass effect and/or inflammatory changes were the most common radiological findings. 80% of patients who had pachymeningitis were male and the most common symptoms were headache and cranial nerve involvements. Skull base was mostly affected, and the most frequent site of involvement was tentorium cerebelli. The main choice of treatment was corticosteroids; but rituximab was added to the treatment in refractory cases (n: 7). In all patients receiving rituximab, neuroradiological findings were either stabilized or regressed.
Conclusion: 21% of the patients who had a diagnosis of IgG4-RD had neurological involvement either at diagnosis or during follow-up. Orbital disease and pachymeningitis were the frequent manifestations and had typical radiologic characteristics. Rituximab may be an efficient choice for refractory cases.

Disclosure
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P004
The impact of healthcare systems on the clinical diagnosis and disease modifying treatment usage in relapse-onset multiple sclerosis: a real-world perspective in five registries across Europe

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Introduction: Prescribing guidance for disease modifying treatment (DMT) in multiple sclerosis (MS) is centred on a clinical diagnosis (CD) of relapsing-remitting MS (RRMS). Guidance

enforcement varies between countries. Using objective features to standardise diagnosis of disease course, ie. to assign RRMS or secondary progressive MS (SPMS), allows examination of impact across health systems on the stated CD and on treatment access.

Methods: Summary demographics and DMT use in 6 cohorts from 5 countries; Czechia, Denmark, Germany, Sweden, and United Kingdom (clinical and portal) with an initially diagnosed RRMS were selected. CD of RRMS and SPMS was standardised using a Decision Tree (DT) objective classifier. Four drivers of DMT prescribing were agreed*a priori*: availability, funding, monitoring and audit. Data were analysed with meta-analysis and univariate metaregression.

Results: The total population (n=64235) had a higher chance of being reclassified from clinical RRMS to DT-SPMS, implying non-random differences and that subjects were retained in a group, RRMS, that could access DMTs. Those with higher EDSS at index ($p<0.03$) and female gender ($p<0.049$) were more likely to be reclassified from RRMS to DT-SPMS. DMT use was higher in RRMS than SPMS overall but lower in the UK for RRMS and SPMS. Use of highly active (HA)DMTs was highest in Sweden. If ever on a DMT (n=53291) a higher proportion stopped in SPMS than in RRMS. Female RRMS (p=0.041) and increasing EDSS in SPMS (p=0.004) was associated decreased likelihood of receiving a DMT as SPMS monitoring (p=0.029) eg in the UK in the absence of SPMS monitoring the % on DMT increased from 14% to 38%.

To establish the impact of CD on receiving DMTs, we looked at the chance of being on treatment in clinical SPMS when classified as DT-SPMS or DT-RRMS. There was a similar chance of starting (p=1) or escalating to a HADMT (p=0.115) but a higher chance of stopping DMTs in clinical SPMS when classified as DT-SPMS vs DT-RRMS (p=0.018). CD SPMS populations were more likely to be on treatment in a prescribing environment with increasing treatment availability ($p=<0.001$), a lack of monitoring (p=0.0008) and audit (p=0.017).

Discussion: Using objective features to standardise the diagnosis allows us to demonstrate that characteristics of healthcare systems: availability, monitoring and audit are associated with modifications to the declaration of a clinical SPMS diagnosis and DMT use.

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Clinical aspects of MS - NMOSD

P005

Change in AQP4-IgG serostatus in NMOSD: a laboratory-based analysis of 1000 patients with serial collections

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Introduction: The frequency and factors associated with changes in AQP4-IgG serostatus in neuromyelitis optica spectrum disorder (NMOSD) remains unknown.
Objectives: This study aims to examine the temporal evolution of AQP4-IgG serostatus.
Aims: To examine the frequency, timing and factors associated with AQP4-IgG serostatus change in NMOSD.
Methods: Patients with AQP4-IgG+ (flow cytometric [FACS] or cell-based assay [CBA]) with ⩾2 samples >30 days apart from 2007-2021 were included. Univariable logistic regression examined if age, sex and titer were associated with serostatus change.
Results: Of 163296 patients sera tested for AQP4-IgG, 5606 were AQP4-IgG+. There were 1000 with ⩾2 tests of which ⩾1 was AQP4-IgG+ (86% female, median age 46 years [IQR=30-59]). The median time between tests was 1.6 years (IQR=0.5-3.5), the median number of tests was 2 (range 2-27) and 56% were tested by FACS. The median FACS titer was 1:1000 (IQR=1:100–1:10000).
Of these, 888 (89%) remained persistently AQP4-IgG+, 59 (6%) became AQP4-IgG-, 27 (3%) were AQP4-IgG- and became AQP4-IgG+, and 26 (3%) had transient seroreversion. Of those that remained AQP4-IgG+, 402 had serial testing by FACS and 89% remained at the same titer or +/-1 dilution at last test.
Of the 59 who became AQP4-IgG-, median time to seroreversion was 1.8 years (IQR=0.6-4.1). Of 27 with FACS titers, the median was 1:100 (IQR=1:10-1:100). Titers of ⩽1:100 were associated with seroreversion (OR=8.91, CI=1.88-35.67, p=0.005), but age and sex were not. Treatments included (17); rituximab (RTX) 8, RTX+intravenous (IV) immunoglobulin 2, azathioprine (AZA) 2, autologous stem cell transplant (AHSCT) 2, inebilizumab (IBZ) 1, mycophenolate mofetil (MMF) 1, none 1. Of those with follow up, 3/15 had attacks after seroreversion.
Of the 27 who seroconverted, the median time was 0.9 years (IQR=0.4-2.4). Of 22 with FACS titers, the median was 1:100 (IQR=1:100-1:1000). Titers of ⩽1:100 were associated with seroconversion (OR=9.45, CI=1.21-73.55, p=0.032), but age and sex were not. Treatments included (4); IV steroids 3, and none 1.
Of the 26 with transient seroreversion, treatments included (9) included; RTX 2, plasmapheresis (PLEX) 1, PLEX+steroids 1, IBZ 1, AHSCT 1, MMF 1, AZA+PLEX 1, RTX+AZA 1.
Conclusions: In a large population of NMOSD patients with serial AQP4-IgG testing, 89% of patients were persistently seropositive. Seroreversion (6%) and seroconversion (3%) were uncommon and were associated with low titers ⩽1:100.

Disclosure
AK has served on advisory boards for Genentech and Horizon Therapeutics. AK serves as an Editor for the*Neurology*journal.
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DMW received fees for consulting/Advisory Boards: Celgene, Horizon, Viela Bio, Genentech, Roche, Mitusbishi Tanabe, TG Therapeutics, UCB Pharma. Research (paid to Mayo): Alexion
JJC is a consultant to Roche, UCB, and Horizon
EPF has served on advisory boards for Alexion, Genentech, Horizon Therapeutics and UCB. He has received speaker honoraria from Pharmacy Times. He received royalties from UpToDate. Dr Flanagan was a site primary investigator in a randomized clinical trial on Inebilizumab in neuromyelitis optica spectrum disorder run by Medimmune/Viela-Bio/Horizon Therapeutics. Dr Flanagan has received funding from the NIH (R01NS113828). Dr Flanagan is a member of the medical advisory board of the MOG project. Dr Flanagan is an editorial board member of the Journal of the Neurological Sciences and Neuroimmunology Reports. A patent has been submitted on DACH1-IgG as a biomarker of paraneoplastic autoimmunity.
SJP has received personal compensation for serving as a consultant for Genentech, Sage Therapeutics, and Astellas.He's received personal compensation for serving on scientific advisory boards or data safety monitoring boards for F. Hoffman-LaRoche AG, Genentech, and UCB.His institution has received compensation for serving as a consultant for Astellas, Alexion, and Viela Bio/MedImmune.All compensation is paid to Mayo Clinic.He has received research support from Alexion, Viela Bio/Med Immune, Roche/Genentech. He has a patent, Patent# 8,889,102 (Application#12-678350, Neuromyelitis Optica Autoantibodies as a Marker for Neoplasia)—issued; a patent, Patent# 9,891,219B2 (Application#12-573942, Methods for Treating Neuromyelitis Optica (NMO) by Administration of Eculizumab to an individual that is Aquaporin-4 (AQP4)-IgG Autoantibody positive)—issued.
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P006
Risk of relapse following COVID-19 or anty-SARS-CoV-2 vaccination in patients with neuromyelitis optica spectrum disorders

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Neuromyelitis optica spectrum disorders (NMOSD) is an immune-mediated inflammatory disorder of the central nervous system. SARS-CoV-2 infections not only affect the lungs but generally all organs including the central nervous system. The underlying pathophysiology for SARS-CoV-2 associated CNS disease is suspected to be immunogenic. Therefore, the question is whether COVID-19 can trigger relapses in NMOSD patients. On the other hand, there have been reports that COVID-19 vaccination may trigger a relapse. The aim of our study was to assess the risk of NMOSD relpase after SARS-CoV-2 infection or after vaccination.
Department of Neurology Medical University of Warsaw is a reference center for treatment of NMOSD patients in Poland.

Nowadays we are taking care on seventy-five patients meeting NMOSD diagnostic criteria. As of March 31, 2022, we registered 47 SARS-CoV-2 infections. Twenty-two SARS-CoV-2 infections were reported in patients prior to COVID-19 vaccination (19 females, 3 males). Mean age of patients was 49±10 years, mean EDSS 4.5±1.5. Twenty (90.9%) patients were on immunosuppressive therapy (rituximab -11, steroids–4, inebilizumab -2, azathioprine -1, satralizumab -1, mycophenolate mofetil -1). Twenty-five SARS-CoV-2 infections occurred after the full course of vaccination (23 females, 2 males). Mean age of patients was 50±12 years, mean EDSS 3.6±1.7. Twenty-three (92%) patients were on immunosuppressive therapy (rituximab - 12, inebilizumab - 1, azathioprine - 3, satralizumab - 3, mycophenolate mofetil - 4). Three patients had a relapse after COVID-19 (within three months). Two of these people were still unvaccinated at the time. These patients were not receiving full immunosuppressive treatment at the time (one patient developed COVID-19 right after the first dose of rituximab, the other patient received the last dose of rituximab 18 months earlier). The third patient was treated with rituximab and was fully vaccinated. NMOSD relapse occurred in 6% of patients confirmed with COVID-19. Thee risk of relapse was even lower (2%) among patients properly treated with immunosuppressants.
Of our seventy-five patients, only two were not vaccinated against SARS-CoV-2. All patients receivedmRNA SARS-CoV-2 vaccines. No vaccine-related NMOSD attack has been reported.
Conclusion: Patients with NMOSD treated with immunosuppressants have a low risk of a relapse due to COVID-19 infection. In our study mRNA COVID-19 vaccines do not increase the risk of a relapse.

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P007
Efficacy comparison of time to first adjudicated attack with inebilizumab vs satralizumab in NMOSD: a matching-adjusted indirect comparison of monotherapy registrational trials

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Introduction: With the recent availability of three novel, safe and effective biologic therapies for neuromyelitis optica spectrum disorder (NMOSD), physicians and patients are faced with the challenge of selecting an appropriate treatment. Inebilizumab (CD19-targeted B cell depletion therapy) and satralizumab (IL-6 pathway blocker) are both indicated for NMOSD patients who are seropositive for aquaporin-4 antibody ($AQP4^+$).
Aims: Matching-Adjusted Indirect Comparison (MAIC) analysis was performed to provide a robust and rigorous trial comparison supporting an informed evidence-based therapy decision.
Methods: This analysis compares the efficacy of inebilizumab and satralizumab. To ensure an unbiased and appropriate cross-study comparison, data from the N-MOmentum (NCT02200770, N=161) and SAkuraStar (NCT02073279, N=41) studies were compared as both were registrational monotherapy studies for inebilizumab and satralizumab respectively. Both were placebo-controlled, employing similar assessments and endpoints including the primary endpoint of time to first adjudicated attack. A detailed MAIC analysis of the $AQP4^+$ population was performed based on prognostic significance as well as differences between the two studies. Seven variables were assessed: sex, age, race, ethnicity, region, baseline EDSS, and prior attacks. Sex, race, and region emerged as the variables significantly different between the two study populations and were the key factors evaluated.
Results: The primary efficacy endpoint of time to first adjudicated attack was met for both the inebilizumab and satralizumab studies with unadjusted hazard ratios (HRs) of 0.227 for inebilizumab and 0.260 for satralizumab (each vs. placebo; statistically significant). Following the MAIC analysis, which adjusts the N-MOmentum trial population to match most closely that of SAkuraStar, the HR for inebilizumab improved from 0.227 to 0.174. The relative risk ratio for inebilizumab vs. satralizumab was 0.67, representing a 33% increase in efficacy for inebilizumab compared to satralizumab for the primary endpoint. Thus, for every 100 attacks that occur in satralizumab-treated patients, only 67 would be anticipated in inebilizumab-treated patients. Multiple sensitivity analyses reinforced the validity of this result.
Conclusions: While cross-study comparisons have limitations, these results suggest a meaningful efficacy advantage of inebilizumab over satralizumab for the prevention of NMOSD attacks.

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P008

International, evidence-based Delphi consensus on the management of AQP4-IgG seropositive NMOSD, with a focus on treatment recommendations for eculizumab, inebilizumab and satralizumab

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Introduction: NMOSD is a rare, debilitating autoimmune disease of the central nervous system that necessitates maintenance therapy to prevent relapse. Three approved monoclonal antibodies have emerged as effective maintenance therapies for AQP4-IgG seropositive NMOSD (eculizumab [Soliris®], inebilizumab [Uplizna™], satralizumab [Enspryng™]), prompting a strong need to consider best practice therapeutic decision-making for this indication.
Objectives/Aims: To develop validated statements on aquaporin-4 (AQP4)-IgG seropositive neuromyelitis optica spectrum disorder (NMOSD) management, via an evidence-based Delphi consensus process.
Methods: An international panel of clinical experts in NMOSD was recruited and were asked to complete a questionnaire on NMOSD management. Their free-text responses, based on their experience and informed by clinical evidence identified via a targeted literature review, were used to generate statements on disease-related themes. Statements were voted on over a maximum of three rounds; participation in at least one of the first two rounds was mandatory. Panel members anonymously voted their level of agreement (6-point Likert scale) per statement. Statements that failed to reach a pre-defined consensus threshold ($\geqslant$ 67%) were revised based on feedback, then voted on in the next round. Final statements were those that met consensus.
Results: Twenty-four experts met participation criteria and completed the Delphi process in November 2021, after two voting rounds. In round 1, 2/25 statements failed to reach consensus and were revised. In round 2, both revised statements reached consensus, resulting in 25 agreed statements: 11 on initiation of or switching between eculizumab, inebilizumab or satralizumab; 3 on monotherapy/combination therapy; 7 on safety and patient population considerations; 3 on biomarkers/patient-reported outcomes; and 1 on research gaps.
Conclusions: An established consensus method was used to develop statements on the most pertinent areas of AQP4-IgG seropositive NMOSD management. These international statements will be valuable for informing decision-making that optimizes patient outcomes and could form the basis for standardized practice guidelines.

Disclosure

Members of the NMOSD Delphi Panel comprise Friedemann Paul (Chair), Romain Marignier (Steering Committee), Jacqueline Palace (Steering Committee), Georgina Arrambide, Nasrin Asgari, Jeff Bennett, Bruce Cree, Jérôme De Seze, Kazuo Fujihara, Saif Huda, Ho-Jin Kim, Najib Kissani, Ingo Kleiter, Satoshi Kuwabara, Marco Lana-Peixoto, Isabel Leite, Lekha Pandit, Sean Pittock, Chao Quan, Sudarshini Ramanathan, Dalia Rotstein, Albert Saiz, Douglas Sato, Adi Vaknin-Dembinsky. F. Paul has received support for Honoraria for lectures and research from Alexion, the German Ministry for Education and Research (BMBF), Deutsche Forschungsgemeinschaft (DFG), Einstein Foundation, Guthy Jackson Charitable Foundation, EU FP7 Framework Program, Biogen, Genzyme, Merck, Serono, Sanofi Genzyme, Novartis, Viela Bio, Bayer, Roche, Parexel and Almirall, UCB, Mitsubishi Tanabe and Celgene. J. Palace has received support for scientific meetings and honorariums for advisory work From Merck Serono, Novartis, Chugai, Alexion, Roche, Medimmune, Argenx, UCB, Mitsubishi, Amplo, Janssen. Grants from Alexion, Roche, Medimmune, Amplo biotechnology. Patent ref P37347WO and licence agreement Numares multimarker MS diagnostics Shares in AstraZenica. Acknowledges Partial funding by Highly specialised services NHS England. R.Marignier serves on scientific advisory boards for Alexion, Horizon Therapeutics, Roche, and UCB and has received speaker honoraria from Alexion, Biogen, Horizon Therapeutics, Novartis, Roche and Sanofi Genzyme. Oxford PharmaGenesis performed the literature review and conducted the Delphi consensus process. This research was funded by F. Hoffmann-La Roche Ltd.

P009

Frequency of NMOSD misdiagnosis in a cohort from Latin America: impact and evaluation of different contributors

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Background: Neuromyelitis optica spectrum disorders (NMOSD) misdiagnosis (i.e., the incorrect assignment of an alternative diagnosis to patients with NMOSD) remains an issue in clinical practice, especially in Latin America where aquaporin-4-antibody testing availability is low, healthcare system structure is limited and resources are scarce. We aimed to determine the frequency and factors associated with NMOSD misdiagnosis in patients evaluated in a cohort from Latin America.
Methods: We retrospectively reviewed the medical records of patients with NMOSD, according to the 2015 diagnostic criteria, from referral clinics in 6 Latin American countries (Argentina, Chile, Paraguay, Colombia, Ecuador and Venezuela). Diagnoses prior to consultation, ultimate diagnoses after consultation, demographic, clinical and paraclinical data, and treatment schemes were evaluated.
Results: 469 patients presented with an established diagnosis of NMOSD (73.2% seropositive for AQP4-Ab) and after evaluation, misdiagnosis was identified in 56 (12%) patients. The most frequent alternative diagnoses were multiple sclerosis (MS; 66.1%), clinically isolated syndrome (17.9%) and cerebrovascular disease (3.6%). NMOSD misdiagnosis was performed by MS/NMOSD subspecialists in 33.9%. Atypical MS syndrome was found in 86% of misdiagnosed patients, 50% had NMOSD red flags in brain and spinal MRIs, and 71.5% were prescribed disease-modifying drugs.
Conclusions: Twelve percent of patients with established NMOSD were identified as having been misdiagnosed. Thus, NMOSD misdiagnosis is relatively frequent in Latin America and it can lead patients to unnecessary and potentially harmful risks. Misapplication of diagnostic criteria and misinterpretation of clinical and neuroradiological findings (especially in relation with MS) are relevant factors associated with misdiagnosis.

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This study was supported by LACTRMIS. None of the authors has any potential financial conflict of interest relating to this poster.

P010
Efficacy subgroup analyses from the phase 3 CHAMPION-NMOSD trial in adults with anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder

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Introduction: CHAMPION-NMOSD (NCT04201262) is a global, open-label, multicentre, phase 3, externally controlled study of ravulizumab (Rav) in adults with anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. Rav binds the same complement component 5 (C5) epitope as eculizumab (Ecu), but due to a longer elimination half-life, the dosing interval can be extended from 2 to 8 weeks while maintaining high specificity for C5 and a similar degree of terminal complement inhibition as Ecu. Here we report pre-specified efficacy analyses in clinically relevant patient subgroups.
Methods: Patients aged ⩾18 years received a weight-based intravenous loading dose of Rav (2400–3000 mg) on day 1, followed by weight-based maintenance doses (3000–3600 mg) on day 15 and then once every 8 weeks thereafter. For ethical reasons, concurrent placebo (Pbo) treatment was precluded owing to availability of Ecu and other treatments; thus, the Pbo arm from PREVENT (NCT01892345) was used as an external comparator. Pre-specified efficacy subgroup analyses of time to first adjudicated on-trial relapse were conducted and safety outcomes were analysed across subgroups.
Results: Of 58 patients in the Rav arm, at baseline, 30 were receiving monotherapy and 28 were receiving immunosuppressive therapy (IST): steroids (n=12), azathioprine (n=7), mycophenolate mofetil (n=6) or other (n=3). No Rav-treated patient experienced a positively adjudicated on-trial relapse. Based on time to first adjudicated on-trial relapse, Rav was superior to Pbo in the monotherapy (hazard ratio [HR]: 0.021; 95% confidence interval [CI]: 0–0.176; relapse risk reduction [RRR]: 97.9%; $p<0.0001$) and IST groups (HR: 0.031; 95% CI: 0–0.234; RRR: 96.9%; $p<0.0001$). Significant differences vs placebo were seen in patients who had previously received rituximab (n=20; RRR: 93.7%; $p=0.0078$) or had not (n=38; RRR 98.1%; $p<0.0001$). Rav was superior to placebo in pre-specified subgroups by age (<45 years or ⩾45 years: RRR: 95.7–97.9%; $p\leqslant0.0012$), sex (RRR: 94.3–98.2%; $p\leqslant0.0068$), Asian and white races (RRR: 95.1–97.8%; $p\leqslant0.0027$) and geographic region (RRR: 91.5–96.1%;$p\leqslant0.025$). The overall safety in the subgroups analysed was consistent with that of Rav across other approved indications.

Conclusions: The robust treatment effect of Rav on RRR was observed across all pre-specified subgroups, including IST use as well as monotherapy, geographic region, age, race and gender.

Disclosure

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SJ Pittock has received personal compensation for serving as a consultant for Genentech, Sage Therapeutics, and Astellas and personal compensation for serving on scientific advisory boards or data safety monitoring boards for F. Hoffman-LaRoche AG, Genentech, and UCB; His institution has received compensation for serving as a consultant for Astellas, Alexion, and Viela Bio/MedImmune. He has received research support from Alexion, Viela Bio/MedImmune, Roche/Genentech. He has a patent, Patent# 8,889,102 (Application#12-678350, Neuromyelitis Optica Autoantibodies as a Marker for Neoplasia) — issued; a patent, Patent# 9,891,219B2 (Application#12-573942, Methods for Treating Neuromyelitis Optica (NMO) by Administration of Eculizumab to an individual that is Aquaporin-4 (AQP4)-IgG Autoantibody positive) — issued; Patents for Kelch11, LUZP4, Septin, MAP1b Abs pending.

M Barnett has received institutional support for research or speaking from Alexion, Biogen, Merck, Roche, BMS, and Sanofi Genzyme; is Research Director, Sydney Neuroimaging Analysis Centre; and Research Consultant, RxMx.

JL Bennett has received personal fees from Viela Bio, Mitsubishi Tanabe, Reistone Biopharma, AbbVie, Clene Nanomedicine, Alexion, BeiGene, Genentech, Inc., and F. Hoffmann-La Roche Ltd and grants from Mallinckrodt, Novartis, Alexion, and the National Institutes of Health. In addition, JLB has a patent 'Compositions and methods for the treatment of neuromyelitis optica' — issued.

A Berthele has received consulting and/or speaker fees from Alexion, Bayer Healthcare, Biogen, Celgene, Novartis, Roche and Sandoz/Hexal. His institution has received compensation for clinical trials from Alexion, Biogen, Merck, Novartis, Roche, and Sanofi Genzyme.

J de Sèze has served on the scientific advisory board and as a consultant for Alexion.

M Levy has received research support from Alexion, Horizon, and Genentech and consulting fees from Alexion, Horizon, Genentech, Sanofi, and UCB.

I Nakashima has received honoraria for serving on the scientific advisory board of Alexion, and by serving as speaker at a lecture meeting held by Alexion.

C Oreja-Guevara has received honoraria for speaking and serving on advisory boards from Biogen Idec., F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Merck, Janssen, BMS, Novartis, and Teva.

J Palace has received support for scientific meetings and honoraria for advisory work from Merck Serono, Novartis, Chugai, Alexion, Roche, Medimmune, Argenx, UCB, Mitsubishi, Amplo, and Janssen. Grants from Alexion, Roche, Medimmune, Amplo Biotechnology and UCB. Patent ref P37347WO and license agreement Numares multitracker MS diagnostics. Shares in AstraZeneca. Acknowledges partial funding by highly specialised services NHS England.

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C Pozzilli has served as speaker, consultant and advisor fees, research support and travel grants from: Alexion, Janssen, Almirall, Biogen, Bristol-Meyer, Hoffmann-La Roche, Merck, Novartis.

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P011

Association of B cell subsets and aquaporin-4 antibody titers with disease activity in participants in the N-MOmentum trial receiving inebilizumab treatment

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Introduction: Inebilizumab (INEB), an anti-CD19 B-cell depleting antibody, is approved to treat neuromyelitis optica spectrum disorder (NMOSD).

Objective: To evaluate the relationship between peripheral blood B-cell subsets and aquaporin 4 (AQP4) immunoglobulin G (IgG)

titers and NMOSD attacks in participants of N-MOmentum (NCT02200770).

Methods: Participants received INEB 300 mg or placebo (PBO), on days 1 and 15 during the randomized controlled period (RCP) and every 6 months in the optional open-label period (OLP). Absolute counts of $CD20^+$ B cells and $CD27^+$ memory B cells were assessed by flow cytometry (RCP + OLP). Plasma cell (PC) gene expression was assessed by quantitative reverse transcription PCR (RT-qPCR) in the RCP. AQP4-IgG titers were determined by cell-based assay (RCP only). All measurements were done in peripheral blood.

Results: In the PBO group, significant increases in $CD20^+$ B cells and $CD27^+$ memory B cells were seen at time of attack relative to the preceding visit ($p < 0.05$). Increases in PC subset were already observed at the preceding visit relative to baseline ($p < 0.01$). During attack, a >2-fold increase from baseline was seen in 4/20 (20%) for $CD20^+$B cells, 3/19 (16%) for memory B cells, and 11/20 (55%) for PC. INEB significantly decreased all B cell subsets. No significant increases in any B cell subsets at time of attack were observed in the INEB group relative to the preceding visit. Changes in AQP4-IgG titer from baseline to attack were not significantly different between treatment groups ($p = 0.15$). At RCP end, 9/50 (18%) of PBO participants vs 59/159 (37%) of INEB participants (p=0.014) had ⩾ 2-fold decrease in AQP4-IgG (0% vs 11% ⩾ 8-fold decrease, $p = 0.008$).

Conclusions: Increased levels of B-cell subsets at time of attack were observed in the PBO but not INEB group, particularly in the PC subset. Inebilizumab treatment was associated with reduction in AQP4-IgG in a subset of participants.

Disclosure

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F. Paul has received research support, speaker honoraria and travel reimbursement from Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, and Teva; is supported by the German Research Council (DFG Exc 257) and the German Competence Network for Multiple Sclerosis; has received travel reimbursement from the Guthy-Jackson Charitable Foundation; and serves on the steering committee of the OCTIMS study, sponsored by Novartis.

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M.A. Smith, M. Gunsior, W.A. Rees,and**K.R. Patterson** are employees and stockholders of Horizon.

B.A.C. Cree reports personal compensation for consulting from Alexion, Atara, Autobahn, Avotres, Biogen, EMD Serono, Gossamer Bio, Horizon, Neuron23, Novartis, Sanofi, TG Therapeutics and Therini and received research support from Genentech.

J.L. Bennett reports payment for study design/consultation from Horizon; personal fees from AbbVie, Alexion, Chugai, Clene Nanomedicine, Genentech and Genzyme; grants and personal fees from EMD Serono and Novartis; and grants from the National Eye Institute. In addition, Dr Bennett has a patent 'Compositions and methods for the treatment of neuromyelitis optica' issued.

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P012

Sensitivity analysis using propensity score methods for primary efficacy outcome in the CHAMPION-NMOSD trial

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Introduction: The complement component 5 (C5) inhibitor, eculizumab (Ecu), was approved for the treatment of anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4+ NMOSD) following the phase 3 PREVENT

trial (NCT01892345). Ravulizumab (Rav) also binds C5 and has a longer elimination half-life than Ecu, allowing an extended dosing interval. In CHAMPION-NMOSD, a global, open-label, phase 3 trial (NCT04201262) in adults with AQP4+ NMOSD, Rav reduced the risk of relapse by 98.6% versus the PREVENT placebo (Pbo) arm, an external comparator. We report results from pre-specified sensitivity analyses used to account for the external Pbo comparator.

Methods: Propensity scores were used to account for potential differences in patient characteristics between the Rav and PREVENT Pbo groups and estimated with a logistic regression using age at first dose, sex, region, use of immunosuppressive therapy (IST), baseline Expanded Disability Status Scale (EDSS) score and historical annualized relapse rate (ARR) as predictors. Time to first adjudicated relapse and relapse risk reduction were analysed using a stabilized inverse probability of treatment weighting (SIPTW) approach. A tipping point analysis (E-value) was used to assess how much unaccounted-for confounding would be needed to mitigate the treatment effect.

Results: Baseline characteristics in the Rav group (n=58) and PREVENT Pbo group (n=47), respectively, were mean age: 47.4 vs 45.0 years; female: 90% vs 89%; Americas: 36% vs 32%; Europe: 29% vs 40%; Asia-Pacific: 34% vs 28%; IST use: 48% vs 72%; median EDSS: 3.25 vs 4.00; median historical ARR: 1.4 vs 1.9. In CHAMPION-NMOSD, no adjudicated on-trial relapse occurred (median follow-up: 73.5 weeks) compared with 20 patients having a relapse in the PREVENT Pbo group (median follow-up: 36.0 weeks); hazard ratio (HR): 0.014 (95% confidence interval [CI]: 0.000–0.103); % reduction: 98.6% (CI:89.7%–100.0%; $p<0.0001$; E-value: 24.7). In the SIPTW analysis, the HR was 0.014 (95% CI: 0.000–0.101); % reduction: 98.6% (CI: 89.9%–100.0%;$p<0.0001$; E-value: 25.1).

Conclusions: Results from the sensitivity analysis were consistent with those from the primary analysis of CHAMPION-NMOSD, indicating that differences in baseline characteristics between the Rav and external Pbo groups did not affect the treatment effect. High E-values suggest that considerable unmeasured confounding would be needed to fully account for the Rav RRR of 98.6%.

Disclosure

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K Allen is an employee of Alexion, AstraZeneca Rare Disease.

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M Levy has received research support from Alexion, Horizon and Genentech and consulting fees from Alexion, Horizon, Genentech, Sanofi, and UCB.

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I Nakashima has received honoraria for serving on the scientific advisory board of Alexion, and by serving as speaker at a lecture meeting held by Alexion.

A Berthele has received consulting and/or speaker fees from Alexion, Bayer Healthcare, Biogen, Celgene, Novartis, Roche, and Sandoz/Hexal. His institution has received compensation for clinical trials from Alexion, Biogen, Merck, Novartis, Roche, and Sanofi Genzyme.

JL Bennett has received personal fees from Viela Bio, Mitsubishi Tanabe, Reistone Biopharma, AbbVie, Clene Nanomedicine, Alexion, BeiGene, Genentech, Inc., and F. Hoffmann-La Roche Ltd and grants from Mallinckrodt, Novartis, Alexion, and the National Institutes of Health. In addition, he has a patent 'Compositions and methods for the treatment of neuromyelitis optica' — issued.

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C Pozzilli has served as speaker, consultant and received advisor fees, research support and travel grants from Alexion, Janssen, Almirall, Biogen, Bristol-Myers Squibb, Hoffmann-La Roche, Merck, and Novartis.

Y Mashhoom is an employee of Alexion, AstraZeneca Rare Disease.

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P013

Pregnancy outcomes in neuromyelitis optica spectrum disorder

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Introduction: Neuromyelitis Optica Spectrum Disorder (NMOSD) is frequently diagnosed in women of childbearing age. Disease activity in NMOSD has been shown to adversely impact maternal and fetal outcomes in some pregnancies but recommendations on mode of delivery are lacking. In addition, comparison studies on NMOSD disease between patients with NMOSD diagnosed prior to pregnancy and those diagnosed after their pregnancies, have not been conducted.
Objectives: In our study, we aim to compare pregnancy outcomes and mode of delivery in women who were diagnosed with NMOSD prior to pregnancy with women who were diagnosed with NMOSD after pregnancy.
Methods: This study utilized the Collaborative International Research in Clinical and Longitudinal Experience Studies (CIRCLES) which began collecting data in 2013 and is ongoing. CIRCLES is a prospective, multicenter, cross-sectional, and longitudinal study of NMOSD cases and controls, and the dataset utilized for the current study included all patients in the CIRCLES cohort who had reported having a pregnancy. Relative risk and two-proportion Z tests were used compare risks between patients diagnosed with NMOSD before and after pregnancy.
Results: We collected clinical information on 148 pregnancies among 110 women with NMOSD diagnosed prior to pregnancy, and 1355 pregnancies among 595 women with NMOSD diagnosed after childbearing years. Of these, 44 patients in the early diagnosis group and 362 patients in the later diagnosis group were known to be Aquaporin 4 (AQP4) IgG positive, while the antibody status of the remaining patients was unknown. The risk of having a C-section delivery was increased in those who had been diagnosed with NMOSD prior to pregnancy compared to those who would be diagnosed later in life (35.3% compared to 22.5%, $p = .0015$). The risk of miscarriage was slightly higher in the patients already diagnosed with NMO (17.9% compared to 14.1%), however this was not statistically significant ($p = 0.208$). The impact of rituximab on pregnancy outcomes will be analyzed as well.
Conclusions: The risk of having a C-section delivery is increased among patients with diagnosed NMOSD while the risk of miscarriage was not significantly different between those diagnosed before pregnancy and those diagnosed after their pregnancy.

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P014

Effectiveness and safety of different therapeutic strategies of Rituximab in NMOSD patients: multicenter cohort study in Latin America

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Introduction: Rituximab (RTX) is an effective drug to prevent NMOSD relapses. However, there is considerable heterogeneity regarding safety aspects number and dosage of infusions and frequency of treatment cycles. We aimed to describe and compare its effectiveness and safety according to patients' characteristics and different regimen strategies in NMOSD patients from Latin America (LATAM).
Methods: observational retrospective multicenter study including patients with NMOSD on RTX from 8 countries and 14 center of LATAM (Argentina, Chile, Ecuador, Brazil, Venezuela, Mexico, Colombia, and Paraguay). Demographics and clinical characteristics were collected and RTX strategies on naïve patients are summarized as follows: scheme A: Two 1000 mg infusions 15 days apart and repeated every 6 months; scheme B: four 375 mg/m2 infusions every week for 4 weeks and repeated every 6 months; scheme C: one 1000 mg infusions and repeated every 6 months; scheme D: Other scheme used (free text and described). Relapse rate and adverse events during follow-up were analyzed considering the different RTX schemes. Poisson and logistic regression analysis were used to assess baseline aspects and disease activity (relapses and time to relapse) during follow-up.
Results: a total of 95 patients were included (82.1% % AQP4-ab seropositive). Mean age at disease onset 38.1 ± 3.5 years, mean disease duration 6.1 ± 1.2 years, mean EDSS at disease onset 3.3 ± 2, mean follow-up time 72 ± 55 months. The most common scheme of RTX used was two 1000 mg infusions 15 days apart and repeated every 6 months in 79 (83.1%) patients followed by scheme C in 7 (7.3%) and then the scheme B in 6 (6.3%) and finally other scheme in 3 (3.2%). In 50 (52.6%) patients, reinfusions of RTX were dependent on CD19 cells reappearance. RTX was changed in 21 (22.1%) patients, 18 (85.7%) due to persistent activity and in 3 (14.2%) due to adverse events. Ten (12.6%) adverse events were observed on scheme A and 2 (33.3%) on scheme B. RTX change due to persistent activity was associated with higher EDSS scores (OR 1.75, 95%CI 1.44-2.34, p=0.03) and age (OR=1.07, 95%CI 1.02-1.17 p=0.04) at RTX initiation but not with RTX scheme (OR= 1.10 95%CI 0.89-1.21, p=0.60), or other analyzed variables related to treatment.
Conclusions: RTX has been effectively used in LATAM. Real world studies on how it is used, and factors related to its effectiveness may help us optimize patients' care.

Disclosure
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P015
Treatment-associated infections in NMOSD and MOGAD patients – retrospective analysis in an outpatient clinic cohort

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Introduction: Immunosuppressants are effectively used as disease modifying drugs to reduce the relapse rate in Aquaporin-4-positive neuromyelitis optica spectrum disorder ($AQP4^+$ NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and seronegative NMOSD. However, these therapies are associated with an increased risk of infection, ultimately leading to treatment discontinuation.
Methods: Here, we retrospectively assessed the frequency and severity of treatment-associated infections in our outpatient cohort of patients with $AQP4^+$ NMOSD, MOGAD and seronegative NMOSD treated with antiproliferative agents (azathioprine, cyclophosphamide, methotrexate, mitoxantrone, and mycophenolate mofetil) or the anti-CD20 antibody rituximab (RTX). Furthermore, we predicted the risk of infection using a multivariate regression model to explore factors that increased the risk of developing infection during therapy.
Results: Overall, we included 86 patients in our study (50 $AQP4^+$ NMOSD, 28 MOGAD, 8 seronegative NMOSD) and analyzed 244 treatments. We observed a higher frequency of infections when patients were treated with RTX compared to antiproliferative immunosuppressants (logOR=1.59, 95%CI=[0.67;2.50], $p=5.75x10^{-4}$). Furthermore, the proportion of patients with severe infections was higher in the RTX group (0.69 vs 0.5). We observed a greater reduction in serum immunoglobulin concentrations in the patient cohort with treatment-associated infections.
Conclusions: Taken together, the higher frequency of treatment-associated infections in patients treated with RTX than in those treated with antiproliferative immunosuppressants should be considered when establishing a disease modifying therapy in NMOSD or MOGAD. Moreover, our data highlights the importance of serum immunoglobulin concentration as a possible biomarker for treatment-associated infections.

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P016
Aquaporin-4 IgG seropositive neuromyelitis optica spectrum disorder and cancer: a data-driven investigation

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Introduction: The association of aquaporin-4 IgG seropositive neuromyelitis optica spectrum disorder (AQP4-IgG NMOSD) and cancer is debated, also according to the recently updated

diagnostic criteria for paraneoplastic neurological syndromes (PNS), which might underestimate this association. Indeed, only patients with isolated myelitis and adenocarcinoma or tumors expressing AQP4 are classified as probable PNS.
Objective: To investigate paraneoplastic AQP4-IgG NMOSD through a data-driven approach.
Aims: To define clinical characteristics and oncological accompaniments of paraneoplastic AQP4-IgG NMOSD, and to evaluate the possible clusterization of these features into specific groups.
Methods: We performed a systematic literature review to identify patients with AQP4-IgG NMOSD and an associated tumor, according to PRISMA guidelines.
Inclusion criteria were: 1. AQP4-IgG seropositivity; 2. history of cancer; 3. no history of CNS metastases or checkpoint inhibitors exposure. We collected demographic, clinical, and oncological data of included patients and performed a hierarchical cluster analysis (HCA). A comparison of resulting clusters was performed.
Results: We screened 1333 records and included 46 studies with 72 patients. Most of these patients were female (57, 79.2%) and median age was 54 (range 14-87). Adenocarcinoma was diagnosed in 30 patients (41.7%), other solid neoplasms in 29 (40.3%), and hematological tumors in 13 (18%). Cancer and NMOSD usually occurred at the same time.
Differences among clusters were driven by the occurrence of optic neuritis, isolated/multifocal attacks, the type of underlying neoplasm, and age at onset. Notably, no differences in time from neoplasm to NMOSD onset, tumor AQP4 staining, and age were noted.
Conclusions: Paraneoplastic AQP4-IgG NMOSD is a heterogeneous entity not limited to the association between isolated myelitis and adenocarcinoma. Cancer screening should be considered according to the herein reported data.

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P017
Most opticospinal demyelination is NMOSD, not MS - a 17-year UK longitudinal cohort study

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Background: There has been significant progress in the classification of central nervous system (CNS) inflammation with the identification of aquaporin-4 (AQP4) antibodies in neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) antibodies in MOG antibody disease (MOGAD) in addition to multiple sclerosis (MS). However, as defined in 2003, patients with opticospinal demyelination (OSD; optic neuritis (ON), short-segment transverse myelitis (TM), and brain imaging not supportive of MS) do not fulfil internationally approved criteria for MS, NMOSD, or MOGAD.
Objective: To evaluate diagnosis and clinical outcomes in a cohort of patients with OSD
Methods: Between 2003-2005, 128 cases of opticospinal demyelination were reported via the British Neurological Surveillance Unit. In 2011, 2015 and 2022 patients and physicians were contacted for clinical, radiological, and serological (e.g., AQP4-IgG and MOG-IgG) data as part of a prospective longitudinal cohort study.
Results: Of 128 reported cases, 67 (52%) patients fulfilled OSD diagnostic criteria. Outcome data at 17 years were available from 60 patients of which 39 (65%) now met NMOSD diagnostic criteria, 14 (23%) had MS and 7 (12%) had OSD. Preliminary data estimates the median time to diagnosis of NMOSD as 107 months (85-261) and to MS as 189 months (79-346). The median age of OSD patients at onset was 37 (25-48) years and 5/7 patients were male. A relapsing clinical course was observed in 6/7 patients with a median annualised relapse rate of 0.22 (0.13-0.49). Three patients received Azathioprine, 1 was on Interferon Beta-1b and 3 did not receive immunomodulatory treatment. At last follow-up the median EDSS was 2.5 (range; 1-6.5) and only 2/7 patients had an EDSS$>$3.5.
Conclusions: OSD is a distinct clinical entity from MS, NMOSD, and MOGAD. However, after 2 decades most OSD patients reached a diagnosis of either NMOSD or MS, so OSD may lie on a spectrum with these conditions. Of the 12% of cases that retained OSD classification at follow-up, all but 1 had a relapsing course but rates of significant disability were low. Future studies should focus on characterising diagnostic and prognostic biomarkers in this unique subtype of non-MS CNS inflammation.

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P018
Mortality estimates in patients with anti-aquaporin-4 autoantibody positive neuromyelitis optica spectrum disorder

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a rare, complement-mediated autoimmune disease of the central nervous system characterised by unpredictable relapses (attacks) that can lead to blindness, paralysis, cognitive impairment, and death. Approximately 75% of patients with NMOSD are seropositive for anti-aquaporin-4 autoantibodies (AQP4+).
Objectives: To examine mortality in patients with AQP4+ NMOSD.
Methods: A cohort of patients with AQP4+ NMOSD from the UK National NMOSD Data Set maintained by Oxford University Hospital (Oxford, UK) was followed over a 6-year period (2014–2020) and used to compare mortality among patients with AQP4+ NMOSD, as characterised by a standardized mortality ratio (SMR) and excess mortality vs the general population. Age- and sex-matched patients from the general population (based on 2019 data among those aged 18-85 years in the UK) were used for comparison. The SMR was calculated by the ratio of observed number of deaths in patients with AQP4+ NMOSD vs the number of deaths expected in the age- and sex-matched cohort of the general population. Excess mortality was calculated by subtracting the expected mortality from the observed mortality in patients with AQP4+ NMOSD. A SMR of $>$ 1.0 was used to indicate excess death; excess mortality was represented by $>$ 0%.
Results: Seventy-four patients with AQP4+ NMOSD were included in the analysis. The mean age was 54 years (standard deviation: 17 years; range: 18-85 years); 65/74 (87.8%) patients were female. Mean and median disease durations were 7.7 and 8.0 years, respectively. The mean annual death rate among patients with AQP4+ NMOSD was 2.64%, with mean and median ages at death of 63and 66 years, respectively. The average weighted mortality rate of the age- and sex-matched general population was 0.71%, resulting in a SMR of 3.72 (95% confidence interval: 3.71–3.72) and an excess mortality rate of 1.93% annually among patients with AQP4+ NMOSD.
Conclusions: The analysis showed that the excess mortality of patients with AQP4+ NMOSD is 1.93%. While NMOSD is known to severely affect the morbidity of patients, these data show that despite treatment, it negatively affects the mortality of patients who are AQP4+.

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P019
Long-term burden of attacks in patients with AQP4+ NMOSD: a simulation study based on results of a network meta-analysis

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a rare, complement-mediated autoimmune disease of the central nervous system, characterised by neuroinflammatory attacks that result in cumulative and irreversible damage. Attacks in patients with NMOSD are unpredictable and can cause blindness, paralysis, and reduced quality of life. A recently published network meta-analysis (NMA) compared eculizumab, satralizumab, and inebilizumab for the treatment of patients with anti-aquaporin-4 autoantibody positive (AQP4+) NMOSD in the absence of concomitant immunosuppressive therapy (IST) use.
Objectives: To generate comparative efficacy estimates over a 20-year time horizon via a Markov model to assess the risk of attacks in patients with AQP4+ NMOSD based on treatment with Food and Drug Administration (FDA)-approved therapies.
Methods: Hazard ratios (HRs) from the NMA associated with time-to-first attack (0.11 for eculizumab versus inebilizumab and 0.1 for eculizumab versus satralizumab) were applied within a Markov model of NMOSD with a time horizon of 20 years. Time-to-first attack was assumed to follow an exponential distribution (consistent with observed data), and the first-attack curve was assumed to apply to subsequent attacks. Outcomes were quality-adjusted life years (QALYs) and attack-free years. Utility adjustments by attack were used to characterise QALYs. Patient-level data from the PREVENT trial were used to characterise the overall time-to-event curve for placebo, to which HRs were applied for active therapies, and to estimate EQ-5D utilities for patients with AQP4+ NMOSD pre- and postattack.
Results: The HRs were applied within the Markov model over a 20-year time horizon; eculizumab was associated with 11.0 additional attack-free years (total: 16.9 years) and 2.7 additional QALYs (total: 11.6 QALYs) compared with satralizumab. In

addition, eculizumab was associated with 10.3 additional attack-free years and 2.4 additional QALYs compared with inebilizumab.
Conclusions: Based on this Markov model, which extrapolated the results of a prior NMA, eculizumab was associated with the longest attack-free time compared with satralizumab or inebilizumab. Patients receiving eculizumab were also projected to experience the highest number of additional QALYs.

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P020
Cognition in patients with neuromyelitis optica spectrum disorders: a prospective longitudinal multicentre study of 217 patients (CogniNMO-Study)

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Background: Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory autoimmune diseases of the central nervous system that characteristically affect the optic nerve, spinal cord, or area postrema. Previous smaller studies showed inconsistent results on cognitive deficits of NMOSD patients.
Goals: To determine the frequency and type of cognitive impairment and to assess whether there are changes over time in NMOSD.
Methods: This prospective, longitudinal, multicentre observational study included data from 217 aquaporin-4-IgG-seropositive (80%) and seronegative NMOSD patients recruited from 17 German Neuromyelitis Optica Study Group (NEMOS) centres. Cognitive functions of NMOSD patients measured by Symbol Digit Modalities Test (SDMT), Paced Auditory Serial-Addition Task (PASAT), and/or Multiple Sclerosis Inventory Cognition (MUSIC) were compared with normative data from healthy controls. Intraindividual cognitive performance at one- and two-year follow-up were analysed. Cognitive test scores were correlated with demographic and clinical variables. Multiple linear regression was used to predict cognitive performance.
Results: NMOSD patients were impaired in SDMT ($p = .007$), MUSIC verbal fluency ($p < .001$), and MUSIC congruent naming speed ($p < .001$) compared to healthy controls. Every fifth patient (19%) showed impaired performance in at least two test scores. This study did not reveal a significant decrease in individual test performance at one- and two-year follow-up. Higher Expanded Disability Status Scale scores were associated with lower test performance. SDMT scores were related to physical and visual disability ($r_s = -.43, p < .001$, and $r_s = -.32, p < .001$). No differences were found between aquaporin-4-IgG-seropositive and seronegative NMOSD.
Conclusion: NMOSD patients are cognitively impaired in information processing speed and verbal fluency regardless of serostatus, without noticeable changes during a two-year observation period. Neuropsychological measurements should be adapted to physical and visual disabilities of NMOSD patients.

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VH has nothing to disclose.
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BK has nothing to disclose.
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Clinical aspects of MS - MOGAD

P021

Dynamic MRI lesion evolution in paediatric MOG-Ab associated disease (MOGAD)

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Introduction: Myelin oligodendrocyte glycoprotein (MOG) antibodies are associated clinically with either a monophasic or relapsing disease course in both children and adults. There are few studies studying lesion evolution in children with myelin oligodendrocyte glycoprotein antibody associated disorder (MOGAD).
Objectives: The aim of this study was to examine MRI lesion evolution over time in a large single-centre paediatric MOGAD cohort.
Methods: We retrospectively identified patients with MOGAD from a tertiary paediatric neurosciences centre (Great Ormond Street Hospital, London, UK) between 2001 to 2022.
Results: A total of 363 MRI scans from 59 included patients were available for analysis. Median age at presentation was 4 yrs (IQR 4-9), 32 (54.2%) were female and 34 (57.6%) were of non-white ethnicities. Twenty-seven children (45.8%) had a monophasic illness and 32 (54.2%) had a relapsing disease course. In the relapsing MOGAD group, median number of

relapses was 4 (range 2-30). Initial presentation was ADEM in 27 (46%), ON in 18 (31%) ADEM-ON in 4 (7%), ADEM-TM in 6 (10%) TM in 2 (3%) ADEM-TM-ON in 1 (2%) and ON-Brainstem syndrome in 1 (2%). There was no difference in demographics or clinical presentation between monophasic and relapsing groups.
Fifteen patients (25.4%) had gadolinium enhancement on initial attack MRI. Seven out of 32 (21.9%) relapsing patients had persistent enhancement on follow-up MRI scans. One patient with a clinical transverse myelitis at presentation was MRI negative. New asymptomatic lesions following first clinical event were seen in 5/27 (18.5%) monophasic patients and 8/32 (25%) relapsing patients. A total of 38/59 (64.4%) had a follow-up MRI scan after the first relapse with an additional 15 patients relapsing prior to follow-up imaging. Complete lesion resolution was reported in 9/38 (23.6%) (8 monophasic, 1 relapsing) following 1st acute attack, 3/32 (9.3%) after 2nd acute attack, and 1/32 (3.1%) following 3rd acute attack, and 0/32 following 4th acute attack. Partial resolution of MRI lesions was seen in 7/20 (35%) monophasic patients and 7/32 (21.8%) relapsing patients at follow-up scans.
Interpretation: Demyelinating lesions in paediatric MOGAD are dynamic and timing of MRI scanning may influence CNS region involvement. Unlike in multiple sclerosis, a significant number of MOGAD patients will have complete lesion resolution at first follow-up, although the ability to repair is reduced following multiple relapses.

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P022
Predicting the risk of long-term relapse in MOGAD

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Introduction: Approximately half of patients with MOG-antibody associated disease (MOGAD) relapse. It is not clear whether early relapsing activity (within 1 year of initial attack) indicates risk of chronic disease. We aimed to identify whether early relapse, along with predictors of early relapses, predicts relapse beyond one year.
Methods: A prospective cohort of 192 MOGAD patients from 5 UK centres with at least 2 years' disease duration and no long-term immunosuppressive treatment during the first year were included. One hundred and eighteen (61%) experienced relapses at any stage.
Univariate Cox regressions for time-to-relapse after the first year were performed with covariates including the presence and number of early relapses, the timing of early relapse (categorized in three-month epochs), decision to treat with corticosteroid and duration of taper (days), age at onset, self-identified race, onset phenotype and seroconversion to MOG antibody-negative. Multivariate Cox-regression models included all previously significant variables, as well as MOG-antibody seroconversion.
Results: Out of 118 relapsing MOGAD patients, we found 49 (25.5%) patients with early relapses with a median number of 1 (range 1-4) relapses.
Univariate analysis revealed an increased risk of long-term relapse with any early relapse (Hazard Ratio [HR] 1.60, CI 1.16-1.89),

relapses in the first (HR 2.24, CI 1.27-3.92) or the last 3-month epoch (HR 2.66, 1.22-5.78), higher numbers of early relapses (HR 1.48, CI 1.16-1.89) and non-white race (HR 1.94, CI 1.08-3.48). Longer duration of early corticosteroid treatment (HR 0.99^{days}, CI 0.996-0.999, p=0.035) was protective.

Following multivariate regression analysis, the number of early relapses and relapse in the first (HR 2.51, CI 1.19-5.27) and third 3-month epochs (HR 3.71, CI 1.52-9.06) were significant, as were days on corticosteroid treatment (HR 0.99^{days}, CI 0.99-0.99; HR 30 days 0.74) and non-white race (HR 2.69, CI 1.45-5.11).

There was an 84% and 99% specificity for long-term relapses in the first 5 years in those with $\geqslant$1 and $\geqslant$2 early relapses respectively, with low sensitivity (20% and 5%).

Conclusion: Our results suggest that early relapses are associated with increased risk of long-term relapsing disease and may indicate a need for long-term immunosuppression as they do not appear to solely reflect early inflammatory phase. Early corticosteroid treatment may have a protective role in preventing relapses beyond one year.

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P023

Assessing initial clinical presentation of myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) based on race in a diverse single academic center cohort

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Introduction: MOGAD is associated with optic neuritis, myelitis, brainstem syndromes, and acute disseminated encephalomyelitis (ADEM). MOGAD can present as a monophasic or relapsing disease. Some patients develop permanent deficits from MOGAD. More research is needed to determine risk factors for a relapsing course, but some research has suggested phenotype at initial presentation may help predict relapse. Per our review of the literature, limited research exists on phenotype at initial presentation based on race. Froedtert Memorial Lutheran Hospital is the only academic medical center in Milwaukee and has a diverse MOGAD cohort.

Objectives: The objective of this study is to assess phenotype of initial presentation based on race in the MOGAD cohort at Froedtert Memorial Lutheran Hospital
Aims: The aim of this study is to improve understanding of initial clinical presentation based on race with the hopes of aiding in prognostication and treatment decisions.
Methods: We queried our electronic medical record for patients with a diagnosis of "neuromyelitis optica" or "neuromyelitis optica spectrum disorder." We subsequently manually reviewed charts for a diagnosis of MOGAD. We reviewed the records to determine the phenotype of initial presentation.
Results: Our MOGAD cohort includes 39 patients. Six of the patients are Black (~15.4%), four patients are Hispanic (~10.2%), and 29 patients are White (~74.4%). Amongst the Black patients, four presented with unilateral optic neuritis (~66.7%) and two presented with myelitis (~33.3%). Amongst the Hispanic patients, two presented with bilateral optic neuritis (50%), one presented with a brainstem syndrome (25%), and one presented with both optic neuritis and transverse myelitis (25%). Amongst the White patients, 15 presented with unilateral optic neuritis (~51.7%), five presented with bilateral optic neuritis (~17.2%), three presented with myelitis (~10.3%), four presented with a brainstem syndrome (~13.8%), one presented with both optic neuritis and transverse myelitis (~3.4%), and one presented with suspected ADEM (~3.4%).
Conclusions: Our results suggest that the phenotype of initial presentation of MOGAD seems to be similar across different races. Improved understanding of initial clinical presentation based on race may aid in understanding of expected prognosis and treatment decisions.

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Allison Block: Nothing to disclose
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P024
Real-world data from the MSBase registry in MOG antibody-associated disease: First insights from the MOGAD substudy

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Introduction: MOG Antibody-Associated Disease (MOGAD) is a rare autoimmune demyelinating disorder of the central nervous system affecting children and adults. Clinical features may overlap with NMOSD or MS, although MOGAD is increasingly recognised as a distinct disease.
Aims: To prospectively collect data on the natural history, clinical and radiological characteristics, therapeutic responses, and outcomes of pediatric and adult MOGAD patients.
Objective: To facilitate an observational international study to determine the clinical, therapeutic and prognostic profile of MOGAD patients using the MSBase registry.
Methods: Interim analysis of the MSBase MOGAD cohort (data extraction on May 11 2022 and start of the registry in August 2021). Inclusion criteria: MOG-IgG-seropositive adult and pediatric patients.Descriptive statistics were used for baseline patient characteristics including demographics, symptoms at first presentation, follow-up duration, disease course, immunosuppressive therapies, and EDSS.
Results: A total of 74 patients were included from Australia (n=30), Belgium (n=29), Italy (n=8), Turkey (n=4), Kuwait (n=1), Saudi-Arabia (n=1), and Croatia (n=1). The female to male ratio was 1.2 (54% female, 46% male) with an average age at diagnosis of 36.7 $\pm$ 17.5 years for males and 35.8 $\pm$ 14.5 years for females. Symptoms at first presentation included optic neuritis (n=34), transverse myelitis (n=13), cerebral syndrome (n=7), brainstem (n=5), and acute diencephalic syndrome (n=3). The median disease duration was 3.3 years for males and 4.4 years for females, and 33 patients had at least 1 relapse (median: 2 relapses, range 1-27). The longest times in person-years on prescribed DMT were with azathioprine, B-cell depleting treatments (including rituximab and ocrelizumab), methylprednisolone, glatiramer-acetate, and interferon beta. The average follow up EDSS showed a stabilisation of 0.6 $\pm$ 1.6.
Conclusions: This real-world data from an international cohort confirms previous national studies that patients are most often in their thirties at presentation and have equal gender distribution between males and females. Most frequent phenotypes at first presentation are optic neuritis followed by transverse myelitis. Prospective data collection using MOGAD-dedicated MOGBase within the international MSBase registry will enable detailed analyses of cohort level data, and facilitiate the identification of optimal therapeutic approaches to improve outcomes.

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GL has institution have received financial compensation for congress attendance, consultancy, research and education by Almirall, Biogen, Celgene, Bristol Myers Squibb, Novartis, Roche, Sanofi, Teva.
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TK served on scientific advisory boards for BMS, Roche, Janssen, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.
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P025

A novel index, neutrophil-to-nonneutrophil ratio (NNR) as the predictive markers of disease activity in myelin oligodendrocyte glycoprotein antibody-associated disease: comparable with neutrophil-to-lymphocyte ratio (NLR)

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Introductions: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a CNS autoimmune disease affecting the brain, spinal cord, and optic nerve. The neutrophil-to-lymphocyte ratio (NLR) is related to autoimmune disease activity. Still, the clinical implication of NLR is unclear in patients with MOGAD.
Objectives: We aimed to investigate the relationship between NRL and disease activity and discover the most useful index correlated with an attack in MOGAD.
Methods: Using a prospective cohort of CNS demyelinating disease, we reviewed adult 42 patients with MOGAD (age 35.54±13.72 years; F: M=23:19), who had 427 blood samples for the analysis of cell count. We calculated NLR as [relative neutrophil count (%)/relative lymphocyte count (%)] and explored other indices to analyze their correlation of them with disease activity (attack vs remission).
Results: NLR during the attack was higher than in remission in MOGAD ($p<0.001$). In addition, eosinophil-to-lymphocyte-ratio (ELR) and platelet-to-lymphocyte-ratio (PLR) were lower during attack than in remission ($p<0.001$ and $p=0.006$). Moreover, we discovered the novel index; neutrophil-to-nonneutrophil ratio (NNR) [relative neutrophil count (%)/ (100-relative neutrophil count (%))], which was also higher during attack than in remission ($p<0.001$). Using the receiver-operating characteristic (ROC) curve analysis, the optimal threshold of 3.65 for both NLR and N-ratio (neutrophil > 78.5%) was used to differentiate between acute attack and remission in MOGAD: sensitivity of 48.15% and specificity of 87.67%.
Discussion: Our study suggests that NLR, ELR, PLR, and NNR could be used as supportive biomarkers for the attack, given that the clinical differentiation between relapses and pseudo-relapses can be challenging. Moreover, the novel index, NNR calculated by the neutrophil count only, may be the simplest and the most useful index to predict an attack in MOGAD.

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P026

Tocilizumab treatment of MOGAD encephalitis non-responder to Anti CD-20 therapy: efficacy and safety during SARS-COV-2 infection

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Introduction: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an autoimmune disorder of the central nervous system distinct from multiple sclerosis (MS) and neuromyelitis optica spectrum disorder. Common clinical presentations include a recurrent optic neuritis, transverse myelitis, acute disseminating encephalomyelitis (ADEM) or ADEM-like syndromes, and brainstem encephalitis.
Objectives/Aims: To report a case of patient affected by MOGAD encephalitis who experienced SARS-CoV-2 infection during the treatment with Tocilizumab.
Methods and Results: We report a case of a 57-year-old Caucasian woman with a 5-year history of a demyelinating disease characterized by bilateral and symmetric fronto-temporo-parietal demyelinating lesions and previously diagnosed as MS. The patient had been treated with severaltherapies, including interferon beta-1a, Natalizumab, anti-CD-20 monoclonal antibodies, with no benefits.Her symptoms and brain magnetic resonance imaging (MRI) lesionsload had progressively worsened, resulting in a significantmotor and cognitiveimpairment.In April 2020, the diagnosis was reviewed and classified as MOGAD+ encephalitis.Thepatient started anti-CD-20 monoclonal antibody therapy, stopped due to lack of efficacycharacterized by increasing MRI lesion load and worsening of cognitive impairment. In February 2022, Tocilizumab, an IL-6 receptor inhibitor, was initiated at the dosage of 8 mg/kg via intravenous route. Further administrations were repeated every four weeksin March and April 2022. The treatment was well tolerated and the patient did not report any adverse event. IL-6 levels decreased and the caregiver reported an improvement in patient's cognitive performances.Furtherneurological examinations showed a mild improvement in motor performances, walking ability, and brainstem and cognitive functions. On April25th, the patient, previously vaccinated with three doses of Pfizer-BioNTech vaccine, tested positive to SARS-CoV-2which resulted in symptoms characterized by.fever, cough, joint pain, and shortness of breath. Two days after the symptoms onset, she started therapy with nirmatrelvir/ritonavirobtaining a dramatic regression of all the symptoms in about24 hourswithout any adverse events.
Conclusions: In light of the lack of literature on the co-occurrence of COVID-19 in Tocilizumab-treated MOGAD patients, the present report highlights the safety and benefit of the use of antiviral therapy in these patients.

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P027

Corpus callosum lesions in MOG antibody-associated disease versus AQP4-IgG+NMOSD and MS

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Introduction: Corpus callosal lesions in myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) have not been well characterised and comparison studies to multiple sclerosis (MS) and aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder (AQP4-IgG+NMOSD) are lacking.
Objectives: To describe the MRI characteristics of corpus callosum lesions in MOGAD and compare to MS and AQP4-IgG +NMOSD.
Methods: We retrospectively identified MRI brain scans of Mayo Clinic MOGAD patients within 6 weeks of a symptomatic attack and compared these to MS and AQP4-IgG+NMOSD. Callosal lesions were analysed for anatomic distribution, lesion characteristics and lesion evolution at follow-up.
Results: Eligible scans (unique patients) were identified: 171 (119) MOGAD, 72 (43) MS and 63 (55) AQP4-IgG+NMOSD. Age (median [range]) differed between MOGAD (28 [3-66]), MS (35 [15-62]) and AQP4-IgG+NMOSD (50 [3-91]), $p<0.001$. Female sex predominated: MOGAD 60%, MS 78% and AQP4 86%, $p<0.001$. Callosal lesions occurred in 38/171 (22%) MOGAD scans, 24/72 (33%) MS and 18/63 (29%) AQP4-IgG+NMOSD, p=0.17. Callosal involvement in the absence of cerebral symptoms (focal deficits or encephalopathy) was rare in MOGAD (5/85 [6%]), including those with isolated optic neuritis (3/67 [4%]). Median (range) maximal callosal T2-lesion diameter in mm was larger in MOGAD (21 [4-77]) than MS (10.5 [2-64], p=0.04) but not AQP4-IgG+NMOSD (25 [5-49]; p=0.93). Midline callosal involvement was more common in MOGAD (18/38 [47%]) and AQP4-IgG+NMOSD (13/18 [72%]) vs MS (2/24 [8%]), $p<0.001$. Longitudinally extensive callosal lesions greater than 2.5 cm were more common in AQP4-IgG+NMOSD (6/18 [33%]) than in MS (1/24 [4%], p=0.03) but not MOGAD (4/38 [11%], p=0.06). Extracallosal lesion extension was more frequent in MOGAD (21/38 [55%]) vs AQP4-IgG+NMOSD (2/18 [11%], p=0.003) and similar to MS (7/24 [29%], p=0.07). Callosal lesion extension bilaterally to parasagittal cortices was unique to MOGAD and occurred in 6/38 (16%) cases. Complete callosal lesion resolution was more frequent in MOGAD (19/34 [56%]) vs MS (3/23 [13%]) and AQP4-IgG+NMOSD (2/13 [15.4%]), p=0.001.
Conclusions: Callosal involvement occurs at similar frequencies in MOGAD, MS and AQP4-IgG+NMOSD. While many MRI features overlapped between groups, features that may favour

MOGAD include larger lesion size, midline involvement, extracallosal extension rather than subependymal lesions, and lesion resolution at follow-up.

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Vyanka Redenbaugh: nothing to disclose
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P028
Myelin oligodendrocyte glycoprotein antibody titers after immune globulin treatment: a case series

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Introduction: Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is a distinct demyelinating disease of the central nervous system. Immune globulin (Ig) has been used for treatment of acute attacks, as well as a maintenance therapy to prevent relapses in MOGAD. Persistent and high-titer MOG-IgG seropositivity has been associated with a higher risk of relapse, but the impact of Ig on MOG-IgG titers is unclear.
Aims: To assess the association, if any, between immune globulin treatment and MOG-IgG antibody titers.
Methods: We conducted a retrospective chart review of patients with a diagnosis of MOGAD followed at our center. Patients with MOG-IgG testing results available before and after initiation of maintenance treatment with Ig were included.
Results: All six patients demonstrated a reduced titer level after treatment with Ig. The median pre-Ig titer was 1:100 (range: 1:20 - 1:1,000), and all patients were seropositive on two or more occasions and had experienced a relapsing course. One patient became seronegative after a pre-Ig titer of 1:20 after over one year of chronic Ig treatment. For the remaining five patients, titers decreased from 1:80 to 1:40 after 7 months of treatment, 1:100 to 1:40 after one year of treatment, 1:100 to 1:40 after 18 months of treatment, 1:1,000 to 1:100 after 9 months of treatment, and from 1:100 to 1:40 after 5 months of treatment. Three patients had their pre-Ig titers drawn within three months of a relapse. Multiple post-Ig titers were available in 3 patients. Of those 3, all remained at a lower-level titer compared to before Ig treatment, though they remained persistently seropositive. Despite persistent seropositivity in the majority of patients, only one experienced a relapse after starting Ig, in the setting of a delayed IVIG infusion.
Conclusions: This case series, while limited by the small sample size and its observational nature, supports that Ig treatment is associated with a decrease in MOG-IgG levels. Despite persistent seropositivity in most patients, the majority of patients remained relapse-free following initiation of Ig therapy.

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P029
MRI T2-Lesion evolution in paediatric MOG antibody-associated disease versus other demyelinating diseases

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Introduction: We recently reported that MRI T2-lesions resolve more often inmyelin oligodendrocyte glycoprotein (MOG)-IgG-associated disease (MOGAD) than aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder (AQP4-IgG+NMOSD) and multiple sclerosis (MS), but paediatric patients were underrepresented. Earlier studies reporting higher rates of MRI lesion resolution in presumed paediatric MS predated testing availability for MOGAD and AQP4-IgG+NMOSD.

Aims/Objectives: To investigate MRI lesion evolution in paediatric patients with MOGAD, AQP4-IgG+NMOSD and MS.
Methods: Our inclusion criteria were: 1) first brain and/or myelitis attack; 2) MRI obtained within 6 weeks of attack nadir; 3) follow-up MRI beyond 6 months after the acute MRI, without interval clinical relapses in that region; and 4) age <18 years at time of attack MRI. An index T2-lesion (the symptomatic or largest lesion) was identified for each patient. MRIs were sorted randomly and independently reviewed by two neurologists, blinded to diagnosis, to determine T2-lesion resolution or persistence on follow-up MRI.
Results: We included21 patients with MOGAD, 8 with AQP4-IgG+NMOSD and 27 with MS; in total 69 attacks (brain, 37; myelitis, 32). Age (median [range]) differed between MOGAD (7 [2–17]), AQP4-IgG+NMOSD (13.5 [4–16]), and MS (15 [3–17]), $p<0.01$. Female sex predominated in all groups: MOGAD (13/21 [62%]), AQP4-IgG+NMOSD (7/8 [88%]) and MS (21/27 [78%]), $p=0.38$. Complete resolution of the index T2-lesion was more frequent in MOGAD (brain 9/15 [60%]; spine 8/12 [67%]) than AQP4-IgG+NMOSD (brain 1/4 [25%]; spine 0/7 [0%]) and MS (brain 0/18 [0%]; spine 1/13 [8%]), $p<0.01$. Resolution of all T2-lesions occurred more often in MOGAD (brain 6/15 [40%]; spine 7/12 [58%]) than AQP4-IgG+NMOSD (brain 1/4 [25%]; spine 0/7 [0%]), and MS (brain 0/18 [0%]; spine 1/13 [8%]), $p<0.01$. The median (range) percentage reduction in T2-lesion area in mm^2 on follow-up axial brain MRI was greater in MOGAD (100 [3-100]) than AQP4-IgG+NMOSD (88 [38-100],$p<0.01$) and MS (54 [0-65],$p<0.01$) and the % reduction in area on axial spine MRI follow-up in MOGAD (100 [31-100]) was greater than AQP4-IgG+NMOSD (34 [0-95], $p<0.01$) and MS (38 [0-100],$p<0.01$).
Conclusions: In a paediatric cohort, T2-lesions on MRI resolved more often in MOGAD than AQP4-IgG+NMOSD and MS. These findings are consistent with reports from adults and suggests differences in T2-lesion evolution relate to disease pathogenesis rather than age.

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Eoin P. Flanagan has served on advisory boards for Alexion, Genentech and Horizon Therapeutics. He has received speaker honoraria from Pharmacy Times. He received royalties from UpToDate. Dr Flanagan was a site primary investigator in a randomized clinical trial on Inebilizumab in neuromyelitis optica spectrum disorder run by Medimmune/Viela-Bio/Horizon Therapeutics. Dr Flanagan has received funding from the NIH (R01NS113828). Dr Flanagan is a member of the medical advisory board of the MOG project. Dr Flanagan is an editorial board member of the Journal of the Neurological Sciences and Neuroimmunology Reports. A patent has been submitted on DACH1-IgG as a biomarker of paraneoplastic autoimmunity.

P030
Bilateral optic neuritis is associated with more severe fatigue in patients with myelin oligodendrocyte glycoprotein antibody-associated disease

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Introduction: Fatigue has been well-characterized in multiple sclerosis and is known to be common among people with neuromyelitis optica spectrum disorder. However, it is unclear whether fatigue is a symptom of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD).
Objective: To assess the fatigue severity in people with MOGAD compared to household controls (HC) and identify factors associated with it.
Methods: In a cross-sectional survey, data were collected from self-identified people with MOGAD and HC. Survey questionnaires collected information regarding demographics, sleep quality measures, comorbidities, MOGAD characteristics, and fatigue severity measured by the Modified Fatigue Impact Scale (MFIS). We compared fatigue severity between MOGAD participants and HC and explored the associations between demographic and disease characteristics and fatigue severity.
Results: There were 180/283 MOGAD and 61/126 HC respondents. Compared to HC, people with MOGAD reported more severe fatigue, as measured by the MFIS total score (49.3 vs. 36.5; adjusted difference: 11.6 [95% CI: 6.6 to 16.6], $p<0.001$) and all of its subcomponents – physical (22.5 vs. 16.7; adjusted difference: 5.5 [95% CI: 3.1 to 7.9], $p<0.001$), cognitive (22.0 vs. 16.6; adjusted difference: 4.6 [95% CI: 2.1 to 7.1], $p<0.001$), and psychosocial (4.8 vs. 3.2; adjusted difference: 1.5 [95% CI: 0.91 to 2.1], $p<0.001$). Additionally, a larger proportion of MOGAD participants (75.6% vs. 44.3%; $p<0.001$) were classified as fatigued using a predetermined cutoff score (MFIS $\geq$ 38; OR=4.7 [95% CI: 2.3 to 9.6], $p<0.001$). Among MOGAD participants, higher age (p=0.04), presence of a history of bilateral optic neuritis (ON) (p=0.02), presence of comorbid conditions (p=0.03), and current use of acute treatment (p=0.04) were independently associated with higher fatigue. MOGAD participants with a history of

bilateral ON showed decreased sleep quality compared to HC as measured by increased number of awakenings (OR=3.3 [95% CI: 1.3 to 9.7]; p=0.02), an association which was not observed in MOGAD participants without bilateral ON.
Conclusions: Fatigue is common in people with MOGAD, and higher age, a history of bilateral ON, comorbid conditions, and recent or ongoing disease activity, determined by using acute treatments, appear to contribute to fatigue severity.

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Clinical aspects of MS - Neuropsychology

P031
Factors associated with depressive mood at onset of MS – an analysis of 781 patients of the German NationMS cohort

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Introduction: Life time prevalence of depression in patients with multiple sclerosis (MS) is high. Depression has a major impact on quality of life and may present during all MS stages, including clinically isolated syndrome (CIS). However, comprehensive analyses of MS risk factors, including smoking, vitamin D (25-OH-VD) levels and Epstein-Barr virus (EBV) antibody levels, associated with depression in patients with early MS are scarce.
Objective / Aims: The aim of this study was to assess risk factors for depression in participants of the German NationMS cohort study.
Methods: We analyzed data of 781 participants with available baseline visit data for demography (age, sex, smoking behavior), clinical characteristics (diagnosis, current relapse, expanded disability status scale (EDSS)), questionnaires (Beck's Depression Inventory II (BDI-II), Fatigue Scale Motor Cognition (FSMC)), 25-OH-VD serum concentration, and EBV nuclear antigen-1 IgG (EBNA1-IgG) antibody levels in serum. Multivariable linear regression (MLR) was carried out with BDI-II score as dependent and the other factors as independent variables.
Results: CIS was diagnosed in 327/781 (41.9%) and relapsing-remitting MS (RRMS) in 454/781 (58.1%) participants according to McDonald 2005 criteria. Mean age was 34.3 years (95% confidence interval (95%CI) 33.6-35.0) and 546/781 (69.9%) were women. The majority (535/781 (68.5%)) were non-smokers. Mean 25-OH-VD serum concentration was 22.2 ng/ml (95%CI 21.2-23.2), yet 398/781 (51.0%) patients were 25-OH-VD deficient (below the lower limit of normal (20 ng/ml)). In all participants, EBNA-1-IgG was detected in serum with mean EBNA1-IgG levels of 1453.8 U/ml (95%CI 1360.4-1547.2).
In MLR analyses, baseline EDSS, MS diagnosis (CIS vs. RRMS), age, sex and EBNA1-IgG levels were not associated with severity of depressive symptoms. However, presence of a current relapse (coefficient (coef.) 1.48, 95%CI 0.27-2.69, p=0.016), severity of fatigue (coef. 0.26, 95%CI 0.24-0.28, $p<0.0001$), 25-OH-VD serum concentration (coef. -0.03; -0.06- -0.002, p=0.034) and present smoking (coef. 0.347; 0.091-0.604,p=0.008) were associated with a higher BDI-II score.
Conclusions: With 25-OH-VD, remote EBV infection and smoking behavior, we investigated major environmental MS risk factors. We demonstrate that EBNA1-IgG titers were not, whereas

smoking and low 25-OH-VD were associated with being depressed around MS onset, contributing to the burden of MS.

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P032

Exploring the presence of anosognosia among MS patients

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Introduction: Cognitive impairment (CI) is present in 40-70% of MS patients. It can appear in the early stages and worsen over time. Often, objectively measured cognitive performance does not match patient's subjective perception of own performance.

Objectives: To compare cognitive performance and subjective perception of cognitive deficits between MS patients and healthy controls (HC).

Methods: 54 HC and 112 MS patients (relapsing-remitting MS -RRMS-; n=65 and progressive MS -PMS-; n=47) underwent neuropsychological evaluation and completed the Perceived Deficits Questionnaire (PDQ), the Modified Fatigue Impact Scale (MFIS) and the Hospital Anxiety and Depression Scale (HADS). Raw scores of cognitive tests were transformed into z scores using HC mean and standard deviation. Also, a global cognitive performance score was calculated. Linear regression models were used to (1) compare MS patients and HC adjusting results by age, educational level and anxiety-depression and (2) explain contribution to PDQ scores of age, educational level, MS phenotype (RRMS vs PMS), anxiety-depression, fatigue and objective cognitive performance.

Results: Differences on cognitive performance were found between both RRMS and PMS compared to HC, PMS showed bigger and more widespread differences with HC, than RRMS. No differences were found on PDQ between MS patients (nor RRMS nor PMS) and HC. Variables significantly predicting PDQ scores in the linear regression model (r^2= 0.501, F(7, 154) = 22.1, p <0.001) were a progressive phenotype of MS (PMS) (β= −5.32, 95%CI -10.25 to -3.93; p=0,035), Anxiety-Depression scores (HADS) (β= 0.57, 95%CI 0.29 to 0.85; p=<0,001), fatigue scores (MFIS) (β= 0.25, 95%CI 0.15 to 0.34; p=<0,001), and cognitive performance (β= −2.96, 95%CI -5.44 to -0.47; p=0,020).

Conclusions: Differences on cognitive performance were found in both MS patient groups, being more intense and widespread on

PMS patients. Conversely no differences between groups were found on deficit perception. Among factors explaining variability on PDQ scores, there is MS phenotype (PMS patients had up to 5.32 points less on PDQ than HC). These findings suggest that anosognosia might be present in PMS patients.

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P033

Temprano – the amsterdam early relapsing-remitting multiple sclerosis cohort: an introduction on the cognitive and psychological functioning of the cohort

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Background and objective: Early multiple sclerosis (MS) remains an understudied phase of the disease. This study follows the Amsterdam "Temprano" cohort of early MS, for which we describe initial baseline findings regarding cognitive and psychological functioning.
Methods: In this interim-analysis, baseline data of 41 recently diagnosed relapsing-remitting MS (RRMS) patients (i.e., 6-12 months after diagnosis, 34 females, age = 36.7±10.1 years) and 16 matched HCs (9 females, age = 38.4±10.3 years) is presented. Neuropsychological examination included the MACFIMS (Dutch adaptation). Cognitive test scores were corrected for age, sex and educational level (based on normative scores) and transformed into *Z*-scores (test and domain specific). Participants were classified as cognitively impaired (CI) when scoring ⩾1.5SD below normative scores on ⩾20% of test scores and otherwise classified as cognitively preserved (CP). Cognitive domains were compared between MS patients and HCs using independent samples*t*-tests. The following psychological symptoms were explored: mood and anxiety (Hospital Anxiety and Depression Scale, cut-off>11), fatigue (Checklist Individual Strength-20R, cut-off>76), sleep problems (Athens Insomnia Scale, cut-off>10) and cognitive complaints (Multiple Sclerosis Neuropsychological Questionnaire, cut-off>27).
Results: In total, 10 out of 41 patients could be classified as CI, compared to 3 out of 16 HCs. The only cognitive domain that differed significantly between MS patients and HCs was visuospatial memory (Z = -0.46±0.78 vs. Z = 0.18±0.57, respectively;p= 0.004). Four patients exceeded the clinical cut-off of anxiety symptoms (10%), 2 patients of depression symptoms (5%), 21 patients of fatigue (51%), 6 patients of sleep problems (15%) and 14 patients of cognitive complaints (34%). No HCs exceeded cut-offs of psychological symptoms, except for fatigue (*N*=3, 19%).
Discussion: These findings replicate previous findings that cognitive impairment is already present in ~25% of the patients early after diagnosis and that visuospatial memory problems are one of the first domains to be affected.

Disclosure
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P034

How to translate PASAT scores into SDMT scores for follow-up of cognition in MS

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Introduction: In situations where clinicians have time to do only one cognitive test in MS, the symbol digit modalities test (SDMT) has in the past years replaced the paced auditory serial addition test (PASAT). This creates a problem for the analysis of conjoined cognitive follow-up datasets.

Aim: To construct a statistical model that translates PASAT-3 scores into predicted SDMT scores.
Methods: Retrospective data was collected in three centers in Belgium, Germany and Switzerland.
A linear model was fitted in Matlab, with SDMT as the dependent variable, and PASAT-3, age, sex and education level as predictor variables. To account for non-linear age effects, age squared was also included in the primary model. To evaluate the importance of the different predictors, per single predictor, the linear model was recalculated using all except that predictor. To avoid overfitting, we used a leave-one-out cross-validation approach.
We then assessed the correlation and mean absolute error (MAE) between the measured and predicted SDMT.
Results: We included 461 PwMS and 147 controls.
Predicted SDMT correlated significantly with measured SDMT (Pearson r=0.69, r^2=0.48, $p<0.0001$). The MAE was 7.9 SDMT points, corresponding to 0.56 standard deviations.
Dropping one variable at a time from the linear model resulted in a decrease in r^2 by 0.24 for PASAT-3, 0.01 for age, 0 for age-squared, 0.02 for sex and 0.02 for schooling level.
Slopes of the regression lines between measured and predicted SDMT were not significantly different in the four subgroups (MS-Belgium, MS-Germany, MS-Switzerland and controls) following an ANCOVA analysis
Conclusions: In this retrospective multi-centre study, we propose a linear model that allows researchers to translate historical PASAT-3 scores into SDMT scores, improving their ability to combine and analyse longitudinal cognitive follow-up in MS patients. The accuracy of our model is in the range of test-retest studies for SDMT.

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P035
Cognitive and MRI profile in primary and secondary progressive multiple sclerosis

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Introduction: Studies comparing frequency and patterns of cognitive dysfunction between primary progressive (PP) and secondary progressive (SP) multiple sclerosis (MS) have yielded conflicting results.
Objectives: We examined the neuropsychological profile of PPMS and SPMS and investigated the relationship between cognitive functioning with structural and functional MRI abnormalities.
Methods: One-hundred eighty-three progressive MS patients (60 PPMS and 123 SPMS) and 75 healthy controls (HCs) underwent 3.0T MRI. MS patients were administered the Brief Repeatable Battery of Neuropsychological tests (BRB-N). Four cognitive domain z-scores were determined from normative data, and then averaged to obtain a measure of global cognition (z-BRB-N). Using hierarchical linear regression analysis, the contribution of lesion volumes, normalized brain volumes, white matter fractional anisotropy (FA) and mean diffusivity (MD) abnormalities, and resting state (RS) functional connectivity (FC) alterations to global cognition in PPMS and SPMS was investigated.
Results: Compared to PPMS, SPMS showed decreased FA and increased MD in the fornix, and lower RS FC within the basal ganglia network. The frequency of cognitive impairment was 32% in PPMS and 41% in SPMS (p=0.19). No significant differences were detected in mean z-verbal memory, z-visuospatial memory, z-attention/processing speed, z-verbal fluency and z-BRB-N between PPMS and SPMS. Linear regression analysis showed that lower z-BRB-N in PPMS was associated with decreased FA in the medial lemniscus (ΔR^2=0.11; p=0.01) and lower normalized gray matter volume (ΔR^2=0.29; $p<0.001$), while in SPMS lower z-BRB-N was associated with reduced FA of the fornix (ΔR^2=0.35; $p<0.001$) and lower normalized white matter volume (ΔR^2=0.05; p=0.03).
Conclusions: PPMS and SPMS had similar neuropsychological profile. Cognitive dysfunction in PPMS and SPMS was related to distinct patterns of structural MRI abnormalities and involvement of different white matter tracts, while RS FC alterations did not contribute to explain their global cognitive functioning.

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P036

Thresholds for defining cognitive impairment in people with multiple sclerosis using an electronic version of a symbol substitution task

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Introduction: Up to 70% of people with Multiple Sclerosis (MS) experience cognitive problems which can be debilitating and impact on day-to-day life. A digital Symbol Substitution Task (SST), a variant of the Symbol Digit Modalities Test (SDMT), was developed as part of a multi-centre project aiming to develop a neuropsychological pathway to routinely assess people with MS attending UK MS clinics for cognitive problems (NEuRoMS; www.neuroms.org). This work presents thresholds for determining cognitive impairment using the newly developed SST.
Methods: This is a cross-sectional study. Data were collected for control participants who do not have MS. The levels of cognitive impairment in people with MS were defined as follows, based on previously published work on a similar digital variant of SDMT known as Multiple Screener: 1) None evident: Score of less than 1.5 standard deviations (SD) below the mean; 2) Possibly mildly impaired: Scores of 1.5 SD or more, and less than 2 SD below the mean; 3) Probably impaired: Score of 2 SD or more below the mean. Data for the SST were also collected for people with MS as part of routine clinical care in three National Health Service (NHS) Trusts. The thresholds defined above were applied to data for people with MS to establish the prevalence of cognitive impairment. This abstract presents findings from a planned interim analysis. Data collection is ongoing.
Results: People with MS (n=632) were mostly female and of mean age 49.1. Most people with MS had relapsing-remitting MS, and had been diagnosed an average of 18.7 years. Control participants (n=41) were mostly female with a mean age of 44.3 years. From control participants who completed the task, the mean score was 47.9, SD 8.6. The thresholds for defining that a patient is possibly mildly impaired and probably impaired are 35.1 and 30.8 respectively. Applying these thresholds to the MS cohort to establish cognitive impairment, there were 329 (52.1%) who were classified as 'None evident', 104 (16.5%) who were classified as 'Possibly mildly impaired', and 199 (31.5%) who were classified as 'Probably impaired'.
Discussion: Pervious research has mainly categorised people into 'impaired' or 'not impaired'. This work however has generated thresholds for defining the severity of cognitive impairment in people with MS using an electronic version of the SST, enabling clinicians to interpret test results more accurately. Further data will be collected to refine these thresholds.

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P037

Information processing speed in multiple sclerosis: the role of demographic, disease variables and cognitive reserve – longitudinal study

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Introduction: One of the frequent consequences of multiple sclerosis (MS) is cognitive impairment that affects 40%-70% of patients over-time. Across cognitive domains, information processing speed (IPS) is the most frequently impaired cognitive domain. The importance of exploring factors related to IPS deficits in MS is crucial to early detection of cognitive impairment.
Methods: Relapsing-remitting MS (RRMS) patients (N= 175) that performed cognitive evaluation diagnosed more than five years, with two-time points (Mdifference in years = 6.46, SD= 1.21). Information processing speed was measured using the MindStreams computerized cognitive battery (NeuroTrax). Demographic and disease related variables including gender, age, disease duration, and duration of disease modifying therapies (DMT) were collected and used for hierarchical linear regression.
Results: One hundred seventy-five RRMS patients, age 45.3±12.23 years, 72.6% females, with disease duration of 13.6±7.74 years at T1. Ninety-two (52.6%) treated with DMT were included in the study. According to the hypothesis, problem-solving at T1 was found to positively predict IPS at T2, while disease duration was found as negatively predictor. In addition, patients who were treated with DMT scored higher at IPS than non-treated patients. The final model was significant ($p<$ .001, R^2 = 14.4%).
Conclusion: IPS performance is related to disease duration, DMT, and problem-solving skills, when the latter serve as indication for cognitive reserve. Although a longer disease duration is related to lower information processing speed, people with MS who are treated with DMT, and have higher cognitive reserve are more preserved cognitively, with higher information processing speed. Our findings highlight the importance of DMT treatment and cognitive reserve as protective factors against cognitive deterioration of people with MS. In addition, considerable attention should be paid for the necessity of cognitive reserve parameters such as problem-solving skills in the cognitive evaluation.

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P038

Hippocampal resting-state functional connectivity and its relation to episodic memory impairment in progressive multiple sclerosis

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Introduction: Hippocampus plays a critical role in memory, being one of the most common and intensively impaired cognitive function in multiple sclerosis (MS), mainly in progressive stages of the disease. Accordingly, functional connectivity (FC) changes in the hippocampus have been reported in MS. However, whether FC changes are adaptative or maladaptative mechanism is a topic of much discussion.
Objective: To investigate hippocampalresting-stateFC abnormalities and their relation to episodic memory impairment in progressive stages of MS (PMS).
Methods: Cross-sectional study of 65 subjects: 30 healthy controls and35 PMS (19 Secondary Progressive MS and 16 Primary Progressive MS).Episodic memory capabilities were assessed with a modified version of Rey Auditory Verbal Learning Test: introduction of two recognition trials in the five learning trials. Participants underwent a magnetic resonance imaging session on which resting-state sequences were acquired. Two-sample t-tests models were used to assess whole-brain differences in the seed-based FC of the bilateral hippocampus. Regression models were used to evaluate between-group differences in memory capabilities. All analysis were controlled for gender, age, educational level, and anxiety-depressive symptoms.
Results: Differences between groups emerged in the sum of the words of the learning trials ($p=0.003$), the delayed recall ($p=0.001$) and the 3rd recognition trial as measured by discriminability index ($p=0.038$) and Criterion Level ($p=0.006$).Compared to controls, PMS showed a decreased FC between thebilateral hippocampi and the right middle frontal gyrus(t= 4.58,$p=0.018$)and an increased FC between the hippocampi and two posterior occipital cortices:extrastriate cortex (t= 4.64,$p=0.022$) and fusiform gyrus (t= 4.38,$p=0.009$).
Conclusions: Decrease in FCbetween thebilateral hippocampi and the right middle frontal gyrusin PMScould be playing a large role in memory impairment suffered by this group. At the same time,increase in FCbetween the hippocampi and posterior occipital cortices in PMS would not act as a compensatory mechanism, rather as another sign of MS progression.

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P039

Repeated forms, testing intervals, and SDMT performance in a large multiple sclerosis dataset

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Introduction: The Symbol Digit Modalities Test (SDMT) is the most reliable and sensitive measure of cognitive efficiency in PwMS, and it is increasingly used in clinical trials and clinical care.
Objectives/Aims: To evaluate how normalization and interpretation of SDMT scores are influenced by repeating forms and the frequency of use.
Methods: A retrospective analysis was completed on 740 people with MS (PwMS) exposed to multiple SDMT administrations. Analyses of SDMT slope accounted for frequency of tests over varying time periods and utilization of alternate- versus same-form conditions.
Results: Estimated mean SDMT change from initial to final administration was +3.79 points per exposure for those exposed to repeated SDMTs over <2 years (n=114, p=0.001) and +0.55 points per exposure for those exposed over ⩾2 years (n=626, p=0.008). A regression model was applied predicting SDMT change using time (years), *Sum of Consecutive Forms (*number of times the same testing form is repeated in a row, after initial exposure),and the time-by-*Sum of Consecutive Forms* interaction term as independent predictors ($p<0.001$). The model showed a significant time-by-*Sum of Consecutive Forms* interaction (β=-0.08, p=0.016), accounting for baseline SDMT, age,

sex, education, disease duration, and *Sum of SDMT Exposures*. A comparable interaction (β =-0.069, p=0.039) was also observed in a model considering*Longest String of Consecutive Forms* (p<0.001).

Conclusion: Repeating the same SDMT form results in greater improvement in SDMT performance as compared to changing form, and the effect is magnified when tests are repeated over shorter intervals. We recommend that alternative versions of timed symbol-digit coding be used in samples that are saturated with many administrations of the SDMT.

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P040

Association between dual-task performance, cognitive reserve, and cognitive function in people with multiple sclerosis

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Introduction: When the motor and cognitive tasks are performed simultaneously, the common areas of the brain are overloaded since they have to share resources between the two tasks. The cognitive reserve can lead to the differential recruitment of brain networks; therefore, it may contribute to variation in cognition among individuals with the same pathologies, and these may differentially affect the cognitive-motor relationship. Patients with a higher cognitive reserve can better withstand disease burden without cognitive impairment. Therefore, the cognitive reserve could also be protective of dual-task performance

Aims: This study investigated the association between dual-task performance, cognitive reserve, and cognitive function in people with multiple sclerosis (pwMS).

Methods: Sixty-four pwMS [mean age= 39.12±8.8 years, mean EDSS=3.37±1.42] performed the motor task (30 s walking in 20 m pathway) with and without cognitive task (phonemic word list generation task, WLG). Dual-task cost (DTC) was calculated as the percent change in distance from a single walking task to a dual task. The Cognitive Reserve Index questionnaire (CRIq) was used to evaluate cognitive reserve. Symbol Digit Modalities Test was performed to assess cognitive processing speed. Perceived dual-task difficulties were assessed using the Dual-task Impact on Daily-living Activities Questionnaire (DIDA-Q).

Results: There was a moderate correlation between CRIq and the number of correct responses during dual-task walking (r=0.461), DTC (r=0.331), and cognitive subscore of DIDA-Q (r=0.313). The hierarchical linear regression analysis demonstrated that DTC, the number of correct answers, and DIDAQ explained 33% of the variance related to the CRIQ. The acquisition of demographic and clinical factors, including age, gender, level of education, and EDSS, explained an additional 31% of the variance.

Conclusion: Building and maintaining cognitive reserve may protect dual-task abilities, which are essential for everyday life activities in pwMS.

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P041

Accelerated hippocampal atrophy in elderly onset multiple sclerosis patients

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Introduction: Multiple sclerosis (MS) with elderly onset (e.g. after the age of 50 years) has been increasingly recognized. Assessing disease-related cognitive and MRI features in elderly patients is extremely challenging, as it is necessary to consider changes due to normal aging.

Objectives: To identify the distribution of recently defined cognitive phenotype in MS patients with elderly onset and its MRI substrates.

Methods: We enrolled 138 MS patients and 80 healthy controls (HC) from eight Italian MS Centers. All patients underwentneuropsychological evaluation including Rao's brief repeatable battery

and Stroop Color Word Test (SCWT) and were classified in cognitive phenotypes (as defined in our previous study:"preserved-cognition", "mild verbal memory/semantic fluency", "mild-multi-domain", "severe-attention/executive", and "severe-multi-domain").103 MS patients and 80 HC also underwent a 3T MRI examination.Forty-six MS patients were classifiedas elderly onset (EO), and remaining ones were equally split in disease duration- (DMS) and age- (AMS) matched groups. By using chi-square test and multiple linear regression models, we compared prevalence and distribution of cognitive phenotypes across the three groups as well as their MRI features.

Results: Compared to DMS, EOMS patients showed a different distribution of cognitive phenotypes with higher frequency of"mild verbal memory/semantic fluency" (p=0.02) and lower frequency of "preserved-cognition" (p=0.04). Although not reaching statistical significance a similar trend was also observed when comparing EOMS with AMS patients. Compared to DMS, EOMS patients showed accelerated atrophy of the hippocampus (p=0.05), while no significant differences were observed between AMS and EOMS.

Conclusions: The distribution of cognitive phenotypes showed that EOMS had a prominent involvement of memory and linguistic abilities. These results are in line with the MRI findings of accelerated hippocampal atrophy, thus suggesting that EOMS is likely to affect more severely brain regions susceptible to aging processes.

Disclosure

The Authors report no conflict of interests related to the present study

P042

Performance differences observed with fixed versus dynamic reference keys within Konectom smartphone-based cognitive processing speed test

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Introduction: Konectom smartphone-based cognitive processing speed (CPS) test is designed to measure information processing speed (IPS) and consists of a symbol-to-digit substitution (S2D) test and a digit-to-digit (D2D) matching test. In the S2D test, symbols are randomly presented one at a time, and a reference key is used to accurately match as many symbols to their corresponding numbers as possible. One of two reference key designs is implemented in each S2D test: fixed (symbol-digit pairings fixed in reference key) or dynamic (symbol-digit pairings in reference key change randomly with each symbol presentation). Though both key designs enable IPS measurement, the dynamic key restricts the use of working memory, which one may predict could have a measurable impact on CPS test performance.

Objectives: To examine the impact of key design on CPS performance and convergent validity with symbol-digit modalities test (SDMT).

Methods: The DigiToms study (NCT04756700) is enrolling people with multiple sclerosis (PwMS) aged 18-64 years with Expanded Disability Status Scale score ⩽ 6.0. All PwMS perform SDMT in clinic. Konectom CPS test is self-administered remotely once per day up to 28 days and in clinic; key design alternates between fixed and dynamic at each performance. We examined impact of key on the following outcome measures: number of correct responses (CPS score), mean S2D correct response time (RT), and mean S2D correct substitution time (S2D ST=S2D RT-D2D RT).

Results: Data from 35 PwMS were used. CPS score was higher (mean difference of 6 correct responses) and S2D RT and S2D ST were shorter (mean difference of 320 milliseconds) for tests performed with a fixed vs. dynamic key (all $p<0.0001$). There were zero incorrect responses for most tests with a range of 0-2 errors across all tests performed irrespective of key design. Correlations between SDMT and CPS outcome measures from fixed and dynamic key tests were significant (all $p<0.0001$) and of similar magnitude (|r|'s=0.739-0.793).

Conclusions: Shorter response time and substitution time suggest working memory contributes to CPS test performance with the fixed key paradigm, whereas reducing the working memory contribution via use of a dynamic key results in a more demanding CPS test. Future work will further characterize each CPS outcome measure and domains of cognitive function that may contribute to performance differences associated with the reference key design.

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Disclosure

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Clinical aspects of MS - Paediatric MS

P043

Inadequate vaccine responses in children with multiple sclerosis

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Objective: Immunizations against Hepatitis B virus (HBV) and Varicella Zoster virus (VZV), are recommended for patients with pediatric onset multiple sclerosis (POMS) and may be required prior to initiation of some disease modifying therapies. However,

the efficacy of routine vaccine administration in POMS has never been studied. We sought to assess the humoral mediated vaccine response to HBV and VZV in children with POMS.
Aims: To identify if there is disparity in vaccination response/acquired immunity of Hepatitis B and Varicella zoster within patients with POMS.
Methods: A multi-center retrospective chart-based review of 62 patients with POMS was performed. Clinical data and antibody titers against HBV and VZV were collected prior to initiation of disease modifying therapy or steroids and compared to institutional control data, using *t*-test and chi squared analysis.
Results: There were low rates of immunity against both HBV and VZV (33 and 25% respectively) among individuals with POMS. Fifteen individuals (24%) were non-immune to both. Compared to institutional control data, individuals with POMS were significantly less likely to be immune to and HBV (p= 0.003, 95% CI: 0.22-0.75) and VZV ($p<$ 0.001, 95% CI: 0.09-0.39).
Conclusions: Individuals with POMS have low rates of antibody-mediated immunity against HBV and VZV, despite receiving the appropriate vaccinations. This suggests an association between POMS and systemic immune dysregulation although further study is needed.

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P044
Association of hormonal dysregulation with clinical- and patient-reported outcomes in pediatric multiple sclerosis

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Introduction: Children with pediatric onset multiple sclerosis (POMS) have higher relapse rates than adults with notable sex-related differences in presentation at the time of puberty. Hyporesponsive hypothalamic-pituitary-adrenal (HPA) axis has also been correlated with more severe disease in adult-onset MS although little is known in POMS.
Objective: To assess integrity of the HPA axis- and sex hormones in patients with POMS and its association with the clinical and patient-reported outcomes.
Aims: 1) To investigate the association of HPA axis- and sex-hormones in POMS, with clinical outcomes; 2) To evaluate association of these hormonal biomarkers with the patient-reported outcomes (PROs).
Methods: Sixty-one individuals (31 Cases and 30 Controls) were enrolled. HPA-axis and sex-hormones were measured in POMS patients within 18 months of disease onset before starting disease modifying therapies and their age-matched controls.Timed 25-feet walk (T25FW), Expanded Disability Status Scale (EDSS) and Single Digit Modalities Test (SDMT) were clinical endpoints. Epworth Sleepiness Scale(ESS), patient health questionnaire-9 (PHQ-9), and pediatric quality of life converted (peds-QLc) evaluated PROs.
Results: Both male and female patients had significantly higher ESS, and PHQ-9, and lower Peds-QLc than controls. Adjusting for age and sex, EDSS had a negative correlation with prolactin (p=0.046, 95%CI: -1.58- -0.02) and cortisol (p=0.037, 95%CI: -1.41- -0.05). T25FW also had an inverse correlation with prolactin (p=0.03, 95%CI: -1.03- -0.04) and cortisol (p=0.02, 95%CI: 1.35-2.64) levels. There was no correlation between SDMT with hormone levels. Lower prolactin was associated with higher ESS (p=0.02, 95%CI: 1.23-1.87) and PHQ-9 scores (p=0.03, 95CI: 1.33-1.97) and lower peds-QLc scores (p=0.01, 95%CI: -1.07 - -0.14), although no sex effect was observed.
Conclusions: Lower prolactin and cortisol are associated with worsened clinical outcomes in POMS.Elevated prolactin levels may also be associated with improved PRO measures and quality of life, serving as a potential biomarker for non-clinical outcomes of the disease in POMS.

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Dr. Dunn holds a US patent for a marker of disease responsiveness. He has received personal compensation for serving as a Consultant for Alexion,as a Consultant for Janssen, as a Consultant for BMS and as a Consultant for TG Therapeutics. The institution of Dr. Dunn has received personal compensation for serving on a Scientific Advisory Board for Progentec Diagnostics.
Dr Jonathan D. Santoro does not have any disclosures.

P045
Depression and anxiety among adolescents with multiple sclerosis: the role of disease duration, disability and illness perception – dyadic study

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Introduction: Over the last decade interest in and knowledge about pediatric-onset multiple sclerosis (POMS) has increased considerably. However, the literature regarding emotional sequala among POMS is still limited, with little attention to the influence of parent-child illness perception on depression and anxiety among adolescents with MS.
Objectives: This study explored the influence of sociodemographic and disease variables on anxiety and depression among

adolescents with MS, with a focus on the role of parent illness perception in adolescents' depression and anxiety.
Methods: The study design was cross-sectional and prospective, and included 32 dyads of adolescents with MS (16 girls and 16 boys) and one of their parents (19 women, 13 men). Among adolescents, we assessed EDSS, depression and anxiety, and illness perception both for adolescents and their parents. We conducted two hierarchal regressions, for the prediction of depression and anxiety separately by age, gender, EDSS, disease duration, and illness perception of both adolescents and their parents.
Results: Adolescents age 15.3 (S.D=2) years, and Mean parents age 45.8 (S.D=5.2), with a mean disease duration of 30 (S.D=21) months and EDSS score of 0.9 (S.E=0.12). The vast majority (94%, 30) were treated with Disease-modifying therapies (DMT). According to the clinical cut-off, 16 participants (50%) identified with clinical anxiety levels, and only 2 participants (6.3%) identified with clinical levels of depression. Both regression models were significant ($p<0.001$ for anxiety, $p<0.01$ for depression). Older age, longer disease duration, and negative illness perception by both adolescents and their parents predict anxiety in the final model ($R^2 = 59\%$). Differently, only adolescents' negative illness perception significantly predicted depression ($R^2 = 39\%$).
Conclusions: Our results showed that adolescents with MS are at higher risk for anxiety compared to depression, especially as they grow up and hold a negative perception about their illness, as well as their parents. Our findings highlight the importance of conducting appropriate psychological evaluation, including among parents, to provide adequate treatment and prevent widespread distress among adolescents with MS.

Disclosure
Roy Aloni: nothing to disclose

P046
Real-world effectiveness of ocrelizumab in a UK multicentre paediatric-onset multiple sclerosis (POMS) cohort

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Introduction: There is a growing consensus favouring earlier use of highly effective disease modifying therapies (DMTs) in paediatric-onset multiple sclerosis (POMS). Real-world effectiveness data on ocrelizumab, a humanised monoclonal antibody that selectively depletes CD20+ B cells, in POMS is limited.
Objectives: The aim of this study was to evaluate the efficacy and safety of ocrelizumab treatment for children with MS in a real-world clinical setting.
Methods: We conducted a prospective study including consecutive paediatric MS patients (<18 years) from three UK tertiary paediatric neurosciences centres who received ocrelizumab. Paired two-tailed t-test was used to compare EDSS, SDMT, lesion volume and grey matter volume pre and on treatment.
Results: We included a total of 60 paediatric relapsing remitting (RR) MS patients, 49 female (81.7%), 41 non-white (68.3%), who had a median age of 14.6 yrs (IQR 13.3, 15.5). Median follow-up period was 1.0 yr (range, 0.1-2.6). Forty-three patients (71.7%) had ocrelizumab as their first-line DMT. The median number of relapses per patient pre-treatment was 2 (range 1-5). Two patients relapsed within one month of starting ocrelizumab. During the follow-up period, a median of 2 (range 1-5) repeated MRI scans were performed (total scans, n=140). Forty out of 43 (93.0%) patients achieved no evidence of disease activity (NEDA-3) at 6-months follow-up; two patients had one new brain lesion each at 6-months and a different patient had a relapse (optic neuritis) without new brain lesions at 6-months post treatment. Total volume of brain lesions on T2-weighted MRI did not change from baseline (mean 2.67 cm^3) to follow-up (mean 3.0 cm^3) (p=0.46) and grey matter volume at baseline was 612.3 cm^3compared to 603.8 cm^3at follow-up (p=0.05). Median EDSS score remained stable during follow-up; 1.5 at baseline vs 1.0 at follow-up (p=0.21). In addition, there was no change in cognitive measures at follow-up; baseline SDMT mean score 46 vs follow-up SDMT mean score 48 (p=0.39). The most common adverse events reported were infusion-related reactions (33/60, 55%), all of which were grade 1 or 2. Serious adverse events were recorded in one patient with enterovirus meningitis, who made a full recovery.
Interpretation: This study confirms that ocrelizumab, which is proven efficacious for adults with MS, is equally effective in POMS with a comparable safety profile. Assessment for long-term efficacy and safety is ongoing.

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Clinical aspects of MS - Progressive MS

P047

Focal cortical damage and intrathecal inflammation associate with disability progression independent of relapses in early multiple sclerosis: a preliminary study

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Background: Among MS patients, focal cortical damage is evident since early disease stage, is associated with intrathecal meningeal inflammation and is a significant negative prognostic factor for the disability accumulation.
Objectives: We evaluated whether cortical lesions (CLs) and intrathecal inflammatory markers influence the disease progression independent of relapsing activity (PIRA) after a diagnosis of relapsing-remitting MS (RRMS).
Methods: [s1]All patients underwent lumbar puncture, with assessment of 69 CSF inflammatory markers using immune-assay multiplex technique,and regular clinical and neuropsychological assessments, including Expanded Disability Status Scale (EDSS) and symbol digit modalities test (SDMT), and a yearly 3T MRI of the brain and spinal cord to evaluate of white matter (WM) lesion number and volume, Gad+ lesions, cortical lesions number (CLs) and volume (CLv). PIRA was defined
as EDSS increase by 1, 0.5 (if baseline EDSS⩾5.5) or 1.5 point (if baseline EDSS=0) confirmed 1 year later, without temporal association with confirmed clinical relapses, or by the loss of 4 points or a 10% decrease in the performance of the SDMT, compared to to the previous assessment.
Results: 82 patients with RRMS (63F/19M, mean age 38.9±12.2 years, median EDSS 2[0-3.5]) werefollowed-up for 5 mean years after the diagnosis and 16 patients had decreased SDMT performance. [s2]Patient who experienced PIRA (n = 31)were older at diagnosis (mean 41.3±11y vs 37.5±12.8y, p=0.055), had larger number of CLs baseline (5.6±5.9 vs2.5±3.1, p=0.017) and CLv (510±577mm3 vs 227±307mm3, p=0.018) when compared with those without PIRA.
After applying a random forest approach using minimal depth and times to root measures to 69 all markers, 10 cytokines/chemokines including MIF, CCL2, sTNFR1, sTNFR2, CXCL12, CXCL13, Osteopontin, LIGHT, CCL3, CCL13 were significantly associated with PIRA.
Conclusions: Intrathecal inflammation and CLs associate with early disability progression independent from relapses in the first years after a diagnosis of MS. Results need to be validated in a larger cohort with a longer follow-up, that would include other instrumental measures of early MS progression.

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P048

Shedding light on the variability of the clinical course of multiple sclerosis: analysis of the influence of myeloid-derived suppressor cells on disease severity

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Introduction: Myeloid derived suppressor cells (MDSCs) are a heterogeneous group of immature cells with a regulatory action in

immune-mediated disorders, including multiple sclerosis (MS). The higher proportion of MDSCs is related to a milder severity of the clinical course in the animal model of MS, experimental autoimmune encephalomyelitis (EAE). Our group pioneered the description of MDSCs in the CNS of MS patients, being mainly circumscribed to areas with a high inflammatory activity. The density of MDSCs was higher in progressive MS patients with a milder clinical course according to the disease duration. Interestingly, the abundance of circulating MDSCs at disease onset correlates with EAE clinical course severity and tissue damage extent as well as the relapse recovery in MS, pointing to MDSCs as feasible bioindicators of disease progression. However, there is a lack of data about the influence of MDSC activity on the degree of disease severity.

Aims: We interrogate whether functional differences of MDSCs are behind the variability of the MS clinical severity.

Methods: MDSCs and T cell distribution were analysed in CNS samples from 20 MS patients with different disease duration by immunohistochemistry against HLA-DR, CD14 and CD3, respectively. Apoptotic cells were determined by TUNEL and the correlation with MDSC density was performed. In the EAE model, two groups of mice with different clinical course severity were identified by clustering analysis. Accordingly, MDSCs from severe/mild EAE mice were obtained for immunosuppression assays and RNAseq analysis.

Results: In the CNS from MS patients, the higher abundance of MDSCs was inversely related to a lower density of $CD3^+$T cells. Interestingly, apoptotic T cell density increased in MS patients with milder clinical courses. In EAE, the differences in the abundance of MDSCs in both groups were not only quantitative, but also functional. RNAseq analysis of MDSCs pointing to a remarkable immunosuppressive phenotype of MDSC obtained from those mice with milder clinical courses. Validation of the gene expression candidates by RT-PCR confirmed the up-regulation of both interferon-induced proteins *ifit1* and*ifit3* in MDSCs from mild EAE clinical course.

Conclusion: Our results indicate that disease severity is related not only to MDSC abundance but also to a robust immunoregulatory function, suggesting that the modulation of MDSCs emerged as a promising strategy to control disease progression in MS.

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P049

Longitudinal evolution of progressive multiple sclerosis: deep understanding with machine learning

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Introduction: Despite great effort in building statistical models from longitudinal data, predicting disability trajectories of new patients with progressive multiple sclerosis (PMS) is very challenging.

Objectives: The objective of our analysis is to apply "Gaussian Process Progression Model (GPPM)", an innovative disease progression model based on Bayesian statistical learning, which is capable of predicting long term disability trajectories from short term clinical data.

Methods: We collected data from five RCTs: 3 trials of primary progressive MS patients (ARPEGGIO, OLYMPUS and ORATORIO) and 2 trials of secondary progressive MS patients (ASCEND and MAESTRO).

Firstly, GPPM was fitted using baseline and longitudinal measurements of the available clinical and MRI biomarkers: EDSS, T25FW, 9HPT (dominant and non-dominant hand), SDMT, gadolinium enhancement lesion count, new enlarging T2 lesions count, T2 and T1 lesion volume and normalized brain volume (NBV). GPPM estimates *group-wise trajectories of biomarkers evolution*, providing a data-driven description of the progression of the pathology, together with*disease scores*, measuring individual rates of disability progression, relative to the population.

Finally, we assessed the impact of the baseline measurements on the estimated individual disease scores, by using a conditional random forest variable importance analysis, in order to investigate whether the predicted disease scores could be predicted at baseline, and by which biomarkers.

Results: A total of 2,940 PMS patients (50,404 observations) were analysed and for each subject a disease score was computed (higher values indicating more advance levels of progression). The variable importance (VI) assessed the relevance of the biomarkers included in the model, and revealed that SDMT (VI=0.002, VI%=100), NBV (VI=0.001, VI%=61.9) and EDSS (VI=0.0003, VI%=19.1) were the variables which, at baseline, had a greater impact on the estimated disease score.

Conclusions: This preliminary analysis is the first application of a longitudinal disease progression model on MS clinical trial data. GPPM estimates individulal disease scores, assessing the individual rates of progression with respect to group-wise disability trajectories. We showed that such scores can be predicted from the values of EDSS, SDMT and NBV at baseline.

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P050

Eight-year analyses of repeated confirmed disability progressions in the OPERA and ORATORIO studies and their open-label extensions

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Background: Time-to-first event analyses neglect information about subsequent progression in patients with multiple sclerosis (MS). Repeated event analyses (REA) provide more comprehensive assessments of long-term disability trajectories.
Aims: To provide an updated analysis of repeated 48-week (48W) confirmed disability progression (CDP) rates on Expanded Disability Status Score (EDSS) during OPERA and ORATORIO and their ongoing open-label extensions (OLE). The rate of repeated 48W-CDP events for 9-Hole Peg Test (9HPT), Timed 25-Foot Walk (T25FW) and composite CDP (cCDP) was assessed in patients with primary-progressive MS (PPMS).
Methods: In the double-blind period (DBP) patients were randomised to ocrelizumab (OCR) or placebo (PBO; ORATORIO [NCT01194570])/interferon beta-1a (IFN; OPERA [NCT012 47324/NCT01412333]) for ⩾120/96 weeks. OLE patients continued OCR (OCR–OCR) or switched to OCR (PBO–OCR)/(IFN–OCR). Repeated 48W-CDP rates were defined as for prior first event CDP analyses, then EDSS, 9HPT or T25FW following rebaselining after the respective initial confirmed progression of the previous event. The Negative Binomial model was used for analysis of repeated CDP events.
Results: In PPMS, after 8 years, continuous OCR treatment reduced the rate of repeated 48W-CDP–EDSS by 23% (rate ratio [RR] [95% CI]: 0.77 [0.63–0.94]; p=0.010), repeated 48W-CDP–9HPT by 35% (0.65 [0.48–0.88]; p=0.005), repeated 48W-CDP–T25FW by 26% (0.74 [0.61–0.91]; p=0.005) and repeated cCDP by 24% (0.76 [0.64–0.90]; p=0.002]) vs PBO-OCR. Annualised repeated event rate ratios (ARER) OCR–OCR/PBO–OCR RR (95% CI) were: 48W-CDP–EDSS: Week (W) 48 (DBP) 0.53 (0.33–0.84) p=0.008, W144 (start of treatment switch) 0.64 (0.44–0.94) p=0.021, W240 (OLE start) 1.24 (0.71–2.16) p=0.456, W432 (OLE) 1.22 (0.64–2.35) p=0.547; similar CDP trajectories were obtained for 48W-CDP–9HPT and 48W-CDP–T25FW. In relapsing MS, after 8 years, continuous OCR vs IFN–OCR reduced the rate of repeated 48W-CDP–EDSS by 27% (RR [95% CI]: 0.73 [0.58–0.93]; p=0.009). ARER (95% CI) for OCR–OCR/IFN–OCR were: 48W-CDP–EDSS: DBP W48 0.41 (0.21–0.79) p=0.007, W96 (DBP end) 0.45 (0.26–0.78) p=0.004, OLE W48 0.84 (0.43–1.64) p=0.610, OLE W336 1.07 (0.52–2.21) p=0.864.
Conclusions: REA more comprehensively capture treatment effects after a first disability progression event. Analyses of annualised repeated CDP provide better insight into the longer trajectory of clinical disease progression, including response to treatment changes.

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P051

"Hidden" symptoms drive progression independent of relapse activity in relapsing-onset multiple sclerosis patients

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Introduction: recent evidence demonstrates progression independent of relapse activity (PIRA) starting from the early stage of relapsing-onset multiple sclerosis (MS).
Objectives: to better characterize early PIRA events, we assessed whether PIRA can involve different functional systems (FS) on the Expanded Disability Status Scale (EDSS) as compared with relapse associated worsening (RAW) at first confirmed disability accumulation (CDA) event.
Methods: Relapsing-onset MS patients with follow-up >/= 5 years (*n*=16,130) were extracted from the Italian MS Registry. CDA was defined by an increase in EDSS score confirmed at 6 months, and classified per temporal association with relapses. EDSS-FS involved in PIRA and RAW events at first CDA were compared using logistic multivariable regression analyses.
Results: over a follow-up of 11.8 + 5.4 years, a total of 8,998 (55.8%) patients experienced at least one CDA. PIRA (n=6,162) accounted for 68.5% of first CDA events. Data on EDSS-FS were available in 6,394 (71.1%) patients. Seventy-nine percent of CDA involved 2 or more FS, without differences between PIRA (79.3%) and RAW (79.6%, p=0.782). In the multivariable analyses (adjusting for sex, age, EDSS, disease course, disease duration, type of onset), PIRA involved more frequently bowel and bladder functions (OR=1.29; 95%CI 1.15-1.44; p<0.001) and cerebral functions (OR=1.54; 95%CI 1.32-1.79; p<0.001). On the other hand, RAW involved more frequently pyramidal (OR=1.13; 95%CI 1.01-1.27; p=0.040) and sensory functions (OR=1.16; 95%CI 1.04-1.29; p=0.006).
Conclusion: in a large, real-world relapsing-onset MS cohort, PIRA was mainly associated with worsening of "hidden "symptoms, such as bowel and bladder functions, cognition and fatigue. Accurate monitoring of these functions and symptoms from the early stage of MS can improve the detection of "silent progression". The analysis on different EDSS-FS involvement in multiple RAW-PIRA events is ongoing.

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Longer-term safety and efficacy of ofatumumab in recently diagnosed and treatment naïve patients is consistent with the overall population in the ALITHIOS open-label extension study

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Introduction: Ofatumumab (OMB) demonstrated superior efficacy and similar safety vs teriflunomide in the Phase 3 ASCLEPIOS I/II trials in the overall population of patients with

relapsing MS (RMS) and a subgroup of patients recently diagnosed (≤3 years) and treatment-naïve (RDTN). In the overall population, OMB has demonstrated well-tolerated safety and sustained longer-term efficacy for up to 4 years in the ALITHIOS open-label extension study.

Objective: To assess the longer-term safety and efficacy of OMB for up to 4 years (data cut-off: 25-Sep-2021) in a subgroup of RDTN RMS patients.

Methods: Efficacy outcomes (annualized relapse rate (ARR), time-to-3/6-month confirmed disability worsening [3m/6mCDW], number of Gd+T1 lesions, annualized T2 lesion rate) up to 4 years were analyzed in two groups: 1) RDTN patients randomized to OMB in ASCLEPIOS I/II and continuing OMB in ALITHIOS (continuous; n=314) and 2) RDTN patients randomized to TER in ASCLEPIOS I/II, switched to OMB in ALITHIOS (switch; n=301). Safety outcomes were analyzed in overall (RDTN patients enrolled in ASCLEPIOS I/II and ALITHIOS, n=546), continuous (OMB in core studies+ALITHIOS; n=314) and switch groups (TER in ASCLEPIOS I/II and OMB in ALITHIOS; n=232).

Results: Mean age at baseline was 36.8/35.7 years, 69.1%/65.8% were female, and the mean EDSS was 2.30/2.22 in the continuous/switch groups. Over ASCLEPIOS I/II+ALITHIOS, the ARR in the continuous group remained low up to 4 years and the cumulative number of confirmed relapses was 42% lower in continuous vs switch group. Within group (ASCLEPIOS I/II vs ALITHIOS) analysis showed that continuous use of OMB was associated with a significant reduction in ARR by 43.1%; switching to OMB resulted in a pronounced reduction in ARR (76.6%). The difference in KM estimates at Month 36 for 3m/6mCDW indicates that risk of events was similar in both the treatment groups after switching to OMB. Treatment emergent adverse events (AEs) occurred in 93.6%/83.2% of the continuous/switch groups and serious AEs were reported in 16.2%/7.8%, respectively. Detailed safety (severity of AEs, treatment discontinuation) and efficacy data will be presented at the congress.

Conclusion: Consistent with longer-term safety and efficacy findings for up to 4 years in the overall population of the ALITHIOS study, these analyses show the favorable benefit–risk profile of OMB in RDTN RMS patients, supporting its use as a first-line therapy at an early stage of the MS disease course.

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P053

Progressive motor impairment from "critical" demyelinating lesions of the cervicomedullary junction

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Introduction: Progressive motor impairment anatomically associated with a "critical" demyelinating lesion is described in people with demyelinating disease. While most "critical" demyelinating lesions are located within the spinal cord, involvement of the cervicomedullary junction (CMJ) could be associated with severe motor impairment given the close anatomical proximity of the corticospinal tracts.
Objectives: To describe the clinical and radiologic presentation of "critical" lesions of the CMJ
Methods: Observational study on people presenting to Mayo Clinic (January 1, 1996 – August 1, 2021) with a CMJ lesion associated with progressive motor impairment attributed to primary demyelinating disease including those with progressive solitary sclerosis (a single CNS demyelinating lesion), progressive motor impairment with a restricted lesion burden (2-5 total demyelinating lesions), and progressive exclusively unilateral hemiparesis (>5 total demyelinating lesions). Individuals were excluded if a non-demyelinating etiology was favoured. Data was extracted by retrospective chart review. Clinical evaluations by Mayo Clinic MS experts documented clinical course, pattern of progressive motor weakness, and EDSS score. Brain and spinal cord MRIs were reviewed by neuroradiologists to characterize the CMJ lesion and determine if there were any additional areas of demyelination.
Results: Forty-one people, 22 females (54%), median age of disease onset 48 years (range, 25- 65) were included. Twenty-nine (71%) had a progressive from onset (primary progressive) and 12 (29%) had a relapse onset (secondary progressive) course with most having progressive hemiparesis (21 (51%)), or progressive quadriparesis (15 (37%)). Median EDSS was 5.5 (range, 2-8.5) at last follow-up (median, 58 months from progression onset, range 12-354). The "critical" CMJ lesion was bilateral in 25 (61%) and unilateral in 16 (39%). Brain MRIs were without additional demyelinating lesions in 16 (39%) and a restricted burden (2-5 total lesions) in 15 (37%). Cervical and thoracic spinal cord MRIs were without additional demyelinating lesions in 25 (61%) and 22/37 (59%) respectively.
Conclusions: Cervicomedullary junction "critical" demyelinating lesions are associated with progressive motor impairment, even with few or no additional MRI lesions. Lesion location is an important determinant of progressive motor impairment in demyelinating disease.

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Clinical aspects of MS - Natural course

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Clinical characteristics and disability progression in late-onset MS

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Background: Multiple Sclerosis (MS) commonly begin between the ages of 20 and 40 years old while a minority are affected later in life. Late-onset MS (LOMS, ⩾ 50 years) represents a less studied population compared to their younger counterparts; adult onset MS (AOMS, < 50 years).
Objective: To compare patient characteristics, disease-modifying therapy (DMT) exposure and disability progression in Swedish LOMS and AOMS patients.
Methods: The nationwide Swedish MS registry was searched for patients with a diagnosis of MS between years 1975 and 2018, with symptom onset ⩾ 18 years and ⩾ 2 recorded Expanded Disability Status Scale (EDSS) scores. LOMS and AOMS were compared regarding clinical and demographic parameters, DMT exposure overall and disability progression using Cox proportional hazard regression models adjusted for age, sex, disease course, calender year at onset, and time-varying DMT exposure.
Results: From a total of 22 092 MS patients, 14 774 patients met inclusion criteria including 1 385 LOMS (female; 66.6%) and 13 389 AOMS (female; 69.9%). The median age (interquartile range, IQR) at symptom onset in LOMS was 54 years (51-57) and 32 years (26-39) in AOMS. Diagnostic delay (time from symptom onset to diagnosis) was comparable in the groups: LOMS; median (IQR): 1.0 (0-3) years and AOMS; 1.0 (0-5) years. A primary progressive MS (PPMS) disease course at onset was more

common in LOMS (29.3%) compared to AOMS (6.9%). LOMS were less likely to receive DMT (66.4%) compared to AOMS (86.1%). Around half of the treated LOMS (54.5%) had been exposed to high efficacy therapies (fingolimod, natalizumab, rituximab, ocrelizumab, alemtuzumab, daclizumab and HSCT) compared to almost two thirds of AOMS (66.1 %). LOMS conferred an increased risk of reaching disability milestone EDSS 4.0 (HR 2.39; 95% confidence interval (CI) 2.02 – 2.82) and EDSS 6.0 (HR 2.35; 95% CI 1.97 – 2.80) from disease onset, compared to AOMS. However, when calculating risk for disease progression from birth, the risk for reaching EDSS 4.0 (HR 0,54, 95% CI 0.46-0.64) and EDSS 6.0 (HR 0.51, 95% CI 0.43-0.60) was lower in LOMS compared to AOMS.

Conclusion: Significant differences in clinical characteristics, treatment approaches and risk for disability progression distinguish LOMS from AOMS.

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Multiple sclerosis science: a unique opportunity to advance scientific developments and patient care

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Introduction: Multiple Sclerosis science - our understanding of MS biology, pathophysiology and treatment - advances over time. As expected, different fields advance at different rates, times and ways. Nevertheless, Kuhn (1962) proposed that scientific development has a clearly defined structure, a repeating cycle of events, applicable to any field, summarised as: normal science within a paradigm (=generally followed definitions, models, methods, beliefs) and a dedication to problem solving, followed by serious anomalies which lead to a crisis, and finally resolution of the crisis by a new paradigm ("paradigm shift"). If Kuhn's cycle is appropriate to MS science, we can position ourselves in the cycle, anticipate the future, and, potentially, influence the rate of scientific progress and patient care.

Objectives: To determine whether MS scientific developments have aligned with Kuhn's cycle and, if so, determine our current position in his cycle.

Methods: We examined evolutionary MS scientific development history to determine if we aligned with Kuhn's proposed structural cycle. We examined recent scientific developments to determine our current position in Kuhn's cycle.

Results: MS science evolution aligned with Kuhn's cycle. Specifically, we have established paradigms (diagnostic criteria, classification of MS types, definitions of clinical situations, clinical trial designs and methods, measurement methods, treatment and monitoring strategies) around which most current research (our "normal science") is based.

Our evaluation of more recent MS research identified multiple studies whose results did not align with these established MS paradigms - challenging how MS is defined, diagnosed, classified, studied, measured, treated and monitored. Our analyses suggest we are now in the anomaly-to-crisis stage of Kuhn's cycle.

Conclusions: There are three main implications. First, the next stage is a paradigm shift, which, historically, is manifest by significant change in multiple aspects of existing paradigms (definitions, methods, models etc.) and during which "everything must be rethought". Second, historically, predictable barriers have slowed progression between the cycle's stages. Third, if we embrace Kuhn's structure of scientific developments, and the implications associated with movement between stages, the MS community is uniquely placed to influence the natural history of our scientific advancement and fast-track patient care developments.

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P056

COVID-19 infection in MS patients and risk of following clinical/MRI disease activity: a propensity score matching study

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Introduction: Several studies in literature suggest that viral infections may trigger multiple sclerosis (MS) relapses. Among these, respiratory tract infections seem to be the most frequent. To date, there are very few data about the association between COVID-19 infection and the risk of relapses in MS.
Objectives: To evaluate the risk of clinical/MRI disease activity after COVID-19 infection in patients with MS.
Methods: We prospectively collected all incident cases of COVID-19 in a population of approximately 1500 MS patients followed by the MS Center of the AOU Città della Salute e della Scienza di Torino University Hospital, from March 2020 onwards. Clinical features and outcome of the COVID-19 infection, and MS clinical/MRI outcomes in the 6 months following COVID-19 infection were recorded. Propensity score matching was used to compare MS clinical/MRI outcomes over 6 months between patients with or without COVID-19 infection, matched for age, sex, disease duration and MS disease-modifying treatment.
Results: 143 patients with COVID-19 infection were identified: 103 F, 40 M, with median age of 46 (range 18-82 years). 132/143 had a relapsing-remitting form of MS, while 11 had a progressive form (primary/secondary). 127/143 subjects were under DMT at the time of the infection. 68/143 patients had already received at least one vaccine dose at the time they contracted the infection. Outcome of COVID-19 was usually favorable with mild disease not requiring hospitalization; severe disease was observed in 14 patients, two of whom died. Symptoms suggestive of long COVID (defined as persistence of symptoms after 4 weeks from the resolution of the infection) were observed in 43 patients (30%). In multivariate forward logistic regression, the only variable predictive of long COVID was anti-CD20 therapy (OR 2.42, $p = 0.027$). No significant differences were found in MS clinical/MRI outcomes (NEDA-3 at 3 and 6 months) after COVID-19 infection, compared to matched MS patients without COVID-19 infection (NEDA-3 at 3 months 78.3% vs 84.8%, p = n.s.; NEDA-3 at 6 months 66.2% vs 76.1%, p = n.s.).
Conclusions: COVID-19 infection does not appear to influence the risk of MS clinical/MRI disease activity in the months following the infection. Persistence of symptoms suggestive of long Covid is quite common in MS patients.

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P057
Early cortical and deep gray matter atrophy predicts disability progression independent of relapse in multiple sclerosis: a 17 year longitudinal study

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Objectives: Among MS patients, the severity of grey matter (GM) atrophy, in both cortical and subcortical regions, correlates with the accumulation of disability.
Aims: We assessed longitudinal changes of global and regional GM atrophy and its role in predicting the long-term disability accumulation and the conversion from relapsing remitting MS (RRMS) to secondary progressive MS (SPMS).
Methods: We retrospectively evaluated 181 RRMS patients, followed-up for 17.3±3.2 years. All patients underwent a 1.5T MRI scanning at diagnosis and after 2 years to assess white matter (WML) and cortical (CL) lesions number and volume, global cortical thickness (CTh) and thickness and volumes of 27 brain regions. SPMS was defined by12-months confirmed disability accumulation, independent of relapse, with a minimum EDSS of 4 and increase by 1.5, 1 or 0.5 EDSS points if the last EDSS before conversion was 0, ⩽5.5, or >5.5, respectively.
Results: By the end of follow-up 39 (21.5%) patients had converted to SPMS in9.08±3.74 years, while78 (43%), 53 (29%) and 32 (18%) patients reached EDSS 3, 4 and6, respectively. Compared to patients who were still in the RR phase,at baseline SPMS group had higher EDSS (median2 [1.5-2.5]vs1.0 [0.0-1.5];$p<0.01$), larger number and volume of WML and CL ($p<0.001$), but similar CTh (2.78±0.27 vs 2.54±0.3,p=0.242). Patients who developed SPMS had more severeglobal CTh reduction over the first two years (annualized percentage change:-1.15±0.27 vs -0.9±0.2,$p<0.001$).
After applying random survival forest, the rate of atrophy in hippocampus, cerebellum and cingulate girus were significantly ($p<0.001$) associated with the probability of converting to SPMS. Grey matter changes in thalamus, hippocampus, supplementary motor cortex and caudatus were significantly associated with the risk of attaining of EDSS 3, while grey matter changes in hippocampus, cerebellum, cingulate gyrus, insula, and thalamus significantly and best associated with earlier achievement of EDSS 4 and 6. Early accumulation of hyppocampus atrophy contributed to 53% of EDSS variance at the end of follow-up.
Conclusions: The evolution of cortical atrophywithin the first 2 years of disease, especiallyinkey brain structures, including deep grey matter, predicts the conversion to SPMS and the probability of developing severe disability. This confirms that early pathological changes in the grey matter significantly contributes to the long term disease progression.

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P058

Stratification of Long-term prognosis in patients with multiple sclerosis: a systematic review

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Introduction: Disease course is highly variable in Multiple Sclerosis (MS) and the prediction of individual long-term prognosis is challenging.
Objectives: To identify demographic, socio-economic, clinical, paraclinical, and therapeutic factors associated with long-term disability in patients with MS.
Methods: We searched PubMed, Embase, and SCOPUS with no predefined search period until April, 30th 2022. We included studies that examined predictors of long-term disability in patients with MS regardless of the disease phenotype.
Results: A total of 200 studies were included. Thirty factors were identified. At baseline, higher age (Hazard ratio (HR)= 0.036-2.3), longer disease duration (HR=1.01-1.8), smoking (HR= 1.63-2.12), vascular comorbidities (HR=1.269-1.51), non-Caucasian ethnicity (HR=1.63-9.7), high disability (HR = 1.19-1.73), disease activity (HR = 1.6-1.9), motor (HR= 0.54-2.47), cerebellar (HR=1.71-3.096) and sphincter (HR=1.3-3.3) symptoms and cognitive dysfunction (HR = 3.07-3.68) were strongly associated with a poor long-term prognosis. Relapses in the previous year increased the hazard of a subsequent disability worsening. Decreased thickness of the retinal layers was independently associated with a three to six-fold risk of EDSS progression. Blood and cerebrospinal fluid (CSF) neurofilaments measurements at baseline were associated with an increase in the hazard of disability. Imaging prognostic biomarkers were mainly initial lesion load (HR = 1.51-3.51) and the presence of spinal cord lesions (HR= 1.9- 4.08). Other putative prognostic factors at baseline such as gender, delayed treatment, positive oligoclonal bands, or brain atrophy showed a weak or inconsistent effect on prognosis. Newly studied factors including slowly expanding lesions on MRI and CSF Kappa index are promising biomarkers for predicting long-term outcomes.
Conclusions: The most robust drivers of long-term disability in MS were related to the degree of initial brain damage and its limited repair capacity. Prevention of modifiable risk factors should be a priority. A combination of these factors is needed to build a composite prediction model.

Disclosure
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Clinical aspects of MS - Epidemiology

P059

A susceptibility network analysis of disease pathways leading to multiple sclerosis

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Introduction: A handful of diseases have been shown to be associated with increased risk of multiple sclerosis (MS).
Objectives: To investigate the patterns of diseases co-occurrence prior to MS onset and compare that to persons without MS.
Aims: To determine MS disease susceptibility pathways that put individuals at high risk of developing MS.
Methods: Disease histories from MS patients and matched population-based controls from birth to onset of MS (determined by a neurologist) or equivalent age in controls (index date) were obtained from the Swedish national patient register. We developed a systematic methodology to derive disease trajectories and directed disease networks separately for cases and controls. In step 1, we analysed and compared these networks using different network centrality measures. In step 2, we reconstructed MS susceptibility pathways by first excluding unrelated diseases and then including diseases that were significantly (multiple testing adjusted value: $P < 0.0003$) more or less prevalent in MS cases than controls. Finally, in step 3, we included the top 10 most frequent diseases prior to MS and their 10 most frequent diseases dependencies in a network to identify the most common pathways to MS.
Results: We included 149,651 pre-onset International classification of diseases (ICD) codes from 18,596 cases of MS and 111,638 pre-index ICD codes from the same number of controls. The MS network topology was significantly different when looking at centrality, transitivity or link analyses to that of controls. Intracranial injuries (S06), disturbance of skin sensation (R20), abdominal and pelvic pain (R10), other sepsis (A41), acute appendicitis (K35), cholelithiasis (K80), dorsalgia (M54), unspecific soft tissue disorders (M79), fracture of lower leg and ankle (S82) were among the most 10 common diagnoses preceding MS through multiple pathways.
Conclusions: Our analysis suggests existence of causal differences in disease occurrence and trajectories between persons with and without MS. The extracted MS susceptibility pathways are subsequently further examined from a clinical perspective investigating how the clinical context can induce the derived relations. These pathways highlight existence of a prodromal phase and/or

disease trajectories towards MS which can be further exploited either to better understand MS aetiology or to be used as diagnostic markers for early detection of persons at high risk of MS.

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P060
Risk of inflammatory reactivation following SARS-CoV-2 vaccine in a large cohort of Multiple Sclerosis patients

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Background: Whether vaccines play a role triggering or reactivating inflammation in Multiple Sclerosis (MS) has been long debated. There are few reports suggesting that Sars-Cov2 vaccines, as well as COVID-19 infection, may exacerbate relapses in MS. Studies on large cohorts are needed to establish the safety of Sars-Cov2 vaccines in the MS population.
Aim: To assess the risk of clinical and radiological reactivation following Sars-Cov2 vaccines in patients with MS.
Methods: Patients with MS with known date of SarsCov2 vaccination were identified among those followed up at the Multiple Sclerosis Center of the Tor Vergata University Hospital. Data on clinical relapses and radiological activity (Gadolinium enhancing and new T2 lesions) in the 12 months before and after vaccination were extracted from clinical charts.
Results: We enrolled 751 patients (64,7% female, mean age 45.9 ± 11.63 years, 89.9% relapsing-remitting, 5.5% secondary progressive and 4.7% primary progressive, disease duration 11.2 ± 8.11 years, median EDSS 2.0 [1.0 - 4.0], 12.1% untreated, 41.1% treated with first line immunomodulators and 46.7% with second line high efficacy treatments). Among them, 96.7% received mRNABNT162b2 (Pfizer), 2% mRNA-1273 (Moderna) and 1.3% other COVID-19 vaccines. In the whole cohort we did not find a significant increase of the rate of patients with relapse in the 12 months after vaccines (2.3%) compared to the 12 months before (2,9%, McNemar test, p=0.5), as well as of the rate of patients with radiological activity (both 11.5%, McNemar test, p=0.13). Similar findings were obtained separately analysing untreated patients, patients treated with first line and treated with second line drugs at the time of vaccination.
Conclusions: Our preliminary results in a large monocentric cohort of MS patients suggest that vaccination with Sars-Cov2 vaccines does not induce disease reactivation. Further analyses are needed to confirm these findings.

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P061
Breakthrough COVID-19 infection after vaccination in people with multiple sclerosis on disease modifying therapies in Latin America: data from RELACOEM registry

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Introduction: In this study we aimed to monitor the risk of breakthrough COVID-19 infection in pwMS on different Disease Modifying Therapies (DMT) included in RELACOEM, a LATAM registry of MS and NMOSD patients infected with and vaccinated against COVID-19.
Methods: retrospective cohort study conducted between May 2021 and December 2021. The primary outcome was the appearance of infection during the follow-up time (at least three months after complete vaccination (second dose)). Specific information was requested (vaccine received, dose, date, symptoms, COVID-19 infection, need for hospitalization, ventilatory assistance, treatment, and evolution). The primary objective of the analysis was to compare the incidence of breakthrough SARS-CoV-2 infections among the vaccinated pwMS in each DMT group. These conditions entail a PCR-confirmed test, and a time lag of at least 14 days from a full vaccination cycle (after the second vaccination dose). Cumulative incidence was reported by Kaplan Meier survival curves as well as incidence density.
Results: A total of 857 pwMS patients from eight countries in LATAM were included. Mean age was 44.3 ±12 years. The most frequent treatment used was fingolimod in 171 (19.9%). Most frequent first and second dose received was Astra-Zeneca (33%). During follow-up, a total of 28 COVID-19 cases were observed for a total exposure time of 150.965 days. The overall cumulative incidence was 3.2% (SE 0.22%) with an overall incidence density (ID) of 1.8 x 10.000 patients/day (95%CI 0.2-3.2). Compared to other DMTs, the incidence rate of breakthrough infections was significantly higher on ocrelizumab (6.02 (95%CI=5.65-7.16, RR=5.17 95%CI 3.27-7.12) and rituximab (6.94 (95%CI=6.15-9.12, RR= 5.93 95%CI 3.55-7.32) compared with other DMTs. No significant differences in the risk of breakthrough were observed for vaccine subtypes.
Conclusion: An increased risk of breakthrough COVID-19 infections was observed in patients treated with ocrelizumab and rituximab.

Disclosure
Authors declare no potential conflicts of interest regarding this research, authorship and/or publication of this article.

P062
The interplay between multiple sclerosis, obstructive sleep apnea, and cognitive function: findings from the Nurses' Health Study

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Introduction: MS is associated with cognitive impairment. However, potential mediating and moderating effects of sleep disorders on cognitive dysfunction in MS have not been sufficiently studied.
Objectives/Aims: To determine whether perceived cognitive dysfunction in multiple sclerosis (MS) is mediated and/or moderated by sleep disorders in US women.
Methods: Data from the Nurses' Health Study Cohort (n=63,866 women) were utilized. All diagnoses, including MS, were self-reported. Diagnosed/suspected obstructive sleep apnea (OSA) was defined by self-reported diagnosis or presence of ⩾3 items (OSA risk factors) resembling the STOP-Bang Questionnaire. An insomnia composite score was constructed from items that assessed insomnia symptoms. Subjective cognitive function in the 2017 wave included several items regarding memory difficulty (converted to a composite score), and three binary outcomes that assessed difficulty instructions/conversations, and navigation of familiar streets. Associations between MS and diagnosed/suspected OSA and insomnia were estimated with linear and logistic regression models. Roles of OSA or insomnia as moderators or mediators between MS and cognition were estimated using the 4-way decomposition method.
Results: Prevalence of both diagnosed/suspected OSA and insomnia symptoms were higher for nurses with MS (NwMS) compared to those without MS. NwMS were about twice as likely to report in difficulty in following instructions and conversations/plots, and almost three times as likely to report difficulty navigating familiar streets. Similarly, NwMS reported more memory impairment (memory composite score beta=0.24,0.14-0.34). In mediation analyses, OSA and insomnia accounted for <5% of the total effect. However, in interaction analyses, interaction between OSA and MS accounted for 34% of the total effect between MS and ability to follow instructions. Interaction between insomnia and MS accounted for 40% of the total effect between MS and navigation.
Conclusions: NwMS who have concomitant OSA or insomnia may experience increased cognitive dysfunction compared to those without sleep disorders. Our findings highlight the important contribution of sleep disorders to cognitive dysfunction in MS.

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P063

The relative contribution of comorbidities on sleep quality among people living with multiple sclerosis in Australia

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Introduction: Over 90% of people living with multiple sclerosis (PwMS) have comorbidities, one of the factors affecting sleep health. Sleep disturbance is prevalent in MS which affects memory, and disease course. There is limited evidence on the contribution of comorbidities to sleep quality.
Objectives: To examine the association between comorbidities in PwMS and sleep quality, and the magnitude of this effect.
Aim: To evaluate the contribution of comorbidity to sleep qualityin multiple sclerosis
Methods: A cross-sectional survey was conducted using the Australian Multiple Sclerosis Longitudinal Study participants to collect data on sleep using Pittsburgh Sleep Quality Index. We used linear regression to examine the association between the total number of comorbidities and the sleep quality index. The relative contribution of groups of comorbidities was determined using general dominance analysis.
Results: We included 1597 individuals (mean age=58.6 years, Females=865) of which 93.6% of them reported at least one comorbidity. A higher total number of comorbidities was associated with an increase in the sleep quality index. All the 13 groups of comorbidities explained 12.68% of the sleep quality index, with mental health disorders having the largest contribution (49.3%), followed by diseases of the nervous system (12.3%), and musculoskeletal disorders (7.2%). Compared to those without any comorbidities (5.40), the individual comorbidities most strongly associated with the sleep quality index were: depression (+1.79), anxiety (+1.74), other immune diseases (+1.72), rheumatoid arthritis (+1.64), myocardial infarction (+1.47), heart disease (+1.41), osteoarthritis (+1.39), and inflammatory bowel disease (+1.30).
Conclusions: Comorbidities have a large impact on sleep quality in people with multiple sclerosis, particularly mental health disorders and diseases of the nervous system. Targeting the groups and individual comorbidities as part of the multiple sclerosis management may play a substantial role to improve sleep health.

Disclosure
The authors declare that they have no conflict of interest.

P064

MS and deprivation on the UK MS register : is wealth always the same as good health?

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Background: The United Kingdom Multiple Sclerosis Register (UKMSR) collects clinical and patient reported outcome data from people with MS (pwMS) and clinicians. Several MS studies have looked at interactions between socio-economic status, diagnosis, treatment access and overall level of disease disability. We used data from ONS (Office of National Statistics) as a comparator.
Aim: Analyse the portal and clinical populations of the UKMSR against ONS data for socio-economic differences in deprivation
Methods: Unique participant Lower Super Output Areas (LSOA) were linked to UK Indices of multiple deprivation (IMD) We took clinical and portal populations and performed analysis in R using chi square and two-proportion z-tests. IMDs were categorised into Quintiles (Q-) 1 (most deprived) to 5 (least).
Results: LSOA data from the UKMSR portal population n=19,287: (74.1%) female, mean age 55.3(±12.5), mean onset age 34.3(±10.7), PPMS 12.7%, RRMS 72%, SPMS 6.2%, OtherMS 9.2%. Clinical LSOA data n=8,521 participants: 72.0% female, mean age 53.3 (±12.9), mean onset age 34.7 (±11.0), RRMS 75.4%, PPMS 8.9%, SPMS 5.8%, other MS (5.7%). Clinical and portal populations shifted over time from areas of higher deprivation at younger ages, to areas of low deprivation in older age. pwMS in their 20s (Clinical 21.6% Portal 21.7%) had the highest proportion inIMD Q1. Q5 had mostly 80+ ages (27.4% and 35.9%).
There was no significant difference between clinical and portal data across quintiles. Except the portal pwMS in their 60s living in areas with lower levels of deprivation than the clinical population in their 60s ($p<0.05$) and 70s ($p=<0.05$). Compared to ONS data, more clinical pwMS lived in areas of lower levels of deprivation in every age group except the 20s (20s p=0.21, all remaining age groups <0.05). This was the same when comparing the portal population against the ONS data (20s p=0.22, all remaining age groups <0.05).
Conclusion: We observed an overall difference between ONS data and the portal and clinical participants of the UKMSR. The UK population showed a gradual shift to living in areas with less deprivation as they aged, this was more pronounced in both the UKMSR populations.

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P065

Online medical education reveals differences between neurologists and PCPs on knowledge, competence, and confidence of the impact of race and ethnicity in multiple sclerosis

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Introduction: Among other factors, optimal patient care requires that clinicians consider how ethnic and racial differences affect the diagnosis and management of MS. Evidence indicates that clinicians are not prepared to effectively address the needs of people with MS (PwMS) of diverse ethnic or racial backgrounds.
Aims: Clinicians will benefit from effective education regarding how race and ethnicity impacts care among PwMS.
Objectives: An online educational activity was developed to assess the ability of continuing medical education (CME) to improve awareness among neurologists and primary care physicians (PCPs) regarding ethnicity and race in MS.
Methods: The online CME activity consisted of a 30-minute video discussion between three MS physician experts. Educational effect was assessed by comparing a matched sample of physicians' responses to four identical questions pre- and post-activity. A paired-samples t-test identified significant differences between pre- and post-assessment responses. Cohen's*d* was used to calculate the effect size. Data for this abstract were collected between April 1, 2022 and April 18, 2022.
Results: Initial data was from a pool of 95 neurologist and 76 PCP learners. Pre-education data indicated that approximately 60% of neurologists and PCPs correctly identified that White patients are more likely to access neurologic care for their MS than Black patients. When asked about the patient ethnicity associated with the highest MS mortality rate, 50% of neurologists and 33% of PCPs correctly identified that Black people have a higher MS mortality rate than PwMS of other ethnicities. When a question was posed about how to address religious-based treatment objections from a PwMS, 76% of neurologists and 47% of PCPs correctly identified that discussing treatment in a way that addresses religious beliefs was most appropriate. When asked about their confidence in managing MS in people of different ethnic backgrounds, only 23% of neurologists and 13% of PCPs reported being confident prior to participation in the program. Preliminary results indicated a positive pre-post educational effect for both physician groups.
Conclusions: Initial results indicated substantial gaps among both groups regarding the impact of race and ethnicity in MS, though the gaps were greater among PCPs and that a positive educational effect was observed in both groups. The final pre-post educational outcomes data will be presented during the poster presentation.

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P067

Epidemiology of multiple sclerosis in Iran in 2021

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Introduction: Evidence has shown an increasing trend in the incidence and prevalence of MS worldwide in recent decades. Iran had the highest prevalence of MS among the Asian countries (72.11/100000).
Objectives: To estimate incidence and prevalence of MS in Iran in 2021.
Method: A cross sectional study was designed to estimate the latest incidence and prevalence rate in Iran. This study was based on data obtained from ministry of health and medical Education (MOHME) and nationwide MS registry of Iran (NMSRI).
MS diagnosis were examined by neurologists based on the latest McDonald criteria.
MOHME and NMSRI provided patients with a wide range of facilities and neurologists registered patients to these systems for receiving care and treatment.
The baseline characteristics of patients, including the sex, year and age of disease onset are collected. The MS incidence and prevalence estimate was calculated by the population data achieved from the Statistical Centre of Iran.
Result: A total of 86256 cases were registered in this study, including 74% females and 26% males (female/male ratio = 2.84:1). The number of incidence cases was 4631 in 2021.
The incidence and prevalence of MS in Iran in 2021 was and 5.45 and 101.512 cases per 100000 people respectively.
The number of pediatric MS (<18 years old) was 4631 of total MS cases.
Conclusion: MS is more common in women. MS prevalence in Iran has increased compared to previous studies while experienced a stable rate of MS incidence.
This study revealed that Iran is a high-risk area for MS disease and MS incidence and prevalence are comparable with the prevailing shapes in developed countries. Also, this study showed that the incidence ratio of MS in Iran is similar to global observed patterns.

Disclosure

Conflict of interest: Sharareh Eskandarieh, Mohammad Ali Sahraian, Mohammad Aghigh and Sajjad Ghane declare that they have no competing interests.
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P068

Risk of stroke in multiple sclerosis (MS): a systematic review and meta-analysis

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Introduction: Endothelial dysfunction and accelerated atherosclerosis could be the results of chronic inflammation in MS which results in increase of cardiovascular events.
Objective: To assess the pooled risk of stroke in patients with multiple sclerosis.
Methods: We searched PubMed, Scopus, EMBASE, Web of Science, Ovid, google scholar and gray literature (references of studies, conference abstracts) which were published up to October 2021. Data regarding the total, first author, publication year, the country of origin, number of MS patients and number of controls, number with stroke and were recorded for all included studies.
Results: The literature search revealed 1026 articles, after deleting duplicates 567 remained. For the meta-analysis, 17 studies were included. Totally, 167833 MS cases were evaluated, of whom 6146 had a history of stroke.
The pooled OR of stroke was 2.98 (95% CI:1.83-4.86)(I^2=99%, P<0.001). The pooled OR of ischemic stroke was 1.45 (95% CI:0.72-2.93)(I^2=96.1%, P<0.001).
Conclusion: The result of this systematic review showed that the risk of stroke in patients with MS is more than the general population.

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P069
Proportion of life and incidence of multiple sclerosis in canadian immigrants

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Introduction: While immigrants to countries at more northern latitudes tend to have a lower incidence of multiple sclerosis (MS) compared to host populations, it is unknown if incidence increases as immigrants spend a greater proportion of their life in host nations.
Objective: To determine whether risk of MS in immigrants varies with proportion of life spent in the new host country.
Methods: We conducted a population-based retrospective cohort study in Ontario, Canada, using linked administrative databases. We included immigrants who arrived in Ontario between 1985 and 2012 and had history of Ontario residence of 2 or more years. Incident MS cases were noted over follow-up until December 31, 2016. We derived proportion of life spent (ρ) in Canada based on age at arrival and time since immigration obtained from linked immigration records. We modelled proportion of life as quartiles (lowest quartile as reference) and evaluated the association between proportion of life in Canada and 10-year incidence of MS using multivariable Cox proportional hazard models, adjusting for sex, socioeconomic status, language, region of origin, and comorbidity burden.
Results: We identified 2,304,302 million immigrants (51.0% women, mean age 33.6 years) who had spent median of 0.09 (Q1-Q3, 0.06-0.16) proportion of their life in Canada. Over follow-up, 1,526 (0.07%) were diagnosed with MS. In fully adjusted models, higher quartiles of proportion of life in Canada were associated with higher risk of MS ($HR_{Q2\ vs.\ Q1}$ 1.26 95% CI 1.06-1.51; $HR_{Q3\ vs.\ Q1}$ 1.24, 1.03-1.49; and $HR_{Q4\ vs.\ Q1}$ 1.34, 1.11-1.62). In a sensitivity analysis limited to those who arrived in Canada at age>15 years, we observed similar associations of MS risk with proportion of life quartile.
Conclusion: We found that MS incidence in immigrants increased with proportion of life spent in Canada. This finding suggests an effect of acculturation on lifestyle and environmental factors contributing to MS risk in immigrants, and further work is required to identify modifiable factors.

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Manav V. Vyas has nothing to disclose.
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P070
Education and income prior to multiple sclerosis onset strongly affects disease severity

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Introduction: It is not known to what extent socioeconomic status preceding disease onset affects MS severity.
Aims: To estimate the effect of pre-disease education, income and marital status on long term EDSS.
Methods: Using data from the Swedish MS register linked to national population registries, data were extracted for 5101 patients with clinically definite MS (symptom onset between ages 23-60 and calendar years 2005-2015). Median (IQR) follow-up was 8.0 (5.7-10.5) years. Outcome was disability, measured by the expanded disability severity scale (EDSS), collected periodically as part of routine care. Mixed models were used to estimate the effects of educational attainment, income, and marital status (1 and 5 years prior to onset) on disability. Models were adjusted

for disease factors (number of relapses in first two years of disease, onset age, disease duration, and for relapse-onset analyses, proportion of disease duration on treatment with high- and modest-efficacy disease-modifying therapies).
Results: In relapsing MS, mean EDSS estimate was 1.17 (95%CI 1.02, 1.32) at start of followup and increased by 0.049 (95%CI 0.045, 0.052) per year of disease. Higher educational attainment and higher salary prior to onset were associated with lower EDSS during follow-up. Completion of upper secondary school and tertiary was associated with 0.32 (95% CI 0.21, 0.43) and 0.53 (95%CI 0.41, 0.65) point lower EDSS, respectively. Every additional 1000SEK (~100EUR) in monthly salary was associated with a 0.06 (95%CI 0.08, 0.04) point lower EDSS. There was no difference between being partnered or never-partnered but being divorced was associated with a 0.29 point higher EDSS (95%CI 0.11, 0.47). Sensitivity analyses using socioeconomic variables 5 years prior to disease onset (with onset age criteria increased accordingly) yielded similar findings.
In progressive-onset MS, education and marital status had no association with disability during follow-up, while income had a sizable association (0.23 points lower for every additional 1000SEK monthly salary in the year prior to onset, 95%CI 0.10, 0.36).
Conclusion: Pre-MS socioeconomic status influenced future disability, independently of treatment exposure in relapsing MS, but to a lesser extent in progressive disease.

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P071
Sex and age differences in the multiple sclerosis prodrome

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Introduction: Evidence of a prodromal phase in multiple sclerosis (MS) has grown. However, little is known of the potential sex and age differences in this phase.
Objectives: To investigate sex and age differences in healthcare utilization during the MS prodrome.
Methods: This was a population-based matched cohort study linking administrative and clinical data. MS cases in the five years preceding a first demyelinating event ('administrative cohort;' n=6,863) or MS symptom onset ('clinical cohort;' n=966) were compared to age-, sex- and geographically-matched controls (n=31,865/4,534). Negative binomial and modified Poisson models were used to compare the rates of physician visits and hospitalizations per international classification of diseases chapter, and prescriptions filled per drug class, between MS cases and controls across sex and age-groups ($<$30, 30-49, $\geqslant$50 years).
Results: In the administrative cohort, men with MS had a higher relative rate for genitourinary-related visits (men: adjusted Rate Ratio (aRR) 1.65, women: aRR 1.19, likelihood ratio test P=0.02) and, antiepileptic (men: aRR 3.44, women: aRR 2.81, P=0.01) and antivertigo prescriptions (men: aRR 4.72, women: aRR 3.01 $P<0.01$). Injury and infection-related hospitalizations were relatively more frequent for $\geqslant$50-year-olds (injuries $<$30/30-49/$\geqslant$50: aRR 1.16/1.39/2.12, $P<0.01$; infections 30-49/$\geqslant$50: aRR 1.43/2.72, P=0.03), while sensory-related visits and cardiovascular prescriptions were relatively more common in younger persons (sensory 30-49/$\geqslant$50: aRR 1.67/1.45, P=0.03; cardiovascular $<$30/30-49/$\geqslant$50: aRR 1.56/1.39/1.18, $P<0.01$). General practitioner visits were relatively more frequent in men (men: aRR 1.63, women: aRR 1.40,$P<0.01$) and $\geqslant$50-year-olds ($<$30/$\geqslant$50: aRR 1.32/1.55, P=0.02), while differences in ophthalmologist visits were disproportionally larger among younger persons, $<$50-years-old ($<$30/30-49/$\geqslant$50: aRR 2.25/2.20/1.55, $P<0.01$). None of the sex and age-related differences in the relative rates in the smaller clinical cohort reached significance ($P\geqslant0.05$).
Conclusions: Sex and age-specific differences in healthcare use were observed in the five years before MS onset. Findings demonstrate fundamental heterogeneity in the MS prodromal presentation.

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P072

The impact of changing diagnostic criteria on the incidence, prevalence and disease impact of multiple sclerosis using Welsh routine data

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Background: Increasing incidence and prevalence of MS has been mapped worldwide with multiple techniques. Large scale health data repositories grant access to large unbiased populations. Case identification depends on data completeness and on algorithmic selection, these are highly system specific. They are of relevance to multiple sclerosis (MS) where diagnostic criteria have evolved over 20 years. The Welsh Secure Anonymous Information Linkage (SAIL) databank contains more that 50 years of primary and secondary health data on >90% population. We used an earlier Canadian routine case finding algorithm and compared it to a UKMSR one to measure MS incidence and prevalence. Algorithmic specificity was tested against the UKMSR dataset.
Aim: To examine incidence and prevalence of MS in Wales using two algorithms through examination of linked data from SAIL and UKMSR.
Method: Using International Classification of Disease (ICD-10) and General Practice READ codes, two algorithms compared the linked UKMSR cohort. Manitoba-M classified a case when MS codes were observed and a set number of events exceeded; dependant on date of initial contact; >=7 if <1998, and >=3 if ^{3}>=1998. Study period 1970-2020. UKMSR-M method classified a case if the date of diagnosis >=6 months after earliest MS code entry in SAIL.
Results: UKMSR-M identified 11,849 MS cases, Manitoba-M found 5,677. From 1970-2019, age-adjusted prevalence of MS per 100,000 = 85.2 for Manitoba-M and 184.5 for UKMSR-M. From 1998-2019, the average age and sex-adjusted annual incidence of MS per 100,000 was 4.57 for Manitoba-M and 9.77 for UKMSR-M. Algorithmic accuracy in 821 confirmed MS cases from the SAIL linked UKMSR population was 73% Manitoba-M and 93% UKMSR-M.
Comparing Manitoba-M (n=5677) & UKMSR-M (n=6669) found despite both groups having similar assessment age (mean±SD, 55±14 v 56.3±16.5); diagnosis age (41.6±13.4 v 46.6±18.5, $p<0.0001$)and age of death (65.3±12 v 71.9±15, $p<0.0001$) was lower in Manitoba-M compared to UKMSR-M only, implying less impactful illness in UKMSR-M. Comparing cases Manitoba-M cases with UKMSR (n=598) data and those identified by UKMSR-M but not Manitoba-M (n=223) showed similar worsening.
Conclusion: We have established a reliable algorithmic case finding method for people with MS in Wales. The newer diagnostic approach identifies more confirmed MS cases with different disease characteristics

Disclosure
Middleton, Witts, Knowles, Craig, Rodgers and Tuite-Dalton have not personal conflicts of interest to declare. The UK MS Register is primarily funded by the MS Society
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Clinical aspects of MS - MS and gender

P073

Regional distribution of white matter lesions and microstructural abnormalities but not gray matter atrophy contribute to explain sex-related differences in cognitive performances in multiple sclerosis

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Introduction: Sex may influence cognitive performances in patients with multiple sclerosis (PwMS). However, the substrates of sex-related cognitive differences in PwMS still need to be fully investigated.
Aims: To explore whether differences in the regional distribution of focal white matter (WM) lesions, WM microstructural abnormalities and gray matter (GM) atrophy may explain sex-related differences of cognitive performances in PwMS.
Methods: Brain 3.0 T MRI scan and Rao's battery were acquired for 287 PwMS (women=173) and 172 healthy controls (HC) (women=92). Using voxel-wise analyses, we investigated sex-related differences in regional T2-hyperintense WM lesions, WM fractional anisotropy (FA) abnormalities and GM volumes between PwMS and HC and their associations with cognitive performances ($p<0.05$, family-wise error [FWE]).

Results: Verbal memory was significantly worse in male vs female PwMS ($p<0.001$), whereas verbal fluency was worse in female vs male PwMS ($p=0.001$).In both female and male PwMS, a higher prevalence of T2-hyperintense WM lesions in cognitively-relevant WM tracts was significantly associated with worse cognitive performances. Such associations were significantly stronger in female vs male PwMS in left anterior thalamic radiation and superior longitudinal fasciculus for global cognition and attention. Female vs male PwMS showed significantly lower FA in most of WM tracts, with a larger effect of MS in females on lowering FA values in the majority of WM tracts. In both female and male PwMS, worse cognitive performances were associated with lower FA values in the majority of WM tracts. Such associations were significantly stronger in female vs male PwMS in many several cognitively-relevant WM tracts for global cognition and verbal memory. A significantly lower GM volume in bilateral frontal orbital cortex and left anterior cingulate cortex was found in male vs female PwMS. In both female and male PwMS, a significantly lower GM volume in several cortico-subcortical brain regions was associated with worse cognitive performances, without between-groups differences.
Conclusions: Sex influences the patterns of WM FA abnormalities and the associations between regional T2-hyperintense WM lesions, WM FA abnormalities and cognitive performances. These sex-related differences may explain heterogeneous cognitive impairment in female and male PwMS.

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P074
Ovarian reserve determination by anti-mullerian hormone (AMH) assessment in women with relapsing-remitting multiple sclerosis at fertile age: multicenter, cross-sectional, case-control study

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Introduction: Relapsing-Remitting MS (RRMS) is more prevalent among women with an incidental peak around thirty years, a critical period in terms of fertility. Controversial evidence exists on the impact of the disease on ovarian reserve. Anti-Müllerian hormone (AMH) is a glycoprotein produced by the ovarian granulosa cells of some early follicles and it is the best endocrine marker for assessing the age-related decline of the ovarian pool in healthy women.
Objectives: To compare AMH levels of patients with RRMS between 18 to 40 years vs age-matched healthy controls and to assess the clinical associations with low AMH levels.
Methods: Observational, prospective, case-control study, including female patients with RRMS of childbearing age, attending Universidad Católica de Chile and Hospital Sótero del Río and healthy controls (HC) obtained from a clinical database at Clínica IVI. A blood sample was obtained and sent to Clínica IVI's laboratory for AMH levels measurement and a questionnaire was filled in the same visit.
Results: 79 HC and 82 RRMS, mean age 32(19-40)years, median age at diagnosis 26(16-38)years, median disease duration 6(1-15)years, median EDSS 1.0(0-4.5), 76(92.7%) were receiving disease-modifying therapy, 57(77%) high-efficacy and 29(38%) with a treatment that contraindicates pregnancy. 60 women (73.2%) have the desire to become pregnant in the future, while 47(57.3%) think that the diagnosis of MS is a limitation for pregnancy planning. Median AMH levels were similar between RRMS women and HC (RRMS 2.59(0.05-0.21) vs. HC 2.2(0.5-10), $p=0.38$) in the whole sample, and between each age category (18-24, 25-39, 30-34, 35-40). 18(22%) of the RRMS had AMH levels <1.5 compared to 11(13.9) of HC ($p=0.22$). An inverse correlation between age and AMH levels was observed in both groups (RRMS Rho -0.215, $p=0.05$; HC Rho -0.279, $p=0.01$). When exploring differences between RRMS women with normal vs. low AMH, no statistically significant differences were observed in current age, age at diagnosis, body mass index, disease duration, or EDSS, while a trend was observed in the presence of autoimmune comorbidity and the presence of low AMH (3/18 vs 3/64, $p=0.08$).
Conclusion: Ovarian reserve does not seem to be related to MS diagnosis. Early assessment of ovarian reserve in women with MS, particularly before 30 years old, could be a useful tool for pregnancy or fertility preservation counselling.

Disclosure
nothing to disclose

Clinical aspects of MS - Pregnancy in MS

P075

Interferon- or peginterferon-beta 1a exposure during pregnancy in women with multiple sclerosis: outcomes on child development

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Introduction: In the treatment of relapsing remitting multiple sclerosis, maintaining disease modifying therapy (DMT) up to or during pregnancy might be required. Interferon-beta is approved for use during pregnancy if clinically necessary and extensive data on pregnancy outcomes after first trimester exposure show reassuring results. However, sufficient data on long-term child development are currently unavailable.
Objectives: To assess child development (body measurements, developmental delays, chronic diseases) until 5 years of age in infants born to mothers with interferon- or peginterferon-beta 1a exposure during pregnancy.
Aims: To provide data on child development after interferon- or peginterferon-beta 1a exposure during pregnancy.
Methods: Eligible cases (interferon- or peginterferon-beta 1a treatment at conception or during pregnancy vs. no DMT-exposure during pregnancy) from the German Multiple Sclerosis and Pregnancy Registry were identified. Data are collected with a standardized questionnaire in regular telephone-interviews during pregnancy and postpartum; data on child follow-up are derived from children's medical check-up booklets. Children will be followed-up until 5 years of age. Development outcomes will be compared between the groups.
Results: To date data on 70 children (interferon-beta 1a, n=54; peginterferon-beta 1a, n=16) of 68 exposed mothers, and 48 children of n=46 unexposed ones (interferon-beta or glatiramer acetate treatment prior to pregnancy) are documented. 6 women in the exposed group continued treatment during pregnancy; 9 also breastfed under therapy. Total median follow-up is currently 2.01 (0.5-6.1) years vs. 1.09 (0.2-6.2) in the control group. Infant data up to 5 years of age are collected, but inclusion of cases and overall follow-up is still ongoing; updated data will be presented at the congress. Rates of congenital anomalies did not differ between the two groups. In the exposed group percentage of developmental delay (documented at least once at a medical check-up) was lower, n=5 (7.1%) than in unexposed cases, n=6 (12.5 %). Body measurements (weight, height and head circumference) at regular check-ups were comparable between exposed and unexposed infants during the observation period.
Conclusion: Preliminary 5-year infant data show no signs that interferon- or peginterferon-beta 1a exposure during early pregnancy adversely affected children's development.

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P076

Pregnancy in women with multiple sclerosis: recommendations from the french multiple sclerosis society

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Objectives: To establish recommendations on pregnancy in women with multiple sclerosis (MS)

Methods: The French Group for Recommendations in Multiple Sclerosis (France4MS) reviewed articles from PubMed and universities databases (January 1975 through June 2021). The RAND/UCLA appropriateness method, which was developed to synthesize the scientific literature and expert opinions on health care topics, was used to reach a formal agreement. 56 MS experts worked on the full-text review and initial wording of recommendations. A group of multidisciplinary healthcare specialists validated the final proposal of summarized evidences.

Results: A strong agreement was reached for all 104 proposed recommendations.They cover diverse topics, such as pregnancy planning, follow-up during pregnancy and in the post-partum, delivery routes, loco-regional analgesia or anesthesia, prevention of post-partum relapses, breastfeeding, vaccinations, reproductive assistance, management of relapses, and disease-modifying treatments. Details will be presented at the ECTRIMS congress.

Conclusion: Such recommendations should be helpful to harmonise counselling and treatment practice for pregnancy in people with MS, allowing for better and individualised choices.

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The patient perspective on family planning needs and priorities in multiple sclerosis: a combined quantitative and qualitative research study

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Introduction: Multiple sclerosis (MS) is often diagnosed in females of childbearing age. Most MS disease-modifying therapies (DMTs) are not approved for use during pregnancy or breastfeeding. Even when available, practice guidelines vary by region, and recommendations can differ between MS clinicians. Therefore, pregnant or lactating females with MS may use other sources, such as peer support via social media, to learn about potential risks of various treatment strategies to both themselves and their baby.
Aims: To gain insight into the patient perspective on DMT use during childbearing and lactation in females with MS via social media listening (SML), personal interviews and patient surveys.
Methods: The SML platform Brandwatch searched select websites for prespecified keywords. Posts in English regarding DMT use around childbearing by women with MS from Jan 2019 to Feb 2022 were fetched. Open-access sources included Twitter, Tumblr, Reddit, forums, blogs and YouTube. After validation, posts were manually categorised by sentiment (positive, neutral or negative), phase of family planning and specific theme. To further understand experiences, interviews were conducted (n=20), and a survey was completed (n=50) by adults with MS aged 18 to 45 y who were pregnant or planning pregnancy, focusing on key themes identified from the SML.
Results: Of 1860 posts, 471 DMT-related posts were analysed in the SML. Major themes in women with MS planning pregnancy (n=116) or currently pregnant/breastfeeding (n=227) were doubts around safety or questions on treatment delay. Across all family planning phases, more posts were observed for those giving

advice (84%) vs seeking advice (16%). DMTs, if recommended by clinicians, were generally perceived as safe. Posts during the postpartum period (n=94) expressed concerns around DMT safety postpartum but also an eagerness to reinitiate DMTs. Among all 471 posts, ocrelizumab had the most mentions (18%), followed by glatiramer acetate (14%) and natalizumab (8%). Results from the interviews and survey are forthcoming and will be presented.
Conclusions: Quantitative results from SML show that women with MS use social media to discuss, share and better understand treatment options during family planning. Such engagement may provide additional peer support and satisfy patient needs in an accessible and multifaceted way. The additional qualitative approach aims to identify new perspectives and needs for family planning in MS.

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P078

The association between reproductive characteristics and disability in iranian female patients with multiple sclerosis: a nationwide registry based cross-sectional study

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Introduction: Multiple sclerosis (MS) majorly affects women's quality of life in their reproductive years. MS occurrence may affect the intention of pregnancy as well as the disability level due to the pharmacological and hormonal alterations during pregnancy. The current study evaluates the reproductive characteristics and their effects on the disability (esp. Expanded Disability Status Scale [EDSS] score) among an Iranian population of female patients with MS (PwMS).
Objectives: To assess the reproductive characteristics and their relationship with disability in female PwMS in Iran
Aims:: To improve the level of MS-related service delivery and health of female PwMS in Iran
Methods: A cross-sectional study was designed on the basis of the nationwide MS registry of Iran (NMSRI) from 2018 to 2021. Data were recorded by neurologists using a standardized minimum data set to evaluate the clinical and epidemiological features of the disease, as well as the effect of MS on patients' life. The most prominent features covered by the registry are demographic characteristics, clinical presentations, MS type, diagnostic and treatments, disease and pregnancy history, and EDDS score.
Results: Among 1120 patients included in the final analysis, those who had a history of pregnancy or abortion had significantly higher EDSS scores ($P = 0.02$ and $P = 0.04$, respectively). Besides, multiparity ($\geqslant 2$) prior to MS incidence was associated with EDSS score $\geqslant 5$ (OR: 2.41; 95% CI: 1.02-5.7; $P = 0.04$). Furthermore, EDSS score $\geqslant 5$ significantly decreased the parity following MS incidence (OR: 3.35; 95% CI: 1.01-11.09; $P = 0.047$).
Conclusions: The disability levels in PwMS may significantly be affected by pregnancy and parity history. Besides, the chances of parity may decrease in higher EDSS scores, which should be considered in the clinical setting.

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P079

Pregnancy substantially reduces the long-term risk of reaching confirmed EDSS 4

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Introduction: Although pregnancy is not harmful to the disease course of MS, there is currently no consensus on its impact on long-term disability outcomes.
Objective: To determine whether pregnancy can reduce the risk of reaching the hard disability milestone of confirmed EDSS 4.
Methods: Women with relapse-onset MS enrolled in the MSBase Registry were surveyed regarding their entire reproductive histories including terminations and miscarriages. Marginal structural models (MSM) incorporating an inverse probability of treatment weighting approach were used to account for the longitudinal nature of our dataset. The stabilized weights were obtained based on logistic regression models, where the numerator included all baseline variables (age, disease duration, baseline EDSS, pregnancy prior to baseline, year of first symptoms [<1995, 1995-2005, 2005-2010, >=2010]) and the denominator included baseline variables and two time-varying covariates (TVC), disease modifying therapy (DMT) class and breastfeeding. Baseline was set at the first EDSS visit in MSBase. Cox Proportional Hazards regression, clustered by patient ID, was used to assess time to reach 6-month confirmed EDSS 4. Schoenfeld's global test was used to check the proportionality assumption.
Results: We included 2,907 women with relapse-onset MS who had an EDSS <=3 at baseline, of whom 743 had at least one pregnancy after baseline; median 1 (range 1-6). We found that pregnancy reduced the risk of reaching confirmed EDSS 4 by 90% (hazard ratio (HR) 0.10, 95% confidence interval 0.03, 0.43, p=0.0017).
Conclusions: We provide evidence that pregnancy has beneficial long-term outcomes for women with relapse onset MS, substantially delaying the time to reach confirmed EDSS 4. Women with relapse-onset MS who wish to have children should be reassured that pregnancy should not harm their long-term outcomes. Although it is possible that unmeasured bias or confounding could affect this result as there may be reasons for women with MS not to become pregnant, potentially associated with their own perceptions of disability progression.

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P080

Expert opinion on the use of contraception in people with multiple sclerosis

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Introduction: The most appropriate use, type, and timing of contraception in people with multiple sclerosis (PwMS) is poorly understood, and specific guidance is absent.
Aims and Objectives: To provide insight into potential clinical guidelines for the use of contraception by PwMS through development of recommendations by a consensus-based program led by international clinical experts.
Methods: A multidisciplinary steering committee (SC) of 13 international expert healthcare professionals (HCPs) identified 15 key clinical questions on the use of contraception in PwMS, which addressed issues relating to patient-centred care, selection of contraception for PwMS, and time needed to use contraception since the last dose of disease modifying therapies (DMTs). Twenty-five clinical recommendations addressing the questions were drafted using evidence obtained from a comprehensive systematic literature review combined with expert opinion from the SC. An extended faculty of 32 HCPs from 18 countries including a patient association representative, and the SC members (n=12), voted on the recommendations. Consensus on recommendations was achieved when ⩾75% of respondents expressed an agreement score of 7–9, on a 9-point scale.
Results: Overall, consensus was achieved on 24 out of 25 clinical recommendations. In detail, consensus in the range of 90–100% was achieved on 11 recommendations, 12 recommendations achieved 80–89% consensus, and 1 recommendation achieved 75–79% consensus (n=44). The strength of recommendations ranged from 7–9. The one statement failing to achieve consensus scored 74.1%. Clinical recommendations are provided on the process of prescribing contraception for PwMS, including the recommended types of HCPs involved and optimal topics to discuss; the range of contraceptive options and the key considerations involved in selecting an appropriate method of contraception; and the timing of starting and stopping contraception in relation to the use of DMTs.
Conclusions: These expert recommendations were based on a robust consensus approach, providing timely and practical guidance on the use of contraception for HCPs treating PwMS and will form the basis of further publications and clinical tools.

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P081

Multiple sclerosis disease activity and disability following discontinuation of fingolimod for pregnancy

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Introduction: Discontinuation of Fingolimod (FTY) ⩾2 months prior to pregnancy is recommended to minimize potential teratogenicity.

The rate of pregnancy-related multiple sclerosis (MS) relapses following FTY-cessation and the influence of the pregnancy are unclear.

Aims: We wish to describe the course of relapse activity and possible diability accumulation during pregnancy and the postpartum year in MS patients with pregnancy-related FTY-cessation.

Methods: Pregnancies of patients who stopped FTY treatment within 1 years prior to or during pregnancy were identified from the German Multiple Sclerosis and Pregnancy Registry. Data was collected through structured interviews and neurologists' notes. Severe relapses were defined as a ⩾ 2.0 increase in expanded disability status scale (EDSS) or new or worsening relapse-related ambulatory impairment. Patients who continued to meet this definition 1 year postpartum were classified as having significant relapse-related disability (SRRD). Multivariable models accounting for measures of disease severity and repeated events were used.

Results: 213 (174 with complete EDSS information) pregnancies were identified. In 69.8% FTY was stopped later than recommended and in 56.8% after conception. Relapses during pregnancy (31.46%) and the postpartum year (44.6%) were common. One year postpartum, 11 (6.3%) had accrued significant relapse-related disability.

Adjusted relapse rates during pregnancy were slightly higher compared to the year prior to pregnancy (relapse rate ratio=1.24, 95% CI 0.91-1.68, P= 0.169).

Conclusions: Relapses during pregnancy following FTY-cessation are common. Approximately 6% of women will retain clinically meaningful disability from these pregnancy-related, FTY-cessation relapses at 1 year postpartum. This information should be shared with women on FTY desiring pregnancy and optimizing multiple sclerosis treatment with non-teratogenic approaches should be discussed.

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P082

Fertility, pregnancy and childbirth in women with multiple sclerosis: a population-based study from 2018 to 2020

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Objectives: We aim to evaluate fertility, pregnancy and childbirth outcomes in women with multiple sclerosis (MS), when compared with the general population, and in relation to clinical features and disease modifying treatments (DMTs).

Methods: This population-based study is a retrospective analysis of routinely-collected healthcare data (including DMT prescriptions), prospectively recorded from 2018 to 2020, on women with MS living in the Campania Region of Italy. Fertility, pregnancy and delivery outcomes were obtained from the Certificates of Delivery Assistance. Linkage to clinical registry was used to extract disease duration, expanded disability status scale (EDSS), and relapses.

Results: Out of 2748 women with MS in childbearing age, 151 women delivered 154 babies. General fertility rate was 56.76 live births per 1000 woman with MS in childbearing age, compared with 107.09 in the Campania Region and 101.45 in Italy. When compared with women with MS without pregnancy, women with MS with pregnancy had younger age (Coeff=-5.41; 95%CI=-7.80, -3.02; $p<0.01$), shorter disease duration (Coeff=-6.20; 95%CI=-10.08, -2.32; $p<0.01$), lower EDSS (Coeff=-0.65; 95%CI=-1.11, -0.20; $p<0.01$), and higher relapse rate (Coeff=0.28; 95%CI=0.02, 0.55; p=0.03). DMT continuation during pregnancy was associated with lower birth weight (Coeff=-107.09; 95%CI=-207.91, -6.26; p=0.03), and exposure to DMTs with unknown/negative effects on pregnancy was associated with higher probability of birth defects (OR=8.88; 95%CI=1.35, 58.41; p=0.02). In particular, we recorded 5 cases of birth defects (Klinefelter syndrome, cleft palate with cleft lip, ostium secundum, short frenulum of lip, and low birth weight with death in the following 7 days), in women exposed to dimethyl fumarate, fingolimod or natalizumab within 3 months from conception. After delivery, DMT escalation strategy was needed in 18.8% women with MS, while 50.7% started on same/similar-efficacy DMTs, and 30.5% did not receive DMT. The probability of breastfeeding was higher in women who were treated with breastfeeding-safe DMTs (OR=5.57; 95%CI=1.09, 28.55; p=0.03).

Conclusions: Fertility rates in women with MS remain far below the general population. Family planning should be discussed in the early stages of MS (i.e., younger age, lower disability, shorter disease duration). Subsequent DMT decisions should aim at successful pregnancy, delivery, and breastfeeding outcomes, while maintaining disease control.

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P084

Aspects of life with focus on family planning and pregnancy among women with MS

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Background: There is an imperative need for appropriate information to MS patients planning to set up a family and receiving disease modifying treatment (DMTs). Studies on how women with MS undergoing pregnancies experience their health and how they receive information on treatment during pregnancy and breastfeeding are scarce.

Objective: To investigate gaps in care of women with Multiple Sclerosis (MS) in respect to family planning and pregnancy after disease onset.

Method: A web-based survey was conducted during the summer 2021 to investigate various aspects of life, including family planning and pregnancy, among people with MS in Sweden.

Patients with MS aged 20-50 listed in the Swedish MS-registry were invited. Sociodemographic and clinical data were linked from nationwide registers. Descriptive data and differences in responses between women with MS who did or did not experience a pregnancy after disease onset were tested with chi2-tests or Wilcoxon rank sum test, where appropriate.

Results: Over 8500 adults with MS aged 20-50 were invited to answer the survey and 4412 (52%) responded of which 3148 (71%) were women, 95% had remitting relapsing MS and 73% an EDSS between 0 and 2.5. 1275had experienced at least one pregnancy after onset of MS and 636 several pregnancies. Women with MS received their information on DMT mainly through their neurologists (75%) or other health care workers. Among women

with MS 42% had talked about family planning with their neurologists. Women who had experienced a pregnancy rated their general health more often as "very good" or "good" (22% resp. 44%) compared to women without any pregnancies (16% resp. 42%). Almost a quarter (23%) of the women that had been pregnant responded that their pregnancy affected their MS positively, while 19% responded that it had affected the MS negatively. Women's decision to breastfeed was affected by DMT use, 28% responded that they had chosen not to breastfeed and 31% had postponed their DMT to be able to breastfeed.

Conclusion: Women with MS responded that pregnancy affected their MS both in positive and negative ways. Many had discussed family planning with their neurologist and rated the neurologist as the main source of information concerning DMT. It is of importance that physicians are up-to date and well informed about possible effects of DMTs on pregnancy and postpartum. A durable choice of DMT to enable breastfeeding without risking mother's MS and child's health is important.

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Clinical aspects of MS - MS symptoms

P085

Association of fatigue with MRI metrics in a large, real-world cohort of people with MS

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Introduction: Fatigue is a common and debilitating symptom of multiple sclerosis (MS). While there is substantial interest in determining if radiologic markers of tissue injury and neurodegeneration can be useful in understanding mechanisms of fatigue, most existing studies have been small and may lack generalizability.

Objectives: To analyze the cross-sectional association of lesion burden and brain compartment volumes with fatigue severity in people with MS in a large real-world cohort and if this varies by key patient subgroups.

Methods: MS PATHS is an international initiative in which standardized data on demographics, disease characteristics, patient-reported outcomes, and magnetic resonance imaging (MRI) measures are acquired during routine care of people with MS from 10 healthcare institutions. MRI outcomes analyzed included brain parenchymal fraction (BPF), gray matter fraction (GMF), and T2 lesion volume (T2LV), which were calculated using the MSPie prototype. Depression and fatigue were assessed via the Quality of Life in Neurological Disorders (Neuro-QOL) and analyzed linearly and categorically (none, mild, and moderate-severe) derived using pre-specified T-score cutpoints. We applied multivariable-adjusted generalized linear models for cross-sectional analysis.

Results: Of the 8328 participants included, 2968 (36%) reported mild fatigue and 1101 (13%) reported moderate-to-severe fatigue. Patients were 72.7% female and 80.5% White, with mean ± standard deviation(SD) age of 48.7±12.1 years and 31.5% with progressive disease. In the multivariable linear regression model, higher baseline GMF was associated with lower Neuro-QOL fatigue T-score (beta=-0.17; 95% CI: -0.31, 0.03, p=0.03). In multinomial models, relative to those with no fatigue, each one-unit increase in the baseline GMF decreased the odds of mild fatigue group by 3.5% (95% CI: 0.9-6.1%) and moderate to severe fatigue by 4.3% (95% CI: 0.5-8.0%). In patients without depression, higher baseline GMF was associated with lower fatigue levels and this was relatively consistent for younger and older adults (for age<50: beta= -0.30; 95% CI: -0.12, -0.48; for age⩾50: beta=-0.20; 95% CI: -0.01, -0.40).

Conclusion: Higher GMF is associated with a lower degree of fatigue in people with MS, and this association may vary based on patients' severity of depression.

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P086

Fatigue prediction model based on CSF protein profile and MRI measures in early relapsing multiple sclerosis

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Introduction: Fatigue is one of the most frequently described and disabling symptoms for many multiple sclerosis (MS) patients, affecting 50-90% of patients during their disease course. Its pathophysiological mechanism is still uncertain and its treatment remains an unmet medical need. So far structural brain damage and immunological processes were regarded as key features in fatigue development, however, these were never combined to model MS-related fatigue.
Aims: To unravel early cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) inflammatory and neurodegenerative predictors of fatigue adopting a machine learning based analysis in MS patients at time of diagnosis.
Methods: We included early relapsing-remitting MS patients (RRMS) who had CSF protein profiling at time of the diagnostic lumbar puncture (LP) and underwent Modified Fatigue Impact Scale (MFIS). We collected 3T brain MRI data (3DFLAIR, 3DT1WI, DIR) performed within 6 months from the LP, CSF immunoassay (BioPlex) levels of 25 inflammatory and neurodegenerative proteins and total (t-), physical (p-), cognitive (c-) MFIS scores. Freesurfer and FSL were used to analyse the structural MRI metrics. We selected the most important CSF and MRI features associated with the MFIS scores using either Random Forest algorithm or regularization approach LASSO.
Results: 103 treatment-naive RRMS (71% females) underwent MFIS questionnaire after a median time of 2 months (interquartile range-IQR- 0-17) from LP. Median t-MFIS score was 22 (IQR 10-39), p-MFIS score was 11 (IQR 5-20) and c-MFIS was 8 (IQR 3-18). Across CSF molecules, features selections analysis identified osteopontin, CCL19, chitinase 3-like 1, CX3CL1, TNFa as determinant of t-MFIS ($p<0.05$), osteopontin, chitinase 3-like 1, CX3CL1, pentraxin-3, MMP2 as determinant of p-MFIS ($p<0.05$) and sTNFR2, osteopontin, pentraxin-3, IL28, CXCL12 and CX3CL1 as determinant of c-MFIS ($p<0.05$). Across the structural MRI measures, paracentral cortical thickness (CT) (β=-38, p=0.03), postero-cingulate CT (β =-43, p=0.01) and deep grey matter volume (DGMV) ($\beta=-2.2*10^{-3}$, p=0.02) predicted t-MFIS; DGMV predicted p-MFIS ($\beta=-1.1*10^{-3}$, p=0.02) and no MRI metrics were found associated with c-MFIS. White matter and cortical lesions did not predict fatigue.
Conclusions: Fatigue appears to be reflected by a specific CSF patten suggesting innate inflammatory processes and by neurodegeneration in GM areas involved in sensory-motor and interoceptive attentional functions.

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P087
Association between frailty and free-living walking performance in people with multiple sclerosis: a multicenter cross-sectional study

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Introduction: There is a significant overlap between signs and symptoms of frailty and disability in people with multiple sclerosis (pwMS). While neurological disability is known to adversely affect both the quantity and quality of walking in MS, the relationship between frailty and walking performance in pwMS has not been well studied yet. Particularly, it is not known if frailty differentially impacts the quantity and quality of walking in the real world in this clinical population.
Objectives: To examine 1) the association between frailty and the quantity/quality of free-living walking and 2) the mediating effect of frailty on the relationship between disability and walking performance in pwMS.
Methods: Ninety-nine people with relapsing-remitting MS [age=49.3 years (SD=9.8); 73.7% female; expanded disability status scale (EDSS) range=2.0-6.0] wore a tri-axial accelerometer for 7 days. Recorded measures reflected the quantity (daily step counts, number of 30-seconds walking bouts, signal vector magnitude (SVM)) and quality (gait speed, step cadence, step/stride regularity, and sample entropy) of walking. For each walking quality measure, the typical (median), best (90th percentile), and worst (10th percentile) values were calculated. Frailty was evaluated through the frailty index method.
Results: Participants were classified as non-frail (n=36), moderately frail (n=28), and severely frail (n=35) based on established frailty index cut-offs. Severely frail participants exhibited worse performance in all measures of walking quantity and quality, except for sample entropy, compared to non-frail individuals. Moderately frail participants had a lower number of walking bouts, lower SVM and lower best values of gait speed compared to the non-frail. Frailty did not mediate the relationship between disability (EDSS) and measures of walking quality. Conversely,

the frailty index had a significant mediating effect on the relationship between disability and walking quantity (daily step counts and number of walking bouts), and fully mediated the relationship between disability and SVM (direct effect: b=-1.01, 95% CI=-3.03,1.01; indirect effect: b=-1.51, 95%CI=-2.71,-0.60).
Conclusions: Frailty negatively affects several aspects of free-living walking in pwMS. The study findings suggest that frailty, rather than disability, may be primarily responsible for the lower amount of physical activity performed by pwMS in the real world.

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Clinical aspects of MS - Clinical assessment tools

P088
Validity of a graded exercise test to measure maximal oxygen consumption in persons with multiple sclerosis

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Introduction: In people with Multiple Sclerosis (pwMS), the accuracy of a graded cardiopulmonary exercise testing (CPET) has been questioned as the test performance may be limited by central and peripheral symptoms rather than cardiorespiratory maximal effort. The failure of obtaining viable results may limit the ability in designing targeted training and may explain heterogeneous results of exercise studies on a group and individual level.
Objectives/Aims: The objectives of the present study are (i) to examine the proportion of pwMS that attain a respiratory exchange ratio (RER) ⩾1.10, a criterion described by the American College of Sports Medicine as the most accurate and objective non-invasive indicator for maximal effort, and (ii) to provide insight into patient characteristics that limit maximal exercise performance.
Methods: Data of n=385 pwMS, who conducted a graded CPET during their rehabilitation stay at Clinic Valens from 07/2010 to 03/2022, were extracted retrospectively. Participants were classified according to the achievement of an RER ⩾1.10 during the test (i.e., criteria attained: Yes/ No). Pearson-Chi-square tests were utilized to determine differences in sex and disease course distribution between both groups. Unpaired t-tests were used to compare mean age, body mass index (BMI), time since diagnosis and Expanded Disability Status Scale-Score (EDSS).
Results: An RER ⩾1.10 was achieved by 59.7% of the participants. The incidence of an RER ⩾1.10 was significantly lower in participants with secondary progressive or primary progressive disease courses than in those with relapsing-remitting disease course ($\chi^2(3)=20.71$, $p \leqslant .001$, Cramer's V= 0.232). Also, participants who attained the criterion were characterised by significant younger age, less time since diagnosis, and lower EDSS ($p \leqslant .05$). Gender and BMI did not influence criteria attainment.
Conclusions: The findings suggest that the validity of a frequently used graded CPET protocol in pwMS is limited. The likelihood to obtain viable results declines with increased age, time since diagnosis and EDSS and further dependents on patient's disease course. We highly recommend inspecting whether gathered spiroergometric data is viable through objective criteria such as the RER before utilizing it for training control in pwMS.

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P089
Measures of lower limb agility during the bipedal hop test corroborate subjective balance and mobility concerns in early multiple sclerosis

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Introduction: Daily physical demands require a highly-integrated neuromuscular system. The goal of early multiple sclerosis (MS) treatment is to prevent and stabilize the disease and achieve 'No Evidence of Disease Activity'. Despite reporting balance and mobility problems, many people with early stage-MS easily pass the Timed 25 Foot Walk Test (T25FWT). The Bipedal Hop Test (BHT) may provide the neuromuscular challenge required to characterize, and thus treat, this subtle gait impairment.
Objective/Aim: To determine whether spatiotemporal gait parameters or EDSS predict subjective reports of balance and mobility problems in early MS.
Methods: Sixty participants of mean age 46.13 years (EDSS ⩽ 3.5; 43 females) completed subjective ratings of balance and mobility using the MS Impact Scale-29, questions 4 to 11. Responses were dichotomized as having balance and mobility problems (0: no and 1: yes). Gait tasks (T25FWT, dual-task walking and the BHT) were performed on an instrumented walkway. Spatiotemporal gait parameters such as speed, hop width, hop length, hop time and cadence were measured. Logistic regression analysis was used to determine whether gait tasks or EDSS score predicted subjective reports of balance and mobility problems.

Results: Hop length (HL) was a significant predictor of subjective balance and mobility problems ($\chi^2 = 8.708$, $p<0.05$) and it accurately predicted balance and mobility problems in 93.2% of cases ($\chi^2= 4.320$, $p<0.05$), after controlling for age and gender. Furthermore, for every 1 unit increase in HL, there was a 9% decrease in the odds of reporting balance and mobility problems. Neither T25FWT, dual-task walking nor other BHT parameters significantly predicted subjective reports of balance and mobility problems.
Conclusions: Spatiotemporal parameters, specifically hop length, measured during the Bipedal Hop Test may offer new insight into balance and mobility problems in early MS. Hop length is a measure of power generation and agility – two characteristics that can be used to design personalized rehabilitation interventions. Future studies investigating minimal detectable change and measurement of treatment efficacy are warranted.

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Maria Williams: Nothing to disclose.
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Michelle Ploughman: Nothing to disclose.

P090
Analytical validation of innovative magneto-inertial outcomes: a controlled environment study

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Introduction: Gait impairment is one of the main causes of disability in multiple sclerosis (MS). Detecting and quantifying gait impairment due to motor weakness, ataxia and spasticity is an important step toward the quantification of disease progression. Wearable devices that integrates new magneto-inertial technologies open the opportunity of continuous home-based assessment of movement.
Objectives: We aim to validate the accuracy and precision of spatio-temporal gait characteristics of MS patients measured by an inertial device against a gold standard (optical Motion Capture). We also aim to explore new digital biomarkers specific of the different component of gait impairment in MS.
Methods: The study included 21 patients suffering from MS, aged from 22 to 62 years (median 38 years) with mild to moderate impairment (EDSS 1.5-5.5) and 11 healthy controls aged from 27 to 62 years-old (median 37 years). Participants were asked to wear an inertial-measurement-unit (IMU) device specifically designed for continuous assessment of patients with neurological diseases (ActiMyo®) as well as Motion Capture markers on both ankles. They were instructed to perform a series of walking exercises (including distractive tasks, half-turns,. . .) at different paces. For the development of new biomarkers, MS related gait abnormalities (ataxia, spasticity, etc.) were identified based on detailed EDSS scoring. External validation was performed by correlating inertial variables with the Expended Disability Status Scale (EDSS), Functional status (FS) scores and Timed 25 Foot Walk (T25FW).
Results: Over 99% of strides identified using the Motion Capture were accurately detected by the IMU device (99% recall), and measured with a centimetric precision (< 3% error on the stride length). Based on full EDSS scoring, we highlight some potential clinical variables (lateral deviation of the stride, variability in stride shape, offset in key gait events,. . .) for continuous assessment of gait in real-life. These gait abnormalities observed by the clinicians were accurately quantified by both the optical motion capture and the inertial device. Overall, digital biomarkers showed good correlations with EDSS and T25FW.
Conclusion: The analysis highlighted that gait characteristics could be accurately identified from inertial recording and could provide meaningful outcomes for assessing disability in MS. Validation in uncontrolled environment is ongoing.

Disclosure
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- Margaux Poleur : nothing to disclose.
- Alexis Tricotis is employed by Synsav, the medium-sized enterprise responsible for ActiMyo® development.
- Laurie Médard: nothing to disclose.
- Nicolas Gevenois: nothing to disclose.
- Dimitri Lozeve is employed by Synsav, the medium-sized enterprise responsible for ActiMyo® development.
- Olivier Bouquiaux : nothing to disclose.
- Alain Maertens de Noordhout : nothing to disclose.
- Mona Michaud is PhD candidate with a funding from Synsav, the medium-sized enterprise responsible for ActiMyo® development.
- Mélanie Anoussamy is employed by Synsav, the medium-sized enterprise responsible for ActiMyo® development.
- Laurent Servais has a patent with non-financial return on the invention of a variable to measure upper limb power using magneto-inertial technology.

P091
Novel method to measure sensorimotor integration among people with MS who report problems with hand dexterity

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Introduction: Subtle problems integrating incoming sensory information with appropriate motor outputs creates finger incoordination that is difficult to detect using standard clinical and neurophysiological tests. In a normal brain, incoming afferents, preceding a motor pulse, will inhibit the motor response (motor evoked potential (MEP)). Insufficient inhibition (disinhibition) will result in a higher MEP ampltidue. The resulting change in

MEP, known as short-latency afferent inhibition (SAI), is a measure of sensorimotor integration (SMI) which can be assessed using combined transcranial magnetic stimulation (TMS) with peripheral nerve stimulation.
Objective/Aims: The aim of this study is to quantify SMI deficits in people with MS who report manual dexterity problems compared to control subjects and examine relationships between the novel neurophysiological measure and clinical tests.
Methods: We assessed SAI in the abductor pollicis brevis muscle of the left and right hands (LH, RH) in 21 right-handed people with MS and 9 sex and age-matched controls. Pinch strength, grip strength, nine-hole peg test (9HPT), Semmes-Weinstein Monofilaments and two-point discrimination were also assessed. Mann Whitney U test was used to compare measures between groups and Spearman correlation to establish relationships between measures.
Results: MS subjects had significantly greater disinhibition in their dominant hand (%TS MEP: MS=151.59(78.48), HC=90.48(23.01); p=0.009), and reduced sensation in their index finger (p=0.03) compared to controls. Although not statistically significant, they also showed impaired manual dexterity (Pinch Strength LH (kg): MS=8.08(4.52), HC=9.65(2.93); p=0.06, Pinch Strength RH (kg): MS=8.75(7.06), HC=9.65(2.92); p=0.07), (9HPT RH (s): MS=22.20(3.71), HC=19.66(2.29); p=0.08) compared to controls. Greater disinhibition was significantly related to weaker pinch strength (R=−0.382; p=0.03) in the RH, and reduced sensation in the index finger was related to longer time to complete 9HPT in the RH (R=−0.524, p=0.003).
Conclusion: Integrated neurophysiological measurement of sensorimotor signaling provides a unique biomarker of subtle manual dexterity impairment in MS and may be useful to predict response to sensorimotor upper extremity rehabilitation interventions.

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P092
Key domains of gait in people with multiple sclerosis based on objective pressure sensitive walkway data

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Introduction: Gait impairment is a hallmark of multiple sclerosis (MS). Because walking is a complex task, no single outcome can provide a fully comprehensive picture of walking impairment. Advanced gait analysis systems often incorporate sensor technologies (e.g. sensor-embedded walkways or body-worn inertial sensors) that enable detection of subtle changes in mobility functioning. However, numerous interdependent gait parameters resulting from these contemporary systems can be difficult to adequately interpret due to the large amount of data. To address this complexity, conceptual gait models based on factor analysis (FA) have been increasingly proposed in recent years, but not within a large cohort of people with MS (pwMS) studied with senor-embedded walkway systems.
Objective: To develop a conceptual gait model based on comprehensive gait data from a widely used gait analysis system with integrated pressure sensors to assist clinicians and researchers with data interpretation.
Methods: As part of a broader standardized gait analysis protocol in routine clinical practice at the MS Center Dresden (Germany), pwMS walked back and forth on an eight-meter pressure sensor walkway (GAITRite system) at comfortable speed. Exploratory FA was applied to reduce the large number of obtained spatiotemporal variables into a fewer number of distinct factors (domains). For this purpose, empirically derived criteria for variable inclusion and factor extraction were used. The robustness of the resulting FA-based conceptual gait model was investigated by sensitivity analyses with respect to methodological inputs. Validation was performed by examining the discriminatory properties of the proposed gait domains
Results: In total, gait data from 901 pwMS with EDSS ⩽6 (72% females, median EDSS 2) was available for inclusion. FA revealed 3 (to 4) distinct domains (factors) accounting for 79.6% of the total variance. Labelling of these factors with reference to previous gait models revealed: pace (and rhythm), variability and asymmetry, with the first factor being most influential.
Conclusion: Using a dimension reduction technique, we were able to identify main gait domains and to categorize spatiotemporal GAITRite outcomes into these domains. In both clinical practice and research settings, appropriate conceptual models can help reduce redundancy in analysing gait alterations or monitoring the effect of interventions.

Disclosure
Dirk Schriefer, Katrin Trentzsch and Heidi Stölzer-Hutsch have nothing to disclose. Tjalf Ziemssen reports consulting or serving on speaker bureaus for Biogen, Celgene, Roche, Novartis, Celgene, and Merck; Sanofi; research support from Biogen, Novartis, Merck, Sanofi.

P093
Longitudinal association of intra-task measures derived from a technology-enabled 9-hole Peg test with disease progression and quality of life in multiple sclerosis

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Introduction: The 9-hole peg test is a common measure of upper-limb function in multiple sclerosis clinical trials. A digitized version called the Manual Dexterity Test (MDT) records peg timing and location information allowing calculation of intra-task measures beyond completion time.

Objectives: To characterize longitudinal associations and determine intra-patient correlations between (a) changes in MDT measures including those with intra-task data, and (b) changes in patient determined disease steps (PDDS), cognitive processing speed test (PST), and Neuro-QoL.
Methods: MDT, PDDS, PST, and upper limb, lower limb, cognition, and fatigue domains of Neuro-QoL were measured by a Multiple Sclerosis Performance Test (MSPT) device in the Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS) network. Patients included had ⩾5 MSPT measures conducted and ⩾6 months of follow-up. Non-traditional MDT attributes were based on distance, speed, peg order, inter-peg time variances, time for specific peg movements, and principal components (PC) analyses of inter-peg times. Traditional MDT attributes included dominant hand, non-dominant hand, and averaged combined hand completion times. Intra-patient longitudinal change associations between individual MDT attributes and PDDS, PST, and Neuro-QoL scores were assessed by repeated measure correlations.
Results: Analyses included 3,525 patients and 44,394 MSPT observations; mean follow-up was 1.2 years. Correlation coefficients (CC) were relatively weak with absolute values >0.05 and <0.2. Traditional MDT measures showed statistically significant intra-patient longitudinal change associations with PDDS, PST, and each NeuroQoL domain. Of the non-traditional MDT measures, the first PC and speed showed significant longitudinal change associations with PDSS, PST, and each NeuroQoL domain. CC for the first PC was lower than the traditional measures in all analyses, but speed was comparable with traditional measures. Other non-traditional MDT measures rarely showed statistically significant associations to any measure and, when significant, the CC was generally smaller than the traditional measures, the first PC, and speed.
Conclusions: These data suggest that overall MDT time is a reliable measure that correlates with changes in disability progression and QoL in MS patients. Among the novel MDT measures assessed using peg timing and location, only speed achieved similar performance.
Study Support: Biogen.

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NC, XJ, CIG, RH, JvB, and NL are all employees of and hold stock/stock options in Biogen.

P094
Personalized pathological maps obtained with T1 relaxometry provide correlates of disability in single multiple sclerosis patients

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Introduction: T1 relaxometry has proven to be sensitive to focal and diffuse brain pathology in multiple sclerosis (MS) patients. Recently methods have been developed to quantify the pathological deviations of quantitative T1 maps (qT1) in MS patients compared to healthy controls (HC), providing personalized qT1 pathological maps.
Objectives and Aims: We aimed to assess the relationship between qT1 pathological maps and patients' disability to evaluate the potential value of this information in clinical practice.
Methods: We included 128 MS patients (72 relapsing-remitting MS (RRMS), 36 secondary progressive MS (SPMS), 20 primary progressive MS (PPMS)), and 98 HC. All individuals underwent 3T MRI examinations, including Magnetization Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE) for qT1 maps and High-Resolution 3D Fluid Attenuated Inversion Recovery (FLAIR) imaging. To calculate qT1 pathological maps we applied the method proposed by Bonnier G. et al. (2019). In brief, we compared qT1 in each brain voxel in MS patients to the average qT1 obtained in HC's same tissue and lobe. The healthy tissue distribution was age-adjusted using generalized linear regression (GLM) and then used to calculate the individual deviation maps in MS patients using z-scores. Further, we averaged the z-scores in lesions and normal-appearing white matter (NAWM). Lastly, a multiple linear regression (MLR) model was used to assess the relationship between qT1 measures and clinical disability, including age, disease duration and diagnosis factors as covariates.
Results: The average T1 z-scores in lesions were significantly higher than in NAWM (lesions: 3.313 ± 1.073, NAWM: 0.698 ± 0.444, [mean $\pm$ SD], $p < 0.001$). The MLR with EDSS showed a strong association between T1 z-scores in lesions and EDSS ($R2 = 0.509$, $\beta = 0.082$, 97.5% CI = 0.024 to 0.139 %, $p = 0.006$) and between EDSS and age ($\beta = 0.009$, 97.5% CI = 0.003 to 0.015 %, $p = 0.002$), disease duration ($\beta = 0.006$, 97.5% CI = 0.001 to 0.015 %, $p = 0.013$), RRMS diagnosis ($\beta = -0.277$, 97.5% CI = -0.485 to -0.070 %, $p = 0.009$), and SPMS diagnosis ($\beta = 0.207$, 97.5% CI = 0.021 to 0.394 %, $p = 0.030$). Specifically, we measured a 17.9% increase in EDSS per unit of T1 z-score in lesions in RRMS patients ($R2 = 0.205$, $\beta = 0.179$, 97.5% CI = 0.0990 to 0.259 %, $p < 0.001$).
Conclusions: We showed that qT1 pathological maps in MS patients provide measures related to clinical disability, supporting the use of those maps in clinical practice.

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P095

Detecting ongoing disease activity in mildly affected multiple sclerosis patients under first-line therapies

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Introduction: The now available range of disease-modifying treatments (DMTs) for relapsing-remitting multiple sclerosis (RRMS) has placed more importance on the accurate monitoring of disease progression for timely and appropriate treatment decisions. However, measuring ongoing disease activity, particularly in mildly affected RRMS patients treated with first-line DMTs, is challenging, since silent disease progression is documented to occur .
Objectives: In order to optimize the assessment of disease progression, this study aims to investigate several established and new composite measures for monitoring disease activity and their potential relation to the biomarker serum neurofilament light chain (NfL) in a clearly defined early RRMS patient cohort with a mild disease course.
Methods: From a total of 301 RRMS patients, a clearly defined subset of 46 patients being treated with a continuous first-line therapy was analysed for loss of no evidence of disease activity (lo-NEDA-3) status and the two confirmed disability accumulation (CDA)-based measures, relapse-associated worsening (RAW) and progression independent of relapse activity (PIRA), up to seven years after treatment initialisation. Kaplan-Meier estimates were used for time-to-event analysis. Additionally, a Cox regression model was used to analyse the effect of NfL levels on outcome measures in this cohort.
Results: In this mildly affected cohort, both lo-NEDA-3 and PIRA frequently occurred over a median observational period of 67.2 months and were observed in 39 (84.8%) and 23 (50.0%) patients, respectively. Additionally, 12 out of 26 PIRA manifestations (46.2%) were observed without a corresponding lo-NEDA-3 status. Jointly, either PIRA or lo-NEDA-3 showed disease activity in all patients followed-up for at least the median duration (67.2 months). Regarding sub-components, radiological progression dominated lo-NEDA-3 and was observed 125 times in the cohort. In contrast, the contribution of each sub-component to PIRA was more balanced. NfL values demonstrated a weak association with the occurrence of RAW; however, no relation was observed for the other disease monitoring measures.
Conclusion: The complementary use of different measures of disease progression helps to illustrate the nuanced representations of disease activity in mildly affected early RRMS patients being treated with continuous first-line therapy.

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P096

Change in gait-related parameters in relapsing-remitting multiple sclerosis patients in relation to clinical measures of progression as anchors

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Introduction: Quantification of gait pattern is an important aspect of evaluating disability (progression) and can provide critical insights within personalized therapy decisions in people with multiple sclerosis (pwMS). Different clinical methods are used to assess progression of the disease. In this context, data acquisition with innovative new sensor-based measurement systems enables an even more targeted gait assessment and sensitive detection of progressive changes in pwMS.
Objective: We analyzed changes in gait-related deficits over a 2-year course in relapsing-remitting pwMS to detect relevant gait parameters that most accurately reflect progression in pwMS in relation to diverse clinical measures of progression as anchors.
Methods: Marker-based gait analyses via the DIERS 4D motion® Lab were performed at a two-year interval on 39 pwMS (mean age: 41.15 ± 9.96, gender: 59% female, median EDSS 2). The patients were asked to walk for 2 minutes on a treadmill at a self-selected speed. Disease progression subgroups were defined by published cut-off values of confirmed disability progression via the Expanded Disability Status Scale (EDSS), the EDSS-plus, 9 Hole Peg Test (9HPT), 25 Foot Walk (T25FWT) and other anchors. Within these subgroups, annual changes in 9 spatiotemporal DIERS parameter trajectories were analyzed by calculating effect sizes. To examine apparent patterns for progression across all anchors, longitudinal trajectories of DIERS parameters were rank-ordered.
Results: A confirmed clinical progression according to EDSS was present in 4 pwMS (10.3%) and 9 pwMS (23.1%) based on the EDSS-plus criteria (10.3% T25FW, 5.1% 9HPT). Within all progression groups, Step Length, Step time and Velocity were part of TOP3-ranked parameters and showed the strongest longitudinal effect sizes of EDSS, EDSS-plus and T25FW based definitions of progression. However, these gait parameters were also most influential in the more stable groups (no confirmed progression) and in the overall cohort, but with lower effect sizes.
Conclusion: Quantitative DIERS parameters could poorly reflect the patterns suggested by clinical disease progression definitions. Our findings underscore the need to focus on multidimensional anchors rather than EDSS-based definitions alone to better capture the disease complexity. More in-depth findings integrating results from additional anchors such as the 2-minute Walk or Multiple Sclerosis Walking Scale (MSWS-12) will be presented.

Disclosure
Katrin Trentzsch, Dirk Schriefer and Maximilian Hartmann have nothing to disclose. Tjalf Ziemssen reports consulting or serving on speaker bureaus for Biogen, Celgene, Roche, Novartis, Celgene, and Merck; Sanofi; research support from Biogen, Novartis, Merck, Sanofi.

P097
Longitudinal clinical and MRI outcomes in relapsing multiple sclerosis patients after short-term ponesimod treatment interruption and re-initiation

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Introduction: Current multiple sclerosis (MS) disease-modifying treatments (DMTs)alterpatients' immune system with varying degrees and speed of reversibility due to different pharmacokinetic and pharmacodynamic profiles. There may beclinical situationssuch as pregnancies, severe infections or live vaccinations where there is a need for fast drug elimination and a fully functioning immune system. For ponesimod, lymphocyte counts return to the normal range in>90% of patientswithin 1 week ofstopping treatment. To further understand the impact of pausing and resuming ponesimod, it is important to evaluate MS disease activity over time following ponesimod treatment interruption and re-initiation.
Objectives: To assess clinical and MRI outcomes in RMS patients at 48 weeks of follow-up after short-term interruption and re-initiation of ponesimod treatment.
Methods: Patients who completed 108 weeks of ponesimod or teriflunomide treatment in the Phase 3 OPTIMUM study and under went an accelerated elimination procedure were eligible to enroll in the open-label extension(OLE)study, where they received ponesimod 20 mg. Of the 567 patientsrandomized toponesimod in the OPTIMUM study,439 (77.4%) entered the OLE and 239 (42.2%) had at least 48 weeks of follow upin OLE. The annualized relapse rate(ARR)and cumulative number of combined unique active lesions (CUALs) following short-term treatment interruption (between core study and OLE) and re-initiation(at start of the OLE) were examined in the239 patients who had been randomized to ponesimod in OPTIMUM and had at least 48 weeks of follow-up in the OLE.
Results: The mean duration of ponesimod treatment interruption (between the end of thecore studyand initiation of the OLE) was 17.6 days (range 13 – 45 days). TheARRat OLE week 48, and considering treatment interruption and re-initiation, was 0.191(95% CI:0.140, 0.261). This was numericallylower than the 2-year ARR of0.234 (95% CI: 0.186, 0.296) with arelative rate reduction (RRR) of18.4% (RRR: 0.816, 95% CI: 0.595, 1.120). At OLE week 48, patientshad1.73CUALs/year (95% CI:1.30, 2.31), which was not statistically significantly different from 1.48 CUALs/year (95% CI: 1.19, 1.82) in the OPTIMUM study.
Conclusions: In this study, based on clinical and imaging outcomes, disease activity at OLE 48 weeks following short-term interruption and re-initiation of ponesimod treatment remained consistent with disease activity observed prior to interruption.

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Kavita Gandhi is an employee of Janssen Pharmaceuticals and may hold stock/stock options of Johnson and Johnson
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Maria Ait-Tihyaty is an employee of Janssen Pharmaceuticals and may hold stock/stock options of Johnson and Johnson
Janice Wong is an employee of Janssen Pharmaceuticals and may hold stock/stock options of Johnson and Johnson
Tatiana Sidorenko is an employee of Janssen Pharmaceuticals and may hold stock/stock options of Johnson and Johnson

P098

Weak grip strength: a harbinger of lower limb agility dysfunction in people with multiple sclerosis having no gait impairment

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Introduction: Weak grip strength predicts morbidity in aging. Whether grip is useful as an indicator of subtle neurological decline in early Multiple Sclerosis (MS) is unknown.
Objective/Aims: 1: To measure grip strength in a large clinic sample of people with MS having no walking impairment (Expanded Disease Severity Scale (EDSS) ⩽ 3.0). 2. To compare measured grip with normative population values, and 3. Determine whether grip predicts performance on a challenging lower limb agility task (bipedal hopping).
Methods: After screening for walking problems, 85 patients performed maximum grip strength test and completed bipedal hopping along an instrumented walkway. Grip strength values were compared to a Canadian normative dataset (Hoffman et al., 2019), creating a percentile rank for age and sex. Lower limb agility was calculated as hop length corrected for height. We used regression modelling to predict the contribution of grip strength when controlling for age and EDSS to lower limb agility.
Results: Nearly 70% of patients were below the 50th percentile for grip strength (n= 59). Age was correlated with percentile grip strength score (r= -.22, p =.04), but not with combined grip strength (p =.06), and neither were related to EDSS (p= .43 and .39, respectively). Longer hop length (corrected for height) was significantly correlated with higher combined grip strength (r= .441, p <.05), but not grip strength percentile rank (p =.133). When controlling for age, and EDSS, weaker grip significantly predicted poorer lower limb agility; shorter hop length (R^2= .264, p< .0001). For every 0.396kg loss of grip strength, there was a 10cm shortening of hop length that was not related to age or sex (β= .396,p< .0001).
Conclusions: Grip strength was a robust indicator of early changes to lower limb agility among people with no apparent MS-related walking impairment. Grip strength is inexpensive, simple to administer, and a potential harbinger of sub-clinical worsening.

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P099

Longitudinal assessment of balance impairment in multiple sclerosis identify patients with silent disease progression

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Background: Since balance maintenance requires several coordinated Central Nervous System functions, it is particularly susceptible to subtle continuous damage occurring in patients with Multiple Sclerosis (MS). Longitudinal balance assessment could help identifying patients with silent progression not evident at clinical examination.
Objectives: To assess balance performance over time in a cohort of MS patients with a Standing Balance Test (SBT).
Methods: 122 MS patients (109 relapsing-remitting, 13 progressive) and 65 healthy controls (HC) underwent SBT and full clinical examination. Patients had a follow-up evaluation after a mean of 12.7 months (SD=5.6). Theta scores (higher values indicating better performance) were derived and corrected for age/sex/height/weight by nuisance regression. Z-score were calculated (scores below 1.5 SD were considered abnormal). A worsening of >=-1 Z-score point was considered clinically meaningful. Disability progression was defined as an Expanded Disability Status Scale (EDSS) >1 increase, if baseline EDSS<5.5 and EDSS>0.5 otherwise.
Results: At baseline, patients had lower theta scores than HC (0.39 *vs* 0.85, p<0.0001) and 27/122 were classified as having balance impairment. Balance-impaired patients had higher EDSS scores than balance-preserved ones (1.9*vs*3.2, p<0.0001). At follow-up, 45/122 patients had a worsening in ΔZ-scores, with 15 (12%) having a clinically meaningful worsening. Although a trend was noted between Δ pyramidal functional-system scores and Δ theta Z-scores (spearman-rho=-0.17, p=0.066), only 6/45

patients with worsening balance had disability progression based on their EDSS scores. Among patients with balance-worsening, only 2/45 experienced a clinical relapse which in one case resulted in increased EDSS score.
Conclusions: Longitudinal assessment with SBT could be a useful tool to early detect "silent" progression in patients with MS and to prompt intervention with a rehabilitation specialist.

Disclosure
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P100
Screening for cognitive impairment in an unselected cohort of patients with MS using BICAMS in outpatient neurology department, Dublin, Ireland

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Introduction: Cognitive impairment (CI) is common in people with multiple sclerosis (pwMS), regardless of disease stage or subtype. While it has been shown to significantly reduce pwMS quality of life, it is typically underreported and may not be recognised by the clinician during their routine consultation. The Brief International Cognitive Assessment for MS (BICAMS) was developed as a short, cognitive assessment tool to help clinicians screen pwMS for CI. It is composed of 3 parts: Symbol Digit Modality Test (SDMT), California Verbal Learning Test (CVLT-II) and the Brief Visuospatial Memory Test (BVMT-R).
Objectives: Our objective was to use BICAMS as a screening tool amongst an unselected cohort of pwMS attending an outpatient clinic to determine the prevalence of CI. We also explored the association with clinical and sociodemographic variables, and CI.
Methods: BICAMS was administered to 238 pwMS who attended the clinic. Age, gender, education, handedness, MS subtype, expanded disability scale (EDSS) and disease duration were recorded. Depression and anxiety were assessed using the Hospital and Anxiety Depression Scale (HADS). Data collected was analysed using IBM SPSS Statistics. Individual test scores were converted to z-scores which are controlled for age, gender, and education. Impairment on individual tests was defined as having a z-score of $\leqslant$ -0.75.
Results: Of the 238 patients, 71% were female; mean age: 45 yrs (12.5); 74% had relapsing remitting MS and 26% had progressive MS with a mean disease duration 12.8 years (8.9). Mean EDSS was 3.0 (2.3). Impairment was seen in 1, 2 or 3 tests in 33%, 23% and 17% respectively. Significant differences in raw scores were seen between those with RRMS v progressive MS on each domain: SDMT 51 (11) v 38 (14), $p<0.001$; CVLT-II 51 (11) v 44 (13), $p<0.001$; BVMT-R 22 (7) v 17 (8), $p<0.001$. No correlation was seen between HADS score and BICAMS scores.
Conclusions: There is evidence of CI in our random patient cohort with 71% of pwMS showing impairment on at least one subtest. Higher prevalence of CI was seen in those with progressive MS. We did not find any correlation between mood and cognitive performance.

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P101
IPAD-based processing speed test CogEval ® as a potential predictor of multiple sclerosis in patients with clinically isolated syndrome

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Introduction: Cognitive impairment in patients with Clinically Isolated Syndrome (CIS) has been associated with a higher risk of conversion to Multiple Sclerosis (CIS-MS) compared to those patients remaining as a CIS (CIS-CIS).
Objectives: Our aim is to study the prognostic value of the iPad®-based application Processing Speed Test (PST) CogEval®in patients with a CIS to predict the accuracy to discriminate a MS.
Methods: Single-center prospective study of patients with a CIS from October 2019 to March 2022. We included patients with a CIS and $\geqslant$1 PST performed within the first 5 years since first symptom. Z scores adjusted by age, sex and level of education were obtained.
Results: Two hundred nineteen patients were included,153 women (69.9%) with a mean ($\pm$SD) age of 37.7($\pm$10.3) years and a mean time from the first symptom to the first PST of 2.7 ($\pm$1.5) years. One hundred ninety patients (86.8%) fulfilled MS criteria (CIS-MS). CIS-MS patients had a higher radiological activity ($p<0.001$) and a higher proportion of IgG oligoclonal bands ($p<0.001$) compared to CIS-CIS patients. CIS-MS patients had a significantly lower Z score (mean [SD] -0.2[$\pm$0,9] in CIS-MS vs 0.4 [$\pm$0,7] in CIS-CIS group, p=0.001) despite a similar EDSS between both groups (mean [SD] 2.0 [$\pm$0,9] vs 1.5 [$\pm$0,6] respectively, p=0.41).
Conclusion (29): iPad-based®PST CogEval®is a simple and easy tool in real-world setting with a potential prognostic value to discriminate CIS patients with higher risk of MS.

Disclosure
Nothing to disclose

P102
Existing claims-based algorithm may overestimate relapses in multiple sclerosis (MS) patients using infusible disease modifying therapies (DMTs) that require steroid premedication

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Introduction: Claim databases lack information on clinical outcomes such as relapses, thus algorithms to estimate MS relapse events were developed.[1,2] These algorithms use MS-related hospitalizations and outpatient steroid prescriptions to identify relapses, which may lead to overestimation, particularly in patients on DMTs that require steroid premedication.[3]
Objective: Assess the strength of a published algorithm[1] and a revised algorithm for correctly identifying relapses in MS patients on intravenous (IV) DMTs requiring steroid premedication: ocrelizumab (OCR) and alemtuzumab (ALM) vs. common therapies that do not: glatiramer acetate, interferon beta, and dimethyl fumarate (BRACE&DMF). Natalizumab (NTZ), an IV monoclonal antibody (mAb) that does not require steroid premedication, was included as a reference.
Methods: This retrospective study used the Truven MarketScan® Commercial & Encounters database with adult MS patients who started OCR, ALM, NTZ, or BRACE&DMF (4/2014-6/2020) with continuous enrollment ⩾24 months before and ⩾12 months after treatment initiation (index date). Relapse was identified via a published algorithm[1] and a revised algorithm that excluded steroid use from the relapse count when given within ±5 days of the infusible DMT. Inverse probability treatment weighting (IPTW) was used to adjust for confounding.
Results: 2,791 patients were included (OCR n=495, ALM n=22, NTZ n=346, BRACE&DMF n=2,274). After IPTW, the observed characteristics (age, sex, region, comorbidities, MS disability level, and pre-index relapses) were balanced across groups. During 12-month post-treatment, using the published algorithm, the proportion of patients with a relapse was 82.4% OCR, 63.4% ALM, and 20.1% NTZ vs. 20.3% BRACE&DMF. With the revised algorithm, the proportion of patients with relapses decreased to 21.7% OCR, 19.0% ALM, and 18.0% NTZ vs. 18.6% BRACE&DMF; resulting in annualized relapse rates (ARR) of 0.34 OCR, 0.24 ALM, and 0.24 NTZ vs. 0.26 BRACE&DMF. Change in relapse rate from the traditional to revised algorithm was most obvious for IV mAbs requiring steroid premedication.
Conclusion: Despite adjusting for steroid use in the revised algorithm, we unexpectedly found similar relapse rates in IV mAbs and BRACE&DMF. This is contrary to clinical trial and practice, suggesting continued overestimation of relapses in IV mAbs due to unmeasured confounding. This algorithm warrants further revision to accurately estimate relapses in the age of mAbs.

Disclosure
Wing Chow, Qiujun (Samantha) Shao, Fei Yang, and Chinmay Deshpande are employees of Novartis Pharmaceuticals Corporation. Mengru Wang is an employee of KMK Consulting, Inc. and works as a consultant to Novartis Pharmaceutical Corporation. Dr. Hersh has received speaking, consulting, and advisory board fees from Genentech, Genzyme, Biogen, Novartis, EMD-Serono, Bristol Myers Squibb, and TG Therapeutics. She has received research support paid to her institution by Biogen, Novartis, Genentech, Patient-Centered Outcomes Research Institute (PCORI) and NIH - NINDS 1U01NS111678-01A1 sub-award. Dr. Conway has received consulting fees from Novartis Pharmaceuticals. He has received speaking fees from Biogen and NeuroLive. He has received research support paid to his institution by Novartis Pharmaceuticals and EMD Serono.

Clinical aspects of MS - Patient reported outcomes

P103
Limitations in different life domains early in the disease course among people with multiple sclerosis in Sweden

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Background: Multiple sclerosis(MS) is associated with heterogeneous symptoms, fatigue being the most common, with considerable negative impact on the lives of People with MS (PwMS).
Objective: To explore self-reported limitations that PwMS experience in different domains of life in relation to symptoms and disease progression.
Methods: A cross-sectional survey was conducted among working-aged PwMS in Sweden including 4052 PwMS who completed the questions on limitations in four life domains (work, family, leisure activities and friends/acquaintances). Multinomial logistic regressions with 95% confidence intervals were performed to ascertain associations.
Results: Of the 4052 PwMS, many reported no limitations in the domains of work (35.7%), family life (38.7%), leisure activities (31.1%) and contact with friends (40.3%). Around a third of the PwMS reported mild limitations on work (37.4%), family life (38.9%), leisure activities (36.8%) and contact with friends (35%). The remaining PwMS reported severe limitations in work (26.8%), family life (22.4%), leisure activities (32.1%) and contact with friends (24.8%). When asked about their most limiting symptom, 49.5% listed fatigue/tiredness. Of PwMS with an expanded disability status scale score (EDSS) zero (26.3%), considerable proportions still reported some form of limitation in the four domains ranging from 39.6% (contact with friends) to 45.7% (leisure activities). Sex, education, area of residence, type of limiting symptom, EDSS and satisfaction with

treatment were associated with limitations in the four life domains, both in the analysis with the whole sample and among PwMS with EDSS zero.
Conclusions: The majority of PwMS reported similar limitations in the work and private domains of life. These limitations appear to occur also early in the disease course (EDSS zero), and where most often associated with invisible symptoms such as fatigue.

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P104

Multiple sclerosis, cognitive impairment and perceived cognitive impairment: factors that drive perception of cognitive impairment differ for self-perception in people with multiple sclerosis and clinicians treating people with multiple sclerosis

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Introduction: Multiple sclerosis can affect people's (PwMS) abilities across a wide range of neurological functions. MS often causes cognitive impairment (CI), fatigue, and depression all of which can influence Quality of Life (QoL). "Self-reported accuracy" in assessing the presence of CI by PwMS has been reported to be sub-optimal. Clinician assessment of CI in PwMS may be suboptimal as well and literature has reported mixed results. Routine screening for the presence of, or change in, CI and factors that may contribute, in PwMS should not be left to "perception" alone when this can be objectively assessed in routine care, as CI can result in unwanted disease related disability.
Objective: To investigate what factors influence self-reported perceived cognitive deficits among patients with Multiple Sclerosis (PwMS) and their clinicians in order to explore what factors drive these perceptions and if they differ between PwMS and clinicians.
Methods: Retrospective review of information obtained prospectively in routine care of PwMS who completed patient reported outcomes (PROs) for fatigue (MFIS), depression (BDI-II) and a Likert scale for quality of life. Physical disability was assessed by the patient's clinician (EDSS). Patient perceived CI by clinicians and PwMS were self-reported along a Likert scale. CI in PwMS was assessed by validated computerized multi-domain cognitive screening battery. Hierarchical regression analyses were performed.
Results: Cohort of PwMS (N=202), 71% female, average age 47.3 +/- 11.3 years. Fatigue ($p < .001$) and cognitive scores ($p < .05$) significantly predicted patient self-perceived cognitive deficits, but not depression ($p = .377$) or physical disability ($p = .213$). Clinician perceived cognitive deficits for PwMS were significantly predicted by multiple factors including cognitive scores ($p < .001$), depression ($p < .001$), physical disability ($p < .05$), age ($p < .05$), as well as self-reported quality of life ($p < .05$). Notably, fatigue did not significantly predict clinician perceived CI in PwMS ($p = .535$).
Conclusion: Factors that impact a PwMS self-reported degree of CI are different than what factors impact the treating clinicians. This variance could adversely influence the decision to screen for CI and potentially miss important disease related impact or change. Early recognition of patient centric treatment needs and or treatment failure is critical to improve care and outcomes.

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P105

Multiple sclerosis, accumulative cognitive impairment and shared decision-making: how the choice is made and what you don't realize about the process

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Introduction: There are multiple disease modifying therapies (DMT) available to choose from to treat people with Multiple Sclerosis (PwMS). Shared decision-making (SDM) is a common approach utilized to guide the choice in this decision making process for patient and clinician. Multiple DMT's vary in route, frequency, efficacy and risks. Cognitive impairment (CI) is common in PwMS and not well recognized by the clinician. Monitoring for CI in PwMS is not common and often insufficient to monitor for CI in multiple cognitive domains (CD). Unrecognized CI across multiple CD might impact the ability of PwMS to participate in an effective SDM process. Increasing CI can affect employment, fall risk, driving and other real world abilities. The Control Preferences Scale (CPS) is the most frequently used patient reported outcome (PRO) to assess individual patient approaches to SDM. Improving treatment outcomes includes an effective discussion and appropriate DMT choice.
Objective: To explore the relationship between CPS with accumulative CD impairment (CDI) in PwMS.
Methods: Retrospective chart review of a PwMS. The following information was collected: Neurotrax cognitive scores (Global, Memory, Executive Function, Visual Spatial, Verbal Function, Attention, Information Processing, Motor Skills, and accumulative cognitive impairment (# CD impaired, #CDI), and CPS.
Results: 735 PwMS, 74.6% female, average age 51.3 ± 11.5 years. 49% PwMS preferred a collaborative approach (CPS:C), 31% prefer an active approach (CPS: A&B), and 15% prefer a passive approach (CPS:D&E). CPS by gender (female): 31.1% (A&B), 53.1% (C), 15.8% (D&E); (male): 35.1% (A&B), 46.5% (C), 18.4% (D&E). PwMS with the highest accumulative CI preferred CPS-A (active) (CDI= 1.44) 4.9% or CPS-E (passive) (CDI= 2.41) 3.9%.Of these CPS groups, 2 or more CDI were noted in CPS: A = 30.6%, B=20.5%, C=24.7%, D=26.9%, E=48.3%; 3 or more CDI: CPS: A=27.8%, B=13.5%, C=17%, D=17%, E=37.9%.
Conclusion: Cognitive impairment in PwMS may reflect an unappreciated problem as it relates to an effective SDM process. 25% of PwMS who choose to share decision making process have 2 or more cognitive domains impaired and those who do not choose to share the decision-making process have an even greater likelihood of accumulative cognitive domains impaired. The path to effective choice of DMT was never more complicated with the ever-expanding risk/benefit issues and un-recognized/under-appreciated accumulative cognitive impairment.

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P106
Capturing qualitative follow up data in a "real-world" study to assess disease modifying therapy use in the multiple sclerosis population before the pandemic and after: an update from the OPTIMISE:MS pharmacovigilance study

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Introduction: Therapeutic disease modifying therapy options in the Multiple Sclerosis population have increased rapidly, but qualitative "real-world" follow up data is limited across many clinical trials being conducted. The OPTIMISE:MS pharmacovigilance study follows patients up for 7 years.
Aims: "Real-world" observational data was collected from 14 participating sites located in the UK and Scotland. Participating study centres aimed to recruit all patients who are able and willing to provide consent to the inclusion criteria of the study. We wanted to determine what proportion of patients had completed follow up visits and had their data entered onto the study database pre and post the COVID-19 pandemic to date.
Methods: OPTIMISE:MS is a "real-world" longitudinal 7 year observational study recruiting 4000 patients with Multiple Sclerosis nationally from the UK and Scotland.All patients enrolled as of 30th April 2022 completed their baseline (n=2507) and at least 1 follow up visit (n=1254) for the study.
Results: 1852 (73%) participants in OPTIMISE:MS are female with age range 18-82 (mean 43.8, SD 10.96) and 671 (27%) participants were male. The majority are of White ethnicity (1970, 78%), with a substantial minority from other ethnic groups. 2346 (94%) have RRMS with a mean time since diagnosis 8.5 years (SD 7.62). The DMT class history at baseline for all patients enrolled onto the study showed that 1130 (45%) were on second generation DMTs when compared to 807 (32%) of patients with no currently taking a DMT. The time (years) since the diagnosis of MS was <5 years in n=1029 (41%) patients. The highest prescribed DMTs documented at the first follow up visit of patients between 2019 and 2022 was Natalizumab (Tysabri) (n=10385) and Dimethyl fumarate (Tecfidera) (n=5406) that was the second highest.When assessing the lowest prescribed DMT for the same time period, Siponimod (n=6) and Interferon beta-1b (Betaferon (n=35) were documented.

Conclusion: The results showed the frequency of follow up visits that had been carried out on the OPTIMISE:MS study for patients recruited to date.The data showed that more work has to be done to ensure that participating sites consistently update the follow up records of their patient cohorts in a timely manner.The OPTIMISE:MS study remained open throughout the pandemic and it was encouraging to see that the DMT prescribing methods for MS patients remained consistently high before, during and after the pandemic.

Disclosure
Nothing to disclose

P107
Baseline characteristics of the SDMT PRO population reveal early cognitive changes in multiple sclerosis patients

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Introduction: As cognitive changes may occur early in multiple sclerosis (MS) regular assessment of the cognitive status is recommended (Kalb et.al. 2018). The Symbol Digit Modalities Test (SDMT) is a validated, sensitive test to detect changes in cognitive processing speed and working memory. A clinically meaningful change is defined as a 4-points or 8-points difference in SDMT raw score (Weinstock et.al 2021) or a 10% difference with respect to pretest values (Benedict et.al. 2017). SDMT in combination with the Brief Visuospatial Memory Test Revised (BVMT-R) proved superior to the single application of the SDMT and showed the best agreement with the overall BICAMS score (Bätge et al. 2019). Whether and to which extent a clinically meaningful change in SDMT and BVMT-R translate into a relevant change in the quality of life or in psychosocial functioning of the patient has not been thoroughly investigated so far.
Aim: SDMT PRO aims to evaluate the relevance of SDMT and BVMT-R changes on everyday life issues of patients with relapsing (RRMS) and secondary progressive MS (SPMS).
Methods: Approx. 130 ambulatory RRMS/SPMS patients have been enrolled in the project to date, recruitment will close in June 2022. Patients` neuropsychological performance on SDMT and BVMT-R will be assessed at baseline, at 12 and 24 months follow-up, along with behavioral data collected from digitized Patient-reported outcomes (PROs), e.g. the Fatigue Scale for Motor and Cognitive Functions (FSMC) by the PatientConceptApp. In addition, each of the PRO dimensions (vocational status, fatigue, mood, cognition) will be monitored throughout the study via the app by means of short ratings based on Visual Analog Scales (VAS). Patients will be stratified in subgroups according to cognitive test performance over time.
Results: Baseline characteristics from the whole SDMT-PRO population will be shown as well as 12 months follow-up data for approx. 30 patients. First interim analysis from baseline characteristics (Penner et. al 2021, DGN 2021) showed that approx. 50% of the enrolled population had clinically significant reduced or borderline SDMT values (47%), while most patients (80.4%) had normal BVMT-R values. Additionally, patients had strong disease burden based on FSMC values.
Conclusions: Continuous evaluation of SDMT changes as well as monitoring of domains relevant for daily living and psychosocial functioning can reveal the impact MS has on the daily life on patients.

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Yekta Kus and **Veronika Eva Winkelmann** are employees of Novartis Pharma GmbH.

P108
Improvements in quality of life over 2 years in patients treated with cladribine tablets for highly active relapsing multiple sclerosis: Final analysis of CLARIFY-MS

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Introduction: It is well recognised that multiple sclerosis (MS) is associated with negative effects on many aspects of patients' quality of life (including physical and mental health) that may not be adequately treated.
Objectives: The CLARIFY-MS study (NCT03369665) was designed to assess health-related quality of life (HRQoL) through the Multiple Sclerosis Quality of Life-54 (MSQoL-54) questionnaire in highly-active relapsing MS (RMS) patients treated with cladribine tablets (CladT) for 2 years.
Aims: To assess changes in the physical and mental health composite scores of the MSQoL-54 questionnaire from Baseline to Month 24.
Methods: Patients with highly active RMS were assigned to receive CladT 3.5mg/kg cumulative dose over 2 years recruited as per the EU label. Changes in MSQoL-54 scores were analysed using a repeated mixed-effects linear model adjusting for baseline MSQoL-54 and Expanded Disability Status Scale scores, age and within-country correlation. Subgroup analyses were carried out with stratification for previous treatment (treatment naïve [n=120] or prior disease-modifying therapy [n=313]). Treatment-emergent adverse events (TEAEs) were also assessed.
Results: In the 482 patients treated with CladT, mean age was 37.4 years and 70.1% were female; 433 patients provided MSQoL-54 data at Month 24. Statistically significant ($p<0.0001$) improvements from baseline were observed for MSQoL-54 physical and mental health composite scores with mean changes of 4.86 (95% confidence interval [CI] 3.18, 6.53) and 4.80 (95% CI 3.13, 6.46), respectively. Changes in MSQoL-54 scores were consistent across naïve and treatment-experienced subgroups. At least one TEAE was experienced by 376 patients (78.0%); most commonly headache, lymphopenia, and nasopharyngitis. TEAEs as cause of treatment interruption occurred in 9 patients (1.9%), and severe or opportunistic infections were rare and in line with prior data. Most post-baseline lymphopenia events were Grade 1–2 (19.9% Grade 1, 42.1% Grade 2); 19.7% of patients had Grade 3 lymphopenia, and no Grade 4 lymphopenia was observed.
Conclusions: Treatment with CladT significantly improved MSQoL-54 physical and mental health composite scores over 2 years. No new safety concerns impacting on the established benefit:risk profile of CladT in patients with highly active RMS emerged.

Disclosure

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Author disclosures:
AS has served on advisory boards for Merck, Novartis, and Sanofi, and has been invited to speak on behalf of Almirall, Biogen, Excemed, Merck, and Teva.
XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with AbbVie, Actelion (Janssen/J&J), Alexion, Bayer, Biogen, Celgene (BMS), EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA), Immunic, Janssen, MedDay, Merck, Mylan, Nervgen, Novartis, Roche, Sanofi, Teva, TG Therapeutics, Excemed, MSIF, and NMSS.
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BB has received consultancy fees, speaker fees, research grants (non-personal), or honoraria from Biogen, Celgene (BMS), Merck, Novartis, Roche, and Sanofi.
DL has participated in speaker bureau for Almirall, Bayer, Biogen, Merck, Novartis, Roche, Sanofi, and Teva; has received consultancy fees from Bayer, Biogen, Merck, Novartis, and Teva; and has received research grants from Bayer, Biogen, Merck, and Novartis.
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FPa has served on scientific Advisory Boards for Almirall, Bayer, Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva; he also received speaker honoraria from the same companies and non-personal research grants for his department from Biogen, Merck, Novartis, and Sanofi.
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NA, **AS**, **AN**, and **BK** are employees of Merck Healthcare KGaA, Darmstadt, Germany.

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A large cohort study evaluating patient reported perspectives on disease burden and early signs of progression in multiple sclerosis in Germany (MSPerspectives)

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Background: Secondary progressive multiple sclerosis (SPMS) is usually diagnosed retrospectively and the transition period is associated with a considerable period of diagnostic uncertainty. Therefore it is imperative to educate and raise patient awareness to recognize, track and communicate subtle signs of progression early on. The data collection presented (MSPerspectives) aims to comprehensively capture the patient perspective on the individual disease course.
Methods: MS Perspectives is a cross-sectional online survey conducted among adult MS patients in Germany between December 2021 and February 2022. The questionnaire included 36 items on sociodemographic and clinical characteristics as well as pharmacological and non-pharmacological treatment. The survey was designed to collect data on patients' self-assessment of MS symptoms, relapse-independent progression, and MS impact on everyday life.
Results: Of 4,555 MS patients who completed the survey, 69.2% reported to have relapsing-remitting MS (RRMS) and 15.1% SPMS. Mean EDSS (when reported) was 2.6 in the RRMS population, 5.4 in the SPMS population and relapse activity in the past 6 months, was reported by 26.9% of the total population, 25.6% of RRMS patients, and 35.9% of SPMS patients. Relapse-independent worsening of symptoms was noted by 88.9% of RRMS patients with marked to severe and in 61,8% with no or mild to moderate disability. As most bothersome symptom, RRMS patients with marked to severe disability mentioned problems with walking (32.1%), whereas fatigue and cognitive problems were reported in RRMS patients with no or mild to moderate disability.
Conclusion: MS Perspectives gives an important insight in MS symptoms and severity as well as treatment utilization in a large-scale cohort. Regarding disease progression especially in patients still classified as RRMS, efforts should be made to increase awareness for SPMS transition in clinical practice, also with focus on less visible signs of progression.

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Monika Christ declares no conflict of interest.
Katrin Schuh is employee of Novartis Pharma GmbH.

P110
Uncovering challenges in achieving health equity in multiple sclerosis care: a deep-dive into the experiences and perspectives of patients and their care teams in general neurology and MS specialty clinics

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Background: Growing evidence suggests that Black patients with MS experience a more aggressive disease course and worse clinical outcomes than White patients. While multi-factorial, health inequities driven by discordances in patient-provider perceptions may impact MS care quality and outcomes.
Objectives: To assess patients' and providers' perceptions of: treatment goals and challenges; shared decision-making practices; and barriers to optimal care.
Aims: Evaluate alignment of patients' and providers' approach to MS care among diverse populations in general neurology and MS specialty clinics.
Methods: Surveys were administered to MS providers (n=55) and MS patients (n=27 White; n=33 Black AA) at general neurology clinics and MS providers (n=73) and MS patients (n=71 White; n=69 Black) at 4 large MS clinics.
Results: Patients surveyed were predominantly female (48% Black patients; 39% White patients) with a mean age of 42 years (Black) and 51 years (White). In general neurology clinics, discordances in patients' and providers' treatment goals were observed, with the top goals being: preventing relapses (Black patients 41% vs White patients 41% vs providers 17%); improving quality of life (40% vs 26% vs 54%); and controlling symptoms (37% vs 44% vs 50%). Providers reported their patients' top challenge was managing symptoms (70%); however, patients reported a broader challenges, including choosing a therapy (Black patients 34% vs White patients 37%), managing symptoms (29% vs 33%), following lifestyle recommendations (27% vs 22%), being able to work (32% vs 19%), and financial concerns (29% vs 37%). Factors important to treatment decisions were preventing symptoms/disability (88% vs 61% vs 87%), quality of life (64% vs 39% vs 24%), and risks/side effects (33% vs 36% vs 54%). Black patients reported having tried fewer number therapies for MS compared to White patients (⩽ 2 therapies in 66% Black vs 39% White). In comparing patient perceptions of care in the general neurology setting to MS clinics, Black patients in both settings reported that they would like to discuss treatment expectations and long-term outcomes with their providers and were more likely to report discrimination because of race or ethnicity in healthcare settings is a barrier to care.
Conclusions: This data highlights critical opportunities to improve care quality through aligning patient and provider goals, improving shared-decision making, and ensuring health equity.

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Evaluation of paramagnetic rim lesions as a marker of disability

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Background: In multiple sclerosis (MS) brain lesions with a paramagneticrim(PRL) detected by brain magnetic resonance imaging (MRi) are considered a potential biomarker of chronic inflammatory active lesions and presence of>4 PRL/ patient seems to correlate with disability accumulation. In this study this correlation was evaluated in a large cohort of patients.
Methods: MS patients under treatment and with disease activity (n=119) were included (RR, n= 99; SP, n= 20). Each of them received one conventional MRi scan with3D-EPI susceptibility weighted image (SWI) acquired with a 3T scanner for the detection of PRLs. MRi data were compared with the clinical characteristics of the patients by descriptive and multivariate analysis. Data were expressed as medians and ranges.
Results: Overall, the patients with PRL were 73/119 (61,3%), PRL number/patient = 3,3 (1-18), the RR 57/99 (57.6%) PRL number= 3,2 (2-18), the SP 16/20 (80%, p<0,05), PRL number = 3,5 (1-10). EDSS= 3.5 (0.0-8.5),disease duration 14,1 years (0-40), previous year ARR 0.11 (0-1), age 48,6 (23-69).Bivariate analysis between PRL presence and baseline clinical and demographic parameters showed association with EDSS that was confirmed by multivariate analysis indicating independently association, but not with other clinical/demographic characteristics as age ARR or disease duration. In addition, multiple linear regression analysis showed high correlation between EDSS and PRL number (r= 0,98; p= 0,001) in the RR patients, but not in the SP patients.
Conclusions: In RRMS, presence of PRLs correlates with disability.Noteworthy one single PRL seems sufficient to increase high EDSS development risk. Also of note is that disability - usually most strictly associated with spinal cord lesions, showed strong correlation with a disease marker located in the brain as PRLs. No correlation instead was observed at the higher EDSS values observed in the SP patients despite a higher PRL number/patient in these patients, probably because of a ceiling effect.

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Beyond clinical factors: the role of social support as a positive environmental factor in reducing work-related difficulties

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Introduction: Persons with Multiple Sclerosis (PwMS) report high levels of unemployment. Perceived social support (PSS) has been proposed as an environmental factor that can mitigate work-related difficulties but has been poorly studied.
Objectives: to study differences in PSS dimensions among three work status groups: Work-Stable, Work-Challenged and Work-Disabled and to analyse the influence of PSS dimensions in missed days, harassment and cognitive and physical work accommodations.
Aims: To explore if PSS is a positive environmental factor in mitigating work-related difficulties.
Methods: 89 PwMS (RRMS 93.3%; PPMS 5.6%; SPMS 1.1%) were included. 60.00% female, mean age: 39.61±10.13 years; education: 13.63±2.84 years; disability (EDSS): 2.51±1.85; disease evolution: 10.10±7.40 years. Measuring instruments: PSS: MOS (Medical Outcomes Study Social Support Survey); Clinical Variables: EDSS, Beck Depression Inventory-II; Employment: Argentine Adaptation of the Buffalo Vocational Monitoring Survey. PSS dimensions include the size of the social network of friends (MOSFriends) and family (MOSFamily) and three types of PSS: emotional/informational, affective and instrumental support.
Results: 44 PwMS were included in the Work-Stable group, 18 in Work-Challenged, and 27 in Work-Disabled. Two generalized linear mixed models (Poisson distribution) were built to test group

differences in MOSfamily and MOSfriends. Deviance difference with a corresponding null model was not significant for MOSfamily (p=0.86), but significant for MOSfriends (χ^2 (2)= 8.74, p<.05); Tukey-corrected contrasts showed a significant difference between Work-Stable and Work-Challenged (1.78, 95% IC[1.06, 3.01], p<.05). Additionally, Kruskal-Wallis tests followed by Dunns's post hoc analysis indicated differences in favour of Work-Stable compared to Work-challenged and Work-Disable on total PSS score (p=0.00 and p=0.00, respectively) and emotional/informational support (p=0.03 and p=0.00, respectively). Also, total PSS score reduces the probability of experienced harassment (OR=0.94, 95% CI [0.90, 0.99], p<.05), MOSFamily increased the amount of cognitive work accommodations (β=0.07, p<.05) and MOSFriends decreased the probability of missed days (OR=0.59, 95% CI [0.37, 0.94], p<.05).
Conclusion: Work-Challenged group experienced a statistically significant decline in PSS. Social network size, total PSS score and emotional/informational support may be relevant for reducing work difficulties.

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P113
Enhancing information extraction from patient reported outcomes: the impact of COVID-19 on people with multiple sclerosis during the UK pandemic

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Introduction: Online registries enable home-based, cost-effective and long-term follow up. The benefits were highlighted during the pandemic where lockdowns limited engagement with health professionals. The UK MS Register has been collecting patient reported outcomes (PROs) over 11 years. PROs consist of a number of questions summed to form a total, however, each question has a scale and addresses a particular problem.
Objectives/Aims: We investigated the responses to individual questions of the Multiple Sclerosis Impact Scale (MSIS-29) and the Hospital Anxiety and Depression Scale (HADS) through a series of lockdowns throughout the evolving crisis.
Methods: We studied 5 timepoints (March 2019, September 2019, March 2020, September 2020, March 2021) spanning the pandemic. ~1000 patients completed all timepoints. We studied how the responses to each questionnaire item changed, evaluating the %patients who reported an increased, decreased or stable rating of each item over each 6-months window (e.g. March-September 2019). We then quantified the change in %patients across windows. Significance was evaluated using permutation testing.
Results: >50% patients stayed stable across all questionnaire items over a period of 6 months and the remaining patients either got better or worse. This fluctuating behaviour is not unexpected in MS. The change in %patients reporting an increased, decreased and stable item rating over 6-months periods did not change significantly for most items. Notably, the items where a significant change was observed, could be directly related to Covid-19 given the nature of the question. These included "feeling stuck at home", "having to cut down time spent on work" and "feeling limited in your social and leisure activities" for MSIS-29 and "feeling frightened something awful is about to happen", "being able to see the funny side of things" and "losing interest in your personal appearance" for HADS.
Conclusions: PROs capture disease specific elements, including MS patients variability and fluctuating symptoms, but are also sensitive to external factors such as the social context. When considering the questionnaires' total scores this information can be lost. Detailed item-level analyses can help disentangle the causes behind observed trends and the relations between disease-related and external factors (e.g. covid in this specific case) adding to the relevance of PROs in monitoring disease long-term.

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]Nicholas has received compensation for advisory boards with Roche, Biogen and Novartis.

Clinical aspects of MS - Economic burden

P114
Working life of people with multiple sclerosis during the COVID-19 pandemic: a cross-sectional survey of working-aged people with multiple sclerosis in Sweden

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Background: The Covid-19 pandemic has led to vast changes in working life and conditions in which we work. These changes may affect people with multiple sclerosis (MS) differently.

Aim: To describe the work participation of people with MS during the Covid-19 pandemic and the consequences of the pandemic on their working lives.
Methods: A web-based survey was conducted in summer 2021 to investigate various aspects of life among people with MS in Sweden, including work and impacts of the pandemic. All individuals aged 20-50 listed in the Swedish MS registry were invited. Individual-level sociodemographic and clinical data were linked from nationwide registers. Differences in the responses by sex, education level (university, yes or no), and type of work (office or manual) were tested with chi^2-tests.
Results: Over 8500 adults with MS were invited and 4412 (52%) responded. The 4164 without full-time disability pension were included, with a mean age of 40.3 and 9.2 years since diagnosis. Overall, 2731 reported no impact on their work situation by the pandemic. Among the 3571 employed or self-employed, 3.2% reported less to do and 9.5% more to do due to the pandemic. Similar proportions reported no impact on work by sex (65.8% v 65.2%, p-value 0.690), but women more frequently stated they had more to do (8.7% v 6.9%, p-value: 0.058). No impact on work was more often reported among those with university education (68.2% v 61.3%, p-value $<$0.001) and fewer reported more to do than those without university education (6.3% v 9.4%, p-value $<$0.001). Fewer with university education were furloughed (Currently: 0.5% v 1.6%, p-value 0.001. Earlier: 5.6% v 6.7%, p-value 0.028). They also pursued further studies to a higher extent (2.3% v 1.4%, p-value 0.028). Office workers reported no impact on work to a higher extent than manual workers (72.4% v 63.6%, p-value $<$0.001), despite more stating they had more to do to (9.4% v 7.1%, p-value 0.023). Current furlough was less common among office workers (0.6% v 1.4%, p-value 0.026), with no differences earlier (6.2% v 6.0%, p-value 0.779). Fewer office workers pursued studies (0.8% v 2.9%, p-value $<$0.001).
Conclusions: Many people with MS reported that the pandemic did not affect their work situation. However, the consequences reported differed among them. Further knowledge of which factors promoted or hindered their work lives during the pandemic is needed to support long-term work participation.

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Clinical aspects of MS - Neuro-ophthalmology

P115
Long-term visual outcomes and underlying structural correlates in relapse-onset multiple sclerosis

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Introduction: Despite evidence for good long-term high-contrast visual acuity (HCVA) outcomes after a first attack of optic neuritis (ON), the colour and low-contrast visual acuity (LCVA) outcomes remain unknown. Colour vision correlates with disability and neuroaxonal loss in MS independent of ON status, whilst LCVA correlates with EDSS, MS functional composite and is more sensitive at detecting prior ON.
Objectives: This study explores long-term visual outcomes following clinically isolated syndrome (CIS) with reference to ON status, disease phenotype at follow-up, and OCT measures.
Methods: This is an OCT cross-sectional sub-study of a 15-year longitudinal study of 94 CIS patients. At 15 years, patients were assessed for conversion to MS and for visual function (Farnsworth-Munsell 100 Hue test, LCVA and LogMAR HCVA). All patients underwent optical coherence tomography (OCT). Linear mixed models adjusted for gender and age were used to explore the effects of ON status and MS phenotypes on long-term visual outcomes. We also explored associations with OCT parameters (macular ganglion cell inner plexiform layer mGCIPL and peripapillary retinal nerve fibre layer pRNFL).
Results: The cohort had median EDSS of 1.75 (IQR 1.5-2.9), 81 (86.2%) had optic neuritis and 76 (80.9%) developed MS (67% RRMS, 13.9% SPMS). Eyes with prior ON had worse Farnsworth Munsell (FM) error (+46.1 units (SE[9.1]), P$<$0.001), Sloan 2.5% (-9.2 letters[1.15], P$<$0.001), Sloan 1.25% (-7.98 letters [0.92], P$<$0.001) and logMAR(+0.08 units[0.016], P$<$0.001) than non-ON eyes.
For all eyes, colour vision showed differences between MS phenotypes: 1) RRMS patients were worse than CIS (FM error -45.2[18.8], p=0.018), 2) SPMS worse than CIS (FM error -74.5[25.2], p=0.004).
For OCT, for every 1um reduction in mGCIPL and pRNFL thickness there was an increase in FM error by 1.93 and 1.62 points respectively (p=0.001 and 0.0002), a reduction in Sloan 2.5% by 0.30 and 0.21 letters respectively (p= 0.001 and p=0.0003), a reduction in the Sloan 1.25% by 0.22 and 0.17 letters respectively (p=0.001 and 0.0008) and an increase in LogMAR by 0.0025 and 0.0019 respectively (p=0.0007 and 0.011).
Conclusions: At 15 years` after CIS, there are significant reductions in colour vision, LCVA and HCVA in ON eyes compared with non-ON eyes. Colour vision can discriminate between CIS and MS converters (RRMS and SPMS). Worse vision is associated with thinner retinal mGCIPL and pRNFL.

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Clinical aspects of MS - Comorbidity

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Anti- CD20 agents are associated with higher incidence and severity of breakthrough COVID-19 infections in vaccinated people with multiple sclerosis - an observational study by the New York Covid-19 Neuro-Immunology Consortium (NYCNIC)

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Background: SARS-CoV-2 influenced all aspects of healthcare and will do so in the future. Early pre-vaccination studies, including our first NYCNIC cohort, demonstrated favorable COVID-19 outcomes in people with MS, though anti-CD20 therapies were associated with increased hospitalization. While SARS-CoV-2 vaccines reduce incidence and severity of infections in the general population, anti-CD20 and S1P modulating agents blunt humoral vaccination response. T cell responses are preserved in anti-CD20-treated-patients, suggesting at least partially intact vaccine-mediated protection. Therefore, data on COVID-19 incidence and severity in vaccinated MS patients is necessary.
Objectives: To identify risk factors of severity of breakthrough COVID-19 infection in vaccinated MS patients before and during the Omicron wave.
Aims: To characterize COVID -19 infection in vaccinated MS patients.
Methods: Demographics, MS, clinical variables (time from last vaccination to infection, vaccine type, booster receipt, antibody presence, ambulatory status, comorbidities) and COVID-19 outcomes were collected on vaccinated MS patients followed at 5 MS Centers through January 31st, 2022. Infections were labeled as "pre-Omicron (prior to Dec 1st 2021) and "During Omicron". Infection severity was measured by a 4-point ordinal scale (home care, hospitalization, ICU, death). Univariate and multivariate regression models were used to assess risk factors for hospitalization.
Results: Our cohort included 209 patients with 211 breakthrough infections (45 pre and 166 during Omicron) with median age 42 (range 19-78), 71% female, 65% Caucasian. Anti-CD20 agents were used by 67% of patients pre- and 62% during Omicron, substantially higher than in first (pre-vaccination) NYCNIC cohort (35%).
In a multivariate model including the entire cohort, adjusting for age, use of anti-CD20 or S1P agents during infection increased risk of hospitalization or worse (p= 0.0454, OR 3.815, 95% CI: 1.028-14.161). In a multivariate model including only patients during the Omicron wave, adjusting for comorbidity, use of anti-CD20 therapies during vaccination increased risk of hospitalization or worse (p=0.0462, OR 3.565, 95% CI: 1.022-12.436).
Conclusions: Anti-CD20 and S1P modulating agents were associated with higher severity of COVID-19 infections in vaccinated MS patients. Compared to the first NYCNIC cohort, use of anti-CD20 was more prevalent, suggesting potential negative impact on vaccine efficacy.

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Polypharmacy and multiple sclerosis: a population-based study

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Introduction: Little is known about polypharmacy in people with multiple sclerosis (MS).
Objectives: To estimate polypharmacy prevalence in a population-based MS cohort and compare persons with versus without polypharmacy.
Methods: Using linked administrative and pharmacy data from British Columbia, Canada, we estimated polypharmacy prevalence, defined as the concurrent exposure to ⩾5 medications for >30 consecutive days, in MS individuals in 2017. Characteristics of persons with/without polypharmacy were compared using logistic regression, with age, sex, comorbidity and socioeconomic-status quintile (SES-Q) adjusted odds ratios (aORs) and 95%CIs reported. The number of polypharmacy-days, the most common medication classes contributing to polypharmacy, and hyper-polypharmacy prevalence (⩾10 medications) were described.
Results: Of 14,227 included MS individuals (75% were women), mean age was 55.4 (SD:13.2) years and 28% (n=3,995) met criteria for polypharmacy in 2017 (median polypharmacy-days=273 [IQR:120─345]). Odds of polypharmacy were higher for women (aOR=1.14; 95%CI:1.04─1.25), older individuals (aORs 50-64-years=2.04; 95%CI:1.84─2.26; ⩾65-years=3.26; 95%CI:2.92─3.63 versus <50-years), and for those with more comorbidities (e.g., ⩾3 versus none, aOR=6.03; 95%CI:5.05─7.22) and lower SES (e.g., most [SES-Q1] versus least deprived [SES-Q5], aOR=1.64; 95%CI:1.44─1.86). Medication classes most commonly contributing to polypharmacy were: antidepressants (66% of polypharmacy-days), antiepileptics (47%), and peptic ulcer drugs (41%). Antidepressants were most frequently co-prescribed with antiepileptics (34% of polypharmacy-days), and peptic ulcer drugs (27%). Five percent of persons (716/14,227) experienced hyper-polypharmacy.
Conclusion: Over 1 in 4 MS persons met the criteria for polypharmacy. Antidepressants, antiepileptics, and peptic ulcer drugs each contributed to >40% of polypharmacy-days. The odds of polypharmacy were higher for women, older persons, and those with more comorbidities, but lower SES.

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COVID-19 in multiple sclerosis: update from the nation-wide Austrian registry

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Background: The COVID-19 pandemic continues to challenge neurologists in counselling patients with multiple sclerosis (pwMS) regarding SARS-CoV-2,disease-modifying treatment (DMT) and vaccination.
Objective: To characterize and describe predictors ofCOVID-19 outcomein pwMS in a nationwide population-based study.
Methods: We included pwMS with a PCR-confirmed diagnosis of COVID-19 established between January 1st, 2020 and December 31st, 2021. COVID-19 course was classified as either mild, severe or fatal. Impact of DMT, specifically antiCD20 monoclonal antibodies (ocrelizumab or rituximab), and vaccinationon COVID-19 outcome was determined by multivariable models adjusted for a-priori-risk (determined by a cumulative risk score comprising age and comorbidities).
Results: Of 228 pwMS with COVID-19 (mean age 43.0 years [SD 12.6], 72.4% female, median EDSS 1.5 [range 0-8.5], 73.1% on DMT [15% on antiCD20]), 90.3% had a mild course and 9.7% a severe course with 3.1% dying from COVID-19.
A-priori-risk robustly predicted COVID-19 severity ($R^2$0.714; p<0.001). Adjusting for a-priori-risk, antiCD20 treatment was associated with increased COVID-19 severity (odds ratio [OR] 3.1; 95% CI: 1.2-11.8; change in$R^2$0.092;p=0.002), but exposure to any other DMT was not. In the registry, 27 patients were fully vaccinated (21 BioNtech-Pfizer, 3 Moderna, 3 Astra-Zeneca; 21 on DMT, 4 on antiCD20) withSARS-CoV-2infection occurring after a median 4 months from vaccination (range 1-9). COVID-19 course was mild in 100% of vaccinated pwMS compared to only 86% in the unvaccinated group.
Conclusions: In a population-based MS cohort, COVID-19 course is primarily predicted byage and comorbidities (explaining about 70% of variance). AntiCD20 treatment is associated with a moderately increased risk, while reassuringly vaccination provides protection from severeCOVID-19. All pwMS should be vaccinated and DMT decisions should then be focused on treating MS rather than the pandemic.

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The 'Coronavirus disease of 2019' is associated with disability worsening in patients with multiple sclerosis

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Introduction: The 'coronavirus disease of 2019' (COVID-19) is an acute infection caused by the novel 'severe acute respiratory syndrome coronavirus-2' which has evolved into an ongoing pandemic with more than six million case fatalities to date. Evidence from large-scale observational studies has consistently shown that simply having MS does not make affected subjects more susceptible to contract COVID-19 nor to become severely ill from the infection, as compared to the general population. Risk factors are similar in both settings and include older age, male gender, cardiovascular comorbidities, African-American ethnicity, progressive disease and B-cell depleting agents. However, the reverse relationship – i.e., the impact of COVID-19 on clinical disability related to MS – remains less well described.
Objectives: To explore whether COVID-19 is associated with accelerated disability worsening in patients with MS.
Methods: Since March 2020, demographics and COVID-19 severity (categorized as ambulatory, hospitalized, death) of patients with MS have been collected at the Belgian National MS Center in Melsbroek in case of COVID-19 diagnosis (i.e., positive polymerase chain reaction test). On February 28, 2022, this database was locked and consisted of 234 unique cases. Clinical disability measures – including Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk Test, 9-Hole Peg Test and Symbol Digit Modalities Test scores – were available from a larger local database, obtained during routine medical follow-up. For each of these parameters, the first two assessments before COVID-19 diagnosis (labelled T0 and T1, respectively; T1 is the closest to COVID-19 diagnosis), and the first thereafter (labelled T2), were retrieved for every COVID-19 case.

Results: Mortality and hospitalisation rate in this cohort was 5/234 (2.1%) and 37/234 (15.8%), respectively. Among the survivors with complete EDSS data (N = 139), mean annualized EDSS score changes between T1 and T2 (i.e., including the COVID-19 infection) were significantly increased, as compared with the respective changes between T0 and T1 (i.e., not including the COVID-19 infection) (0.09 versus 0.36, p = 0.008). Similar effects were not found for the other clinical outcome measures.
Conclusions: COVID-19 infection is associated with global disability worsening in patients with MS. Our findings highlight the importance of preventive measures against COVID-19 spreading within this population.

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P120
Polygenicity of comorbid depression in multiple sclerosis

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Introduction: Persons with multiple sclerosis (PwMS) and depression experience increased disability progression and mortality. Identification of individuals with a high risk for depression may facilitate earlier detection or treatment, which may be accomplished using polygenic scores (PGS). Previous polygenic studies of depression considered depression as a primary disorder, not a comorbidity and thus findings may not translate for PwMS. BMI is a known causal risk factor for both MS and depression and its association may highlight phenotype differences in depression.
Aims: We aimed to improve the understanding of comorbid depression in PwMS by investigating PGS.
Methods: We used samples from three countries/sources: Canada, UK Biobank (UKB), and USA (CombiRx MS clinical trial). Individuals were grouped into cases (PwMS-depression) and compared to 3 control groups: PwMS-no depression, major depressive disorder (MDD)-no immune disease, and healthy persons. We employed various depression definitions including lifetime DSM-IV diagnoses, self-reported diagnoses, and depressive symptoms (PHQ-9). We generated PGS for MDD and BMI and tested the association with five depression definitions in PwMS using regression.
Results: We included individuals of European genetic ancestry: N=370 (Canada, 213 MS), 96,676 (UKB: 1,390 MS), and 602 (USA, all MS). Age, sex, education, income, and smoking status were similar across the three samples. Meta-analyses of the three samples revealed, as expected, PwMS-depression had a higher cumulative MDD genetic burden compared to both PwMS-no depression (5 depression definitions OR: 1.34-1.42, $P<0.001$) and healthy controls (OR: 1.54, $P<0.001$). MDD PGS did not differ between PwMS-depression and those with MDD-no immune disease (P=0.5). BMI PGS was not associated with PwMS-depression compared to any controls. Sex-stratification of the PwMS-depression vs. PwMS-no depression analyses revealed females (OR females: 1.29-1.60, $P<0.001$) had estimates like the unstratified, whereas for males with MS, findings were no longer significant (OR males: 1.04-1.50, P=0.5).
Conclusions: Higher MDD genetic burden was associated with ~30-40% increased odds of depression in PwMS, irrespective of the depression definition, compared to both PwMS-no depression and healthy controls. PwMS and comorbid depression had a similar MDD genetic burden compared to MDD-no immune disease.

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When to screen for osteoporosis in multiple sclerosis patients? A new risk score

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Introduction: Due to the demographic development and improved treatment options, the role of comorbidities is of increasing importance in the medical care of patients with MS (pwMS). A higher risk of osteoporosis is well known in chronic autoimmune diseases, and is also described in MS. While there

are several screening indications in the elderly or in patients with rheumatoid arthritis, there are no generally accepted recommendations when to perform bone mineral testing in pwMS under the age of 65 years.

Objectives/Aims: We aimed to determine risk factors of osteoporosis in pwMS and to develop a risk score which can be applied in daily routine.

Methods: Densitometry (hip and lumbar spine) was performed in 159 pwMS and 81 age- and sex-matched healthy controls (HC) with age ⩽65 years. Osteoporosis was defined according to WHO criteria as a bone density of 2.5 SD or more below the mean of young adults. Risk factors were identified by multivariate regression analysis.

Results: Osteoporosis occurred more frequently in postmenopausal pwMS and male pwMS as compared to HC. Besides age, sex, menopausal status in females, body-mass-index (BMI) and smoking, a higher degree of disability - as assessed by the EDSS - was identified as MS specific risk factor, whereas the cumulative steroid dose was not associated with osteoporosis risk. Based on these risk factors, we developed an MS-specific risk score which allows to determine the individual probability of osteoporosis.

Conclusion: This risk score allows individual screening recommendation for pwMS and, subsequently, early prevention of osteoporosis, probably reduction of fractures and morbidity.

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Clinical aspects of MS - Digital health and global networks

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Remote assessment of the impact of lockdown measures on mental health in multiple sclerosis patients

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Background: Post-traumatic stress disorder (PTSD) has been reported in up to 15% ofgeneral population during and after the first wave of the COVID-19 pandemic. The pandemic has acted as a catalyst for the application of telemedicine in neurology.

Objectives: to evaluate the presence of PTSD symptoms as effect of the lockdown measures in people with MS (PwMS) using an e-health application specifically built for remote management of PwMS, SMcare2.0® application.

Methods: Between March 4, 2020 and July 5, 2020 (T0) PwMS who were using (n=290) the app were asked to fill in the Impact of Event Scale - Revised (IES-R) questionnaire to evaluate the presence of PTSD symptoms. The IES-R has 3 subscales: intrusion, hyperarousal, avoidance. The total IES-R score ranges from 0 to 88. A cut-off value of 33 of the total score was used to define the presence of PTSD symptoms (PTSD+). Only those PwMS who filled-in the questionnaire the first time were asked to answer again it when the lockdown measures were abolished (T1). Clinical and demographic data were extracted from the Italian MS register application and linked to the IES-R results. Baseline clinical characteristics of PwMS (classified on the basis of IES-R

score) and the proportion of PTSD+, the subscales and the total score at T0 and T1 were compared.
Results: During the lockdown 90 PwMS (31% response rate) completed the IES-R (62 F; mean (SD) age 40.1(1.0) years; median (IQR) EDSS score 2.3 (1-8); mean disease duration (SD) 10.7 (0.7)). Mean (SD) baseline subscales values were: intrusion 15.9 (7.1), hyperarousal 10.7 (5.0), avoidance 15.4 (6.7). Mean (SD) total IES-R score was 42.0 (17.0), 63 (70%) patients scored above 33 and were identified as having recently developed PTSD symptoms. No significant difference were found between PTSD+ and PTSD- patients in terms of age, EDSS and disease duration.
At T1, when the lockdown measures were removed, the IES-R scores were significantly reduced in comparison to T0 scores (intrusion 8.6 (8.9), hyperarousal 6.0 (5.8), avoidance 8.4 (8.5), total score 4.8 (1.9), $p<0.0001$). The number of patients classified as PTSD+ was significantly reduced in comparison to T0 (16 (17.8%), $p<0.0001$).
Conclusions: Our study demonstrated that PwMS during and after lockdown manifested post-traumatic stress symptoms. Furthermore, our results show how e-data collected can be useful in remotely monitoring patients and can be easily linked to clinical data collected by disease registries.

Disclosure
The authors have nothing to disclose.

P123
Identification of distinct adherence profiles for smartphone sensor-based tests (Floodlight) in a study of people with progressive multiple sclerosis (CONSONANCE)

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Introduction: High levels of adherence to active Floodlight tests were previously reported in a short-duration study. However, information on long-term adherence to remote, smartphone-based assessments remains poorly characterised.
Objectives: To characterise long-term patterns of adherence/engagement to smartphone-based tests included in a provisioned precursor to Floodlight™ MS in people with progressive MS treated with ocrelizumab in CONSONANCE (NCT03523858).
Methods: Participants were asked to perform smartphone sensor-based tests assessing their cognition (weekly), upper extremity function (daily) and gait and balance (daily) with a precursor to Floodlight MS. The proportion of time that the protocol schedule was complied with in rolling weekly cycles was assessed (e.g. tests performed 7 times a week=100% adherence). Longitudinal variability in adherence rates was captured over the first 2 years of the study; included participants had uploaded ⩾2 years of digital data at the time of analysis. Unsupervised Hierarchical Agglomerative Clustering was used to identify adherence patterns. Optimal size and number of clusters was determined by comparing model loss functions.
Results: Of 633 enrolled participants, 327 were included in the analysis. Five optimal clusters emerged: (1) High Adherence (n=128, 39.1%; high engagement [⩾90% of the daily/weekly tests taken] on all sensor-based tests consistently over 2 years); (2) Slowly Decreasing (n=86, 26.3%; gradual decrease to 57% adherence [about 3 days a week] on all tests at the end of Year 2); (3) Fast Decreasing (n=59, 18.0%; fast disengagement reaching <13% adherence [once a week] on all tests by the end of Year 1); (4) Low Adherence (n=40, 12.2%; lowest engagement with <9% of adherence from Week 24); (5) No-Gait (n=14, 4.3%; high adherence [⩾79%] on all upper extremity function and cognition tests, but poor adherence [<6%] on all gait tests, over 2 years). On average across all clusters, 91.1% of participants provided data for ⩾1 test per week over the 2 years. Demographics and clinical characteristics for each cluster will be presented.
Conclusions: The cluster analysis revealed non-linear adherence patterns to sensor-based tests, which predict future adherence. Understanding such patterns will help interpretation of sensor data and inform design choices for improved engagement. Ongoing patient interviews are being carried out to understand additional factors behind the identified adherence patterns.

Disclosure
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G Pointeau is an employee of F. Hoffmann-La Roche Ltd.
F Dondelinger is an employee of and shareholder in F. Hoffmann-La Roche Ltd.
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P124
Teleneurology as a tool to overcome disparities for access to multiple sclerosis care

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Background: Utilization of teleneurology for MS care rapidly expanded during the COVID-19 pandemic to maintain healthcare access. Disparities in telehealth use have been described in other health conditions, but not in a MS population.
Objectives/Aims: To evaluate longitudinal utilization of teleneurology across age, race, geographic factors, and insurance categories to identify potential disparities in utilization at a single academic MS center (Cleveland Clinic).
Methods: MS patients attending a specialty clinic in Cleveland, a medium-sized city, who completed ⩾2 visits at least 24 months apart from 1/2019 to 6/2021 were studied. Patients with fully in-person care were compared to patients with <50% or >50% teleneurology care. Categories of age, race, geographic factors,

and insurance were compared using Kruskal-Wallis tests and pairwise Wilcoxon rank sum tests with Bonferroni correction for multiple comparisons.

Results: 892 patients met the inclusion criteria and completed 3710 visits during the study timeframe: mean age 49.1±11.7 years, 73.7% female, 85.6% white, median disease duration 11.2 years [0.15; 60.3], and relapsing-remitting 62.3%. 37% patients were fully in-person, 37.2% patients had <50% teleneurology care, and 25.8% patients had >50% teleneurology care. There were no significant differences for race (white, black, other), insurance type (Medicare, Medicaid, private, non/other), area deprivation index (ADI), and residence location (rural vs metropolitan) in the use of teleneurology. Use of teleneurology care varied based by age, with older patients utilizing more in-person care. In person care was 23.4% for ages 18-39, 38.5% for ages 40-60, and 47.8% for those greater than 60 ($p<0.001$). Patients residing in greater Cleveland had significantly more in-person care (55.3%) compared to residents residing in Ohio outside of the greater Cleveland area (34.7%) and outside of Ohio (10.1%) ($p=0.031$).

Conclusions: There were no significant differences in teleneurology utilization across race, insurance, ADI or rural vs metropolitan residence, suggesting it is a broadly accessible tool to overcome disparities in access to MS care. Utilization of teleneurology care for older and local patients was lower, which may be due to decrease demand in these groups. Future studies should assess the optimal integration of teleneurology and in-person visits in MS management.

Disclosure

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JB has nothing to disclose

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P125

MS-Selfie: a subscription-based online portal to assist people in the self-management of multiple sclerosis

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Introduction: At the start of the COVID-19 pandemic, multiple sclerosis (MS) services had to be rapidly reconfigured due to healthcare staff being redeployed to frontline medical services. In addition, many non-urgent services, including MS services, had to be provided remotely. In response to the pandemic, many people with MS (pwMS) had little access to current, up-to-date information on COVID-19 and how to manage MS during the pandemic. In response to the unprecedented demand for information, I launched a new online question and answer portal called MS-Selfie, which has subsequently evolved into a self-management portal for pwMS.

Objectives: To present metrics of the use of MS-Selfie*, an MS self-management portal, and its evolution over the last two and half years.

Aims: To introduce the wider MS community to the MS-Selfie self-management portal.

Methods: The MS-Selfie was originally configured to run Google sites and was transferred to Substack, a subscription-based platform, in June 2021. Substack provided online metrics. In addition, results of a user survey of 199 respondents, done between 29-11-2021 and 31-12-2021, are presented.

Results: As of the 18-May-2022, MS-Selfie has 6,448 email subscribers and 72,695 unique visitors to the substack site. An anonymous survey of users completed showed that 99.5% of users would recommend MS-Selfie to a friend or a colleague. 82% of respondents wanted only one or two newsletters per week. 78% wanted a podcast to accompany the newsletters, but not necessarily all of the time. 93% of respondents rated MS-Selfie as good, very good or exceptional. 92% of respondents felt there was a need for a formal MS self-management course; 55% want an online course only, 44% want a hybrid course (online and face-2-face), and less than 1% want a face-2-face course only. 87% of users were satisfied with the funding model to support the MS-Selfie site.

Conclusions: When faced with the COVID-19 pandemic, many people with MS turned to the internet for answers to their questions. Providing a real-time question and answer portal that has subsequently evolved into an MS self-management portal has identified an unmet need to educate pwMS on how to self-manage their MS.

*MS-seflie = https://gavingiovannoni.substack.com/

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Pathology and pathogenesis of MS - Pathology

P126
Hyaluronan mediates the modulation of T cell responses by inflammatory astrocytes in EAE

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Introduction: Inflammatory astrocytes, characterized by increased expression of immune genes and neurotoxic properties, can be found in the center and expanding edge of active demyelinating, as well as in chronic multiple sclerosis (MS) lesions. However, their role in the progression of MS pathogeneses remain elusive.
Objective: Our study aims to determine the prevalence of inflammatory astrocytes throughout the experimental autoimmune encephalomyelitis (EAE) model of MS, and to use *in vitro* and*in vivo* approaches to uncover how inflammatory astrocytes interact with infiltrating immune cells, specifically T cells, in the context of MS.
Methods/Results: We have identified novel cell surface markers to identify inflammatory astrocytes in EAE. Using flow cytometry and confocal microscopy, we show that the frequency of inflammatory astrocytes is significantly increased in the acute and chronic stages of EAE. We further observe that inflammatory astrocytes extend their processes and physically envelop T cells that have infiltrated the CNS parenchyma in EAE. In addition, we have found that *in vitro* generated inflammatory astrocytes increase expression of all three hyaluronan synthases. We have shown before that hyaluronan, primarily released by astrocytes in the central nervous system (CNS), accumulates in MS and EAE lesions and supports the infiltration of encephalitogenic T cells. We show here that inhibiting hyaluronan synthesis in cultured inflammatory astrocytes, using the oral drug 4-methylumbelliferone (4-MU), reduces their inflammatory profile. In addition, co-culturing T cells with inflammatory astrocytes increases their viability, and this is reduced by pretreatment of astrocytes with 4-MU.
Conclusions: Together, our findings suggest that inflammatory astrocytes play a pathogenic role in the progression of EAE through their interactions with T cells, which is supported by their release of hyaluronan. This novel mechanism of supports new avenues for the development of disease modifying therapies by targeting inflammatory astrocytes and hyaluronan.

Disclosure
Jacqueline Reid: nothing to disclose

P127
Cross-regional homeostatic and reactive glial signatures in multiple sclerosis

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Introduction: Multiple sclerosis (MS) is a compartmentalized multifocal progressive inflammatory disease of the central nervous system (CNS). A comprehensive understanding of the disease demands not only to assess the roles of heterogeneous cell populations but also to understand the pathological mechanisms underlying lesion formations in different CNS compartments.
Objectives: To analyze single-cell gene expression signatures between three major CNS compartments and compare levels of cross-regional heterogeneity focusing on homeostatic and reactive glial subtypes.
Methods: We performed a comprehensive single-cell and spatial transcriptomic analysis of 15 leukocortical, 10 cerebellar and 12 spinal cord tissue blocks obtained from MS and matched control subjects. Specifically, we carried out fluorescence multiplex *in situ*RNA hybridization on all control and MS tissue samples and performed droplet-based single-nucleus RNA sequencing (snRNA-seq) on 8 leukocortical, 6 cerebellar and 6 spinal cord samples.
Results: We generated an integrated cell type-specific transcriptomic map of MS pathology spanning three major CNS sites affected by MS. Investigating the similarity among cell types between these regions, we observed a strong level of molecular heterogeneity between homeostatic glial subtypes highlighting astrocytes and oligodendrocytes. Under disease conditions, however, neuron and macroglial subtypes showed a strong overlap in their transcriptomic response towards chronic inflammatory demyelination. More specifically, we identified an oligodendrocyte white matter subtype-specific downregulation of a muscarinic receptor and, additionally, found an upregulation of myelin-associated transcripts in lesion-rim associated oligodendrocytes along white matter tracts.
Conclusion: Our findings demonstrate that integrated computational workflows are highly suitable to identify common cell type-specific signatures across different CNS regions and help identify novel therapeutic targets with subtype-specific expression patterns. In particular, our unbiased*in silico*approach was able to identify a white matter specific oligodendrocyte subtype that was associated with previously discovered pro-myelinating therapeutic target gene expression. Collectively, our data suggest that cross-regional glial transcriptomic signatures overlap in MS, with different reactive glial cell types capable of either exacerbating or ameliorating pathology.

Disclosure

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P128

Multimodal bioinformatic analysis of clinical, neuropathology and molecular profiling of progressive MS

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Introduction: Compartmentalized inflammation, persisting in intrathecal niches, such as choroid plexus (CP), leptomeninges and perivascular spaces, together with degree of lesion activity, contribute to multiple sclerosis (MS) immunopathology. However, the exact correlation between these inflammatory components in progressive MS is unclear.
Methods: Quantitative neuropathological analysis of white matter (WML) and grey matter lesion (GML) load, along with that of inflammatory levels (scored 0, 1, 2, 3) in CP, leptomeninges and perivenular infiltrates, and that of degree of lesion activity was quantified in 40 post-mortem MS cases. Analysis of 89 inflammatory mediators was performed in paired CSF samples obtained from the same MS cases.
Results: Meningeal and perivascular inflammatory levels were significantly correlated ($R=0.83, p<0.01$). There were significantly ($p<0.01$) negative correlations between degree of CP ($R=-0.65$), degree of perivascular inflammation ($R=-0.61$), extent of GML ($R=-0.57$), number of meningeal tertiary lymphoid structures, TLS ($R=-0.51$) and time from progression to wheelchair (EDSS=7).
Regression analysis and feature ranking methodologies derived the most relevant CSF protein pattern for each inflammatory compartment: CXCL13, CCL26 and sTNFR1 for meningeal TLS; CXCL13, fibrinogen, PDGF-b, CCL7 and CCL11 for CP inflammation; and CXCL13, osteocalcin and fibrinogen for perivascular inflammation.
Cluster analysis based on the neuropathological profiles of the 40 MS cases identified two groups: C1 (22 subjects) and C2 (18 subjects) differing in terms of: highest levels of perivascular inflammation (mean 1.05 in C1; vs 2.33 in C2), elevated number meningeal TLS (mean 0.05 in C1 vs 1.6 in C2), high level of GM demyelination (mean 28.5% in C1 vs 68% in C2) and high number of RIM+ lesions (mean 0.5 in C1 vs 2.5 in C2). The two clusters were significantly different in terms of the age at death (mean 60.7 yrs in C1 vs 53.3 in C2) and the time from progression to wheelchair (mean 5.2 yrs in C1 vs 2.7 in C2). Feature selection analysis show that the 2 groups differ for a specific CSF signature, including CXCL13, IL-9, Fibrinogen, NF-L, sCD30, LIGHT and sTNF-R1.
Conclusions: Degree of perivascular inflammation, number of meningeal TLS and of RIM+ lesions, together with extent of GML, represent neuropathological features that primarily contribute to distinguish more rapid and severe progressive MS, as reflected by a specific CSF inflammatory pattern.

Disclosure

The authors have nothing to disclose related to this work.

P129

Diffusely abnormal white matter and elevated grey matter demyelination imply rapid and severe progression in atypical multiple sclerosis

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Introduction: The extent, distribution and activity of focal white matter lesions (WML) and diffuse cortical grey matter lesions (GML) are relevant drivers of multiple sclerosis (MS) progression. However, abnormalities in the non-plaque WM and GM, evident pathologically and by non-conventional MRI, also impact disease outcome, though the specific clinical/pathological correlates and the potential surrogate markers are unclear.
Methods: Neuropathological morphometric analysis of WMLs and GMLs, degree of lesion activity, inflammation in intrathecal niches (leptomeninges, choroid plexus-CP) and perivenular infiltrates was performed in 40 progressive MS cases. Protein analysis of paired CSF samples from the same MS cases was also carried out.
Results: Stratification based on neuropathological profile identified MS424 as anomalous. Clinically MS424 had one of the

shortest disease durations (10 vs mean 29.6 years) and youngest age at death (39 vs mean 57.4 years old). Neuropathological analysis determined: increased number of rim+, active and chronic active lesions, absence of inactive lesions; and elevated and diffuse GMLs (79.2%) with WML load (31.76%). There was also increased meningeal and perivascular inflammation, with no CP inflammation.

The main feature differentiating MS424 was the wide extent of diffusely abnormal WM (DAWM), identified by: loss of LFB staining with intact PLP/MOG immunostaining; diffuse microglia activation; increased number and altered morphology (twisted) of blood vessels and high tissue deposition of collagen IV and fibrinogen.

A novel algorithm, based on color thresholding applied to different ROIs, confirmed that DAWN had a percentage of normal LFB stained myelin in the range 2-15%, compared to 0% in WML and 64-93% in normal-appearing WM (NAWM). Similar approach identified cell number and derived cell density in DAWM, WML and NAWM, which had a cell count of 877 ± 164, 685 ± 270 and 1148 ± 246 respectively.

Median absolute deviation analysis of CSF protein pattern revealed a unique MS424 profile (high CCL19, CCL23, Pentraxin, IL-1β, IL-6, CXCL11, CXCL9, MIF, CCL2). IPA pathway analysis revealed this inflammatory pattern to be mainly associated to glia activation and alterations of blood brain barrier (BBB).

Conclusions: DAWM, in addition to extensive GML, may represent a unique pathologic substrate of more rapid and severe progressive MS.

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Disclosure

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P130

Deciphering the relationship between haptoglobin genotype, myeloid cell iron uptake and lesion rim formation in multiple sclerosis

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Background: In multiple sclerosis (MS), chronic inflammatory disease activity can be depicted by iron accumulation at the lesion edge, leading to paramagnetic rim lesions (PRLs) visible*in vivo* by iron-sensitive magnetic resonance imaging (MRI). In general, presence of PRLs is associated with a more severe disease. The plasma protein haptoglobin binds free iron-containing hemoglobin, forming haptoglobin-hemoglobin (Hp-Hb) complexes, which are bound by the scavenger receptor CD163 expressed on a subtype of myeloid cells. The three human Hp genotypes, Hp1-1, Hp2-1 and Hp2-2, show different haptoglobin sizes, hemoglobin binding and antioxidative capacities (the latter lowest for Hp2-2). Different Hp genotypes could influence iron uptake via CD163 and further processing in MS lesion rim myeloid cells, representing an important mechanism underlying lesion expansion and disease progression.

Methods: Using snap-frozen post-mortem tissues of 21 MS cases with chronic MS lesions with or without rim-related iron accumulation, we stained for myelin, non-heme iron, P2RY12, CD68, C1QA, CD163, heme-oxygenase-1 (HMOX-1) and hepcidin, both on protein and RNA levels by immunohistochemistry and multiplex *in situ* hybridization. 99 MS patients were scanned using iron-sensitive 3 Tesla MRI. PRLs were counted in the images. Haptoglobin was genotyped for all post-mortem and*in vivo* cases using PCR.

Results: In post-mortem MS, $CD163^+$ myeloid cell numbers were associated with iron uptake at lesion rims ($r = .44$, $p = .047$). Expression of HMOX-1 and hepcidin was enriched in rim-associated myeloid cells and correlated with the presence of $CD68^+$ cells. Further, we noted a trend between an enrichment of $iron^+/CD163^+$ myeloid cells in patients with Hp2-1/Hp2-2 vs Hp1-1. In line, we observed a higher MSSS ($p = .041$) and a trend of increased PRL numbers in patients with Hp2-1/Hp2-2 vs Hp1-1. The disease course of MS patients with at least one PRL was worse than in those without any PRLs (MSSS, $p = .014$). Also, patients with Hp2-1/Hp2-2 genotypes had a more severe clinical outcome than those with a Hp1-1 genotype ($p = .041$).

Interpretation: We found CD163-HMOX1-hepcidin upregulation and iron enrichment to be associated with lesion rim myeloid cells in MS. Hp genotype may be a critical determinant of disease severity and could predict occurrence of PRLs in MS patients. Our study unravels the haptoglobin-CD163-iron axis as an important activator of myeloid cell pathology in progressive MS.

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P131

Evolutionarily conserved signatures of microglia in health and disease

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Introduction: Single cell profiling of gene expression has illuminated the heterogeneity of immune cells and accessible phenotypes across organs and under a myriad of conditions. These

efforts—typified by recent studies aiming to identify signatures of microglia—typically entail pre-enrichment of cell populations, even from distinct species, using a limited set of surface markers or morphological traits. This step introduces potential bias and subjectivity that may alter the gene expression states that are discerned.
Objective: To determine signatures of microglia in humans and mice in the context of central nervous system (CNS) inflammation and homeostasis.
Methods: We queried the NCBI GEO for datasets of single-cell transcription within CNS tissue from healthy subjects, multiple sclerosis (MS) patients, and mice afflicted with experimental autoimmune encephalomyelitis (EAE). In total, this yielded data on over 135,000 human cells—encompassing a spectrum of lesion chronicity in patients with progressive and relapsing-remitting MS—and 12,000 murine cells. Datasets were pre-processed for quality control and harmonized according to species prior to cross-species integration by canonical correlation analysis using Seurat v4. We developed classifier models of microglia using logistic regression with LASSO regularization.
Results: Unexpectedly, markers closely linked in the literature to microglia, including Iba-1, were found to be expressed in non-microglial myeloid cells.Other markers previously ascribed to microglia in one species, such as Hexb, failed to represent useful markers in the other species. We identified intra- and inter- species signatures of microglia using machine-learning methods that form the basis of future studies.
Conclusions: Whole-brain, single-cell gene expression data, unencumbered by bias introduced by prior cell enrichment, enable identification of transcriptional signatures of cell types across species. Signatures of microglia during CNS inflammation identify potentially targetable pathways to understand their role in disease and limit tissue injury.

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Pathology and pathogenesis of MS - Experimental models

P132
Siponimod favours expression of less pro-inflammatory, alternatively activated microglia in a microglia repopulation model of progressive multiple sclerosis - implication for neuroprotection

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Background: In progressive forms of multiple sclerosis (MS), central nerveous system (CNS)-resident immune cells such as microglia are contributors of chronic inflammation. The second generation sphingosin-1-phosphate receptor modulator siponimod, licensed for secondary progressive MS, exerts presumably modulatory properties on microglia.
Aim of the study: We hypothesized that depleting microglia during experimental autoimmune encephalomyelitis (EAE) might lead to a renewal of neuroprotective microglia in the presence of siponimod in a mouse model of progressive MS.
Methods: We induced EAE in CX3CR1CreER/iDTR mice to perform a conditional microglia knock out (MG^{ko}). Siponimod was administered from one day after immunization (dpi) orally dissolved in rapeseed oil. Microglia depletion was induced during the chronic phase of EAE, mice were sacrificed during subsequent repopulation of microglia. CNS, blood and lymphatic organs were analyzed by flow cytometry.
Results: Siponimod reduced EAE scores significantly, while MG^{ko} showed a trend towards worsening of EAE. Repopulating microglia were characterized by lower expression of steady state markers and upregulation of inflammatory markers (CD86, MHC-II). Siponimod reduced expression of pro-inflammatory markers (CD86, MHC-II) and, additionally, elicited upregulation of alternative activation markers (CD206) during repopulation. Immune cell composition was unaffected apart from restrained $CD19^{+}$B cells and $CD4^{+}CD25^{+}FoxP3^{+}$ regulatory T cells in lymph nodes by siponimod. Macrophages in the brain directly correlated with lower microglia numbers. Histologically, immune cell infiltration in the spinal cord was reduced both following MG^{ko} and stronger under siponimod treatment,.
Conclusions: Siponimod treatment reduced pro-inflammatory repopulating microglia after a conditional MG^{ko} and favoured the renewal of less pro-inflammatory, alternatively activated, potentially phagocytic microglia. This effect adds more mechanistic insight regarding microglia modulatory properties of siponimod with implications for putative neuroprotection during progression.

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P133

Transcriptomic analysis reveals that RGC-32 regulates the expression of axonal guidance molecules in reactive astrocytes

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Introduction: Reactive astrocytes play a crucial role in the pathogenesis of multiple sclerosis (MS) and its murine model, experimental autoimmune encephalomyelitis (EAE) through their ability to express complex molecular machineries capable of mounting and perpetuating cellular processes leading to neuroinflammation and tissue remodeling. We have previously shown that Response Gene to Complement (RGC)-32 modulates transforming growth factor (TGF)-β-induced extracellular matrix secretion and the ability of astrocytes to undergo reactive changes during acute EAE, but the molecular programs underlying these effects are still not well understood.
Objectives and Aims: To better characterize the transcriptomic programs and the mechanistic pathways activated by RGC-32 in reactive astrocytes.
Methods: We performed next-generation RNA sequencing on brain neonatal astrocytes isolated from wild type (WT) and RGC-32 knock-out (KO) mice, either unstimulated or stimulated with TGF-β. Functional enrichment analysis was then used for the generation of Gene Ontology categories. An Enrichment Map was generated, and connectivity analysis of gene networks was performed by using the Cytoscape and STRING platforms. Results were then validated by using Real-Time PCR. Spinal cords from WT and RGC-32 KO mice with EAE (at days 0 and 14) were stained by immunohistochemistry for the astrocyte marker GFAP, and for axonal guidance molecules (AGM).
Results: Lack of RGC-32 had a significant impact on the transcriptomic programs normally associated with brain development and neurogenesis but whose re-expression is usually seen in reactive astrocytes. Connectivity analysis revealed that genes coding for AGM were particularly affected. We found lower transcript levels of ephrin receptor A type 7 (Epha7) ($p<0.01$), plexin A1 (Plxna1) ($p<0.05$), and Slit guidance ligand 2 (Slit2) ($p<0.01$) in RGC-32 KO astrocytes. Moreover, our results showed that RGC-32 is necessary for the expression of EPHA7 in reactive astrocytes at the peak of EAE, as we found a lower number of EPHA7/GFAP-double positive cells in RGC-32 KO mice ($p<0.05$).
Conclusion: These findings suggest that RGC-32 regulates TGF-β's ability to trigger complex molecular programs in reactive astrocytes. The regulation of AGM might be a major modality by which RGC-32 facilitates reactive astrogliosis during neuroinflammation.

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P134

Remibrutinib inhibits neuroinflammation driven by B cells and myeloid cells in preclinical models of multiple sclerosis

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Introduction: Bruton's tyrosine kinase (BTK) is a key signaling node in B-cell receptor and Fc receptor signaling. BTK inhibitors (BTKi) are an emerging oral treatment option for patients suffering from multiple sclerosis (MS). Remibrutinib (LOU064) is a potent, highly selective covalent BTKi with a promising preclinical and clinical profile for MS treatment.
Objective: To assess the mechanism of action and efficacy of remibrutinib in experimental autoimmune encephalomyelitis (EAE) mouse models for MS.
Methods: Two different EAE models in the C57BL/6 mouse that are induced by immunization with human or rat myelin oligodendrocyte glycoprotein (HuMOG and RatMOG EAE) were used in the study. Target engagement was assessed in tissue and clinical disease activity was determined. Serum antibody levels, biomarkers, as well as central nervous system tissue transcriptome were analysed.
Results: Remibrutinib inhibited B-cell dependent HuMOG EAE at daily oral doses of 3 and 30 mg/kg and strongly reduced neurological symptoms. *Ex vivo* MOG-specific T cell recall response was inhibited, but not polyclonal T cell response, indicating selective B cell inhibition. Similarly, remibrutinib did not reduce total immunoglobulin G antibody levels. At the efficacious dose of 30 mg/kg, remibrutinib showed strong BTK occupancy in the peripheral immune organs and in the brain of EAE mice. Remibrutinib also inhibited RatMOG EAE, indicating that myeloid cell and microglia inhibition contributes to its efficacy in MS. This is supported by anti-inflammatory effects detected in a single-cell RNA sequencing of brain and spinal cord. In addition, remibrutinib significantly reduced neurofilament light chain serum levels.

Conclusions: Remibrutinib exhibited dose-dependent efficacy in a B cell-driven EAE model. In addition, it revealed efficacy on clinical scores and anti-inflammatory effects by acting on myeloid cells and microglia. These findings support the view that remibrutinib may represent a novel treatment option for patients with MS.

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P135

Influence of diet and MOG_{35-55}-peptide preparation on severity, survival, incidence and body weight in murine experimental autoimmune encephalomyelitis

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Introduction: Diet and microbiome influence the pathophysiology of autoimmune diseases potentially via dietary fiber which modulates gut microbial activity and local immune surveillance. Recently, it was shown that a diet rich in cellulose reduced the number of mice developing opticospinal encephalomyelitis, but did not affect disease severity in a spontaneous model of experimental autoimmune encephalomyelitis (EAE). This difference in the models seemed unlikely, so we set out to test the effect of diet and optimize incidence, severity and reproducibility in the myelin oligodendrocyte glycoprotein 35-55 (MOG_{35-55})-peptide induced EAE-model in C57BL/6 mice.
Methods: We compared the effects of a pro-fermentative diet (VRF1, rich in fiber) vs. a low-fermentative diet (AIN93M, low fiber) on EAE pathology. To verify the effects of emulsion quality on disease induction, we used sonication (+son) or inversion (-son) to mix antigen and adjuvant (study groups: $VRF1^{-son}$, $VRF1+^{son}$, $AIN93M^{-son}$, and $AIN93M+^{son}$). The study was performed twice to assess reproducibility of effects.
Results: *Incidence*: The high fiber VRF1 diet was associated with lower incidence (first study: 63 % and 75 % for –son and +son, respectively; second study 50 % and 75 %), while mice fed AIN93M were more prone to develop EAE (first study: 100 % for both –son and +son; second study 38 % and 88 %). In a subset of the second study, $AIN93M+^{son}$ mice were treated with 150 µg MOG_{35-55} peptide and 240 ng PTX, or 75 µg MOG_{35-55} peptide, 120 ng PTX incidences were 100 % and 88 %.
Scores:Disease scores were highest in the $AIN93M+^{son}$ groups in both studies, followed by $AIN93M^{-son}$.
Survival: Survival in all groups fed VRF1 was 100 %, while survival rates dropped for animals fed AIN93M (first study: 25 % for +son, 63 % for –son).
Differences in severity were consistent with weight, expression of inflammation associated genes (RTqPCR) as well as brain/liver histology.
Conclusion: Both diet and emulsification (sonication) of MOG_{35-55}peptide influence incidence, severity and reproducibility in EAE. A low fermentative/low-fiber diet improved the robustness of the model while a pro-fermentative diet reduces incidence and severity. Taken together, our findings support a critical – potentially translatable – role of dietary fiber in reducing auto-immune potential.

Disclosure
The authors are employees of Synovo, a developer of anti-inflammatory drugs and corresponding disease models.

P136

Aquaporin-4 prevents exaggerated astrocytosis and structural damage in retinal inflammation

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Introduction: Aquaporin-4 (AQP4) is the molecular target of the immune response in neuromyelitis optica (NMO) that leads to severe structural damage in the central nervous system (CNS). While optical coherence tomography (OCT) analyses suggest that structural damage occurs in the retina of NMO patients, the functional relevance of AQP4 in the retina has not been investigated.
Methods: Here, we tested the role of AQP4 in the retina in MOG(35-55)-induced experimental autoimmune encephalomyelitis (EAE) using OCT, OCT angiography, immunohistology, flow cytometry and gene expression analysis in wild type and *Aqp4*$^{-/-}$ mice.
Results: No direct infiltrates of inflammatory cells were detected in the retina. Yet, early retinal expression of TNF and Iba1 suggested that the retina participated in the inflammatory response during EAE in a similar way in wild type and *Aqp4*$^{-/-}$ mice. While wild type mice rapidly cleared retinal swelling, *Aqp4*$^{-/-}$ animals exhibited a sustainedly increased retinal thickness associated with retinal hyperperfusion, albumin extravasation, and upregulation of GFAP as a hallmark of retinal scarring at later stages of EAE. Eventually, the loss of retinal ganglion cells was more pronounced in *Aqp4*$^{-/-}$ mice than in wild type mice.
Conclusions: In conclusion, our data illustrate that AQP4 expression is critical for retinal Müller cells to clear the interstitial space from excess vasogenic edema and prevent maladaptive scarring in the retina during remote inflammatory processes in the CNS.

Disclosure
The authors declare no competing interests.

P137

Investigation of stem cell mobilization using G-CSF and plerixafor in experimental autoimmune encephalomyelitis

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Background: Immune reset using autologous hematopoietic stem cell transplantation (AHSCT) is an auspicious approach to treat patients with highly active Multiple Sclerosis (MS). Stem cell mobilization can be achieved using G-CSF or plerixafor. Until now, it remains unclear whether those treatments might lead to an exacerbation of the disease and which approach is more effective regarding stem cell mobilization.
Aim of the study: Investigation of G-CSF and plerixafor administration at different time points in experimental autoimmune encephalomyelitis (EAE) regarding clinical and immunological effects and stem cell mobilization.
Methods: The study was approved by the local authorities (LANUV, 81-02.04.2020.A462). C57BL6 mice were immunized with MOG_{35-55} and treated with pertussis toxin on days 0 and 2. Mice were treated during the different phases of EAE with G-CSF (62.5; 125; 250 µg/kg/d) subcutaneously twice a day for four days or plerixafor (5 mg/kg/d) once. Mice were scored daily by a blinded observer on a 10-point scale and weighted. Short- ($Lin^-Sca1^+c\text{-}kit^+CD34^+$) and long-term ($Lin^-Sca1^+c\text{-}kit^+CD34^-$) stem cells in the blood were assessed after mobilization. The degree of differentiation and extent of mobilization were investigated following cultivation and analysis of colony forming units (CFU).
Results: Treatment during the acute and chronic phase showed a trend of dose-dependent worsening in G-CSF. Using the lowest G-CSF dosage with no clinical effect during the acute phase, we depicted no effect on EAE following treatment before symptom onset and during the chronic phase, while plerixafor also had no impact with early treatment and treatment during the acute phase but variable effects during the chronic phase. Plerixafor induced a strong mobilization of stem cells ($p<0.05$), while G-CSF showed the same trend in all dosages, however, lacking significance. Moreover, plerixafor led to higher numbers of CFUs (n=10) compared to the lowest dosage G-CSF (62.5 µg/kg/d; n=3).
Conclusions: Neither mobilization with G-CSF nor plerixafor induced severe negative effect on EAE. However, plerixafor induced a stronger mobilization of hematopoietic stem cells in conjunction with the potential to form higher numbers of CFU, arguing for a more potent approach regarding mobilization with a potential for translation into clinical practice.

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P138
Changes of demyelination in the entire visual pathway in the cuprizone-induced mouse model of multiple sclerosis

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Introduction: The cuprizone (CZ) mouse model is a well-established demyelinating model of multiple sclerosis (MS). The visual pathway is frequently used to study aspects of pathological changes in MS, specifically, visual evoked potential (VEP) latency as a primary endpoint in MS remyelination clinical trials. However, myelin loss in the entire visual pathway in the CZ model has not been well characterised.
Aim: To assess myelin loss and other neuroinflammatory changes that occur in the CZ model of de/remyelination along the holistic murine visual pathway, including the optic nerve, optic tract, dorsal lateral geniculate nucleus (dLGN) and primary visual cortex (V1).
Methods: Adult C57B mice (n=46, 1:1 male and female) were fed a diet of 0.2% CZ in chow*ad libitum* for 6 weeks(6W) followed by regular chow for 2 weeks (7W & 8W). Electrophysiological recordings, including VEP and electroretinogram (ERG), were repeated at 2, 4, 6, 7 & 8 weeks. Animals were sacrificed at each time point and eyes, optic nerves and brains (dLGN, V1) were collected and processed for immunoassays and histology to assess levels of demyelination, glial activation, synaptic plasticity and neuroaxonal loss along the entire visual pathway.
Results: Amplitude of VEP is significantly reduced at 6W of CZ treatment (17.7 ± 5.5mV) compared to baseline (26.4 ± 6.7mV) ($p\leqslant0.0001$), followed by a complete recovery after cessation of CZ diet (25.6 ± 3.9mV). However, no significant changes in latency were observed. We noted no changes in the amplitude in the scotopic threshold response or a- and b-wave amplitudes/implicit times in ERGs across all timepoints, indicating CZ has no significant effect on retinal function. Histology revealed subtle changes in morphology of axons, the core of 6W appearing less uniform than the subpial region compared to control and 8W, but no significant change in g-ratio between groups. Immunofluorescence showed a significant decrease (33%) in myelin basic protein in the dLGN and V1 of CZ animals but no change in the optic nerves compared to controls. Additionally,

we also observed increased glial activity and altered synaptic plasticity in the visual pathway in CZ mice.
Conclusion: We observed differential patterns of demyelination throughout the visual pathway in CZ-induced de/remyelination, with limited changes in the anterior pathway and more severe demyelination in the posterior portion. VEP latency delay mainly reflects demyelination in the anterior visual pathway in mice.

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Pathology and pathogenesis of MS - Genetics/Epigenetics

P139
Extensive evidence for aberrant B cell hypomethylation in relapsing-remitting multiple sclerosis

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Introductions: Multiple Sclerosis (MS) is a chronic inflammatory disease characterized by autoimmune attack and destruction of myelin and neuroaxonal degeneration in the central nervous system (CNS). We and others have found widespread differences in DNA methylation between MS cases and healthy controls in B cells. Importantly, B cells have come under renewed interest due to the striking effectiveness B cell-depleting agents.
Objectives: To further characterize epigenetic changes and their functional consequences in $CD19^+$ B cells collected from persons with MS (PwMS).
Methods: We measured DNA methylation in $CD19^+$B cells sorted from peripheral blood using Infinium HumanMethylationEPIC arrays from relapsing-remitting (RRMS) (n = 26) and healthy controls (HC) (n = 15), which we compared and integrated with 2 previously reported cohorts, namely PMID 31053557 (RRMS n = 12, HC n = 10), run on Infinium HumanMethylation4550K array, and PMID 34911760 (RRMS n = 29, HC n = 24), run on reduced representation bisulfite sequencing (RRBS). We compared the sites that overlap depending on the amount of evidence per site in a stepwise meta-analysis using the METAL pipeline. We subsequently functionally overlapped the results with publicly and locally available data from other omics types.
Results: A meta-analysis of the three B cell cohorts revealed 7 051 differentially methylated CpGs between RRMS and HC (with adjusted p-values < 0.01 and a 5% effect size) in 3 833 genes, where ~80% of the CpGs displayed hypomethylation in RRMS vs controls. Pathway analyses of the cohorts implicated dysregulation of genes involved in cell-to-cell communication, cell migration, and immune activation.
Conclusion: Our observations establish that B cells from PwMS patients acquire a distinct epigenetic profile connected to changes in pathways of importance for B cell functions across three separate cohorts and different technological platforms. These findings provide additional insights into the role of B cells in MS and as a therapeutic target.
Keywords: MS, Multiple Sclerosis, B-cells, Epigenetics, DNA Methylation, EWAS, Meta-analysis

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P140
Cellular signature changes in non-lesional tissue from multiple sclerosis donors revealed by single-nucleus RNA-seq and spatial transcriptomics

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Recent investigations of cell type changes in Multiple Sclerosis using single-cell profiling methods have focused on active lesional and peri-lesional brain tissue. However, an important question is

the extent to which so-called "normal-appearing" non-lesional tissue in individuals with Multiple Sclerosis accumulate changes over the life span. Here, we compared non-lesional brain tissue from donors with a pathological diagnosis of MS from the Religious Orders Study/Memory and Aging Project (ROSMAP) cohorts to age- and sex-match neurological controls. We profiled 81 samples using single-nucleus RNA-seq from three brain regions: dorsolateral prefrontal cortex (DLPFC), normal appearing white matter (NAWM) and the pulvinar in hypothalamus (PULV), from 15 control individuals (CTRL), 5 Multiple Sclerosis (MS) cases, and 9 individuals with other brain pathologies. After a rigorous multi-iteration quality control workflow, we retained 194,706 single-nucleus transcriptomic gene expression profiles. These profiles encompassed all of the major cell classes such as oligodendrocytes, OPCs, astrocytes, microglia, endothelial cells, glutamatergic neurons and GABAergic neurons. We identified region- and cell type-specific changes in samples from donors with MS and other neuropathologies: these included the cell stress/heat shock-related gene CRYAB in NAWM oligodendrocytes, SPP1 in NAWM microglia, and FTH1 in DLPFC and PULV microglia. To validate our findings, we sample-matched 4 CTRL and 8 MS/other pathology donor tissues spanning all three brain regions and generated in total 33 spatial transcriptomics Visium data sets. Our observations implicate dysregulation of oligodendrocytes and microglia even in NAWM, as well as additional signatures in regions that undergo grey matter atrophy, such as the DLPFC and the pulvinar. These latter findings suggest cell type changes that may precede or be associated with the demyelinating aspects of MS and other potentially related pathologies. Overall, our investigation sheds additional light on complex heterogeneous cell type changes and their detrimental impact in Multiple Sclerosis and other neuropathologies in multiple brain regions.

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P141
Limited cross-ancestry portability of european-derived multiple sclerosis polygenic risk scores: a study in ~50,000 individuals of south asian ancestry from the Genes & Health cohort

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Background: Genome-wide association studies (GWAS) examining Multiple Sclerosis (MS) risk have been used to construct polygenic risk scores (PRS), which capture an individual's cumulative genetic burden. These PRS are strongly associated with MS in populations of European ancestry. However, due to differences in allele frequencies and linkage disequilibrium, it is not known how well these scores perform in other ancestral backgrounds.
Objective: To evaluate the performance of MS PRS derived from European GWAS in individuals of South Asian ancestry.
Methods: We identified individuals with MS (n=40) and without MS (n=44353) in the Genes and Health cohort, a longitudinal genetic cohort study of ~50,000 British South Asians. PRS were derived using PRSice-2 using the clumping-and-threshold approach with external weights from the IMSGC 2019 GWAS and an external Linkage Disequilibrium reference of European 1000 genomes samples. PRS were calculated both including and excluding the MHC region. Discriminative performance was evaluated using Nagelkerke's pseudo-R2 metric and corresponding P-values, with adjustment for age, sex, and the first six genetic principal components. The optimal scores were selected using permutation-based P values.
Results: The best-performing PRS were significantly associated with MS (PRSMHC: pseudo-R2 0.0127, p=0.00429, SNPn=1660; PRSnon-MHC: pseudo-R2 0.0115, p=0.00871, SNPn=1494). The best-performing PRS therefore explained 1.27% of variance in disease status, falling substantially short of previously documented scores of up to 3% in European cohorts. As with European cohorts, scores including the MHC outperformed scores excluding this region.
Conclusion: European-derived PRS perform poorly when applied to South Asian populations, although still have some utility in distinguishing cases from controls. This drop-off in performance is likely explained by cross-ancestral differences in allele frequencies and LD. These results emphasise the need for GWAS in ancestrally diverse populations to generate PRS with greater cross-population portability.

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P142
Tissue specific splicing of genes implicated in determining the severity of multiple sclerosis

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Introduction: Through international collaboration, we have recently completed a Genome-Wide Association Screen (GWAS)

of severity in multiple sclerosis (MS). This study has identified the first genetic variant with genome-wide significant evidence of association with disease severity. This variant maps to a regulatory region lying between two genes that are highly expressed in the central nervous and in innate immune cells. Both of the implicated genes have multiple isoforms that have known tissue specific expression patterns, raising the possibility that the variant might influence the function of one or both genes by altering their splicing, perhaps in a tissue specific manner.

Aim: To establish the cell-type/tissue specific expression of transcripts within these two genes and to correlate this expression with the MS associated variant.

Method: RNA extraction and cDNA synthesis from human monocytes, neutrophils and brain tissue were prepared according to standard protocols. To detect known and novel transcripts we designed a gene specific tiled PCR and analysed the PCR products on an Agilent Bioanalyser 2100. Genotyping of the MS severity associated variant was completed using Taqman methodology on a Quantstudio 7K Flex.

Results: We have confirmed the known cell type specific transcript expression of these two genes and identified a novel intron retention transcript in monocytes that requires further investigation. Having established the transcript specific expression profile we are expanding these findings by correlating this with genotype in a larger cohort of up to 100 individuals.

Conclusion: Identifying the disease relevant transcript and cell type is of critical value to guiding further experiments to understand the pathogenic function of this MS severity associated variant in disease progression.

Disclosure

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Somatic mutations in STAT3 are common in CD8+ cells in multiple sclerosis patients and controls

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Introduction: Somatic mutations occur throughout the lifespan and lead to mosaicism of cells. Somatic mutations have a central role in cancer, but there are also rare autoimmune diseases in which somatic mutations play a major role. We have recently shown that somatic mutations with low allele fractions are preferentially detectable in CD8+ cells and these mutations are especially enriched in the STAT3 gene in multiple sclerosis (MS) patients and controls. Activating gain-of-function STAT3 mutations in CD8+ cells have been associated with rheumatoid arthritis in patients with large granular lymphocytic leukemia.

Objectives: Risk factors of MS are relatively common and cannot fully explain the low prevalence of MS. Hence, stochastic factors may be involved. Somatic mutations are stochastic factors with an established role in cancer; their role in non-malignant diseases is also gaining attention.

Aims: To analyze somatic mutations in the STAT3 SH2 domain in peripheral blood CD8+ cells in MS patients and controls.

Methods: CD8+ cells were enriched by positive separation with CD8 antibody MicroBeads (Miltenyi Biotec) in 94 MS patients and 99 age- and sex-matched controls. PCR amplicons targeting the exons 20 and 21 of STAT3 were prepared and sequenced using the Illumina MiSeq instrument with 2x300bp reads. We designed and used a novel variant calling method, optimized for large number of samples, very high sequencing depth and small target genomic area.

Results: A median sequencing depth of 74552x was obtained for exon 20 and 46912x for exon 21, which allowed the detection of somatic variants with very low allele fractions. Overall, we discovered 64 somatic mutations, of which 63 were non-synonymous and 77% were previously known gain-of-function mutations. The median allele fraction was 0.07% (range 0.007-1.2%). There were 26 (28%) MS patients vs. 24 (24%) controls with mutations (p=0.62). Two or more mutations were found in 9 MS patients vs. 2 controls (p=0.03). Known gain-of-function mutations were found in 19 (20%) MS patients vs. 22 (22%) controls (p=0.86).

Conclusions: Somatic mutations in STAT3 are surprisingly common and suggest a selection advantage of the mutated CD8+ clones. Although there were only minor differences in the mutation carrier frequencies in MS patients vs. controls, these results reveal a possible mechanism for clonal dysregulated immune responses. Mutation in an autoreactive clone could underlie chronic autoimmune disease.

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Prediction of conversion from optic neuritis to multiple sclerosis: novel application of a genetic risk score

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Background: Optic Neuritis (ON) is a frequent first feature of multiple sclerosis (MS), but a formal diagnosis of MS may be delayed by years. The challenge is to distinguish MS-ON from other forms of ON at time of presentation. MS is heritable with numerous common genetic variants associated with disease risk.
Aim: To investigate if a multiple sclerosis genetic risk score (MS-GRS) aids prediction of MS at time of diagnosis of ON as a clinically isolated syndrome (CIS).
Methods: We studied individuals in the United Kingdom Biobank, a longitudinal database containing phenotypic and genetic data on 500,000 individuals. We retrieved diagnoses of MS and ON from retrospective (before baseline visit) and prospective (after baseline visit) self-report, hospital, and GP records, and analysed the co-occurrence of MS and ON. We developed MS-GRS based on 310 single nucleotide polymorphisms (SNPs) and eight HLA alleles associated with MS risk in previous studies. We assessed the power of MS-GRS to discriminate between MS and healthy controls using receiver-operator characteristics-area under the curve (ROC-AUC). We analysed whether, in those with a diagnosis of ON (which includes ON as CIS), MS-GRS improved prediction of conversion to MS using a Cox model adjusting for known MS risk factors (age of ON diagnosis, sex).
Results: We identified 2103 individuals with MS, 266 with MS-ON and 421 with non-MS-ON by end of cumulative follow-up. The MS-GRS was discriminative of MS (ROC-AUC=0.753). People with non-MS-ON had lower MS-GRS than those with MS-ON (mean 3.02 (SD 1.29) vs 3.71 (1.17),$p<0.0001$), whereas individuals with MS-ON had similar MS-GRS to MS cases without ON (3.62 (1.22) vs 3.71 (1.17),$p=0.32$). In those with an initial presentation ON (n=529, n=121/529 progressing to MS after median (IQR) 21 (12-35) years follow-up), MS-GRS improved prediction of future MS compared to a model using diagnosis age and sex alone, with a hazard ratio of 1.31 (95% CI 1.09-1.59,$p<0.005$) per SD increase in MS-GRS. We were able to stratify individuals into groups of low (4%), medium (23%), or high (43%) future MS risk.
Conclusion: People with MS-ON have the same MS genetic risk as other MS cases. This novel application of MS-GRS improved risk stratification for future MS diagnosis of ON, including ON as CIS. An MS-GRS integrated into a risk model combined with other demographic characteristics may be found useful for personalising investigation and treatment in individuals with CIS.

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P145
Implication of DNA methylation changes at chromosome 1q21.1 in the brain pathology of primary progressive multiple sclerosis

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Introduction: Multiple Sclerosis (MS) is a highly heterogeneous inflammatory and neurodegenerative disease of the central nervous system with an unpredictable course toward progressive disability. Understanding and treating progressive forms of MS remains extremely challenging due to the limited knowledge of the underlying mechanisms.
Objectives: To identify DNA methylation and gene expression changes that associate with progressive MS states using genetic, epigenetic, and network analysis approaches.
Aims: In this study, we aimed to examine the molecular changes that associate with the MS course.
Methods: We examined the molecular changes that associate with primary progressive MS (PPMS) using a cross-tissue (blood and post-mortem brain) and multilayered data (genetic, epigenetic, transcriptomic) from independent cohorts.
Results: We first identified and replicated hypermethylation of an intergenic region within the chromosome 1q21.1 locus in the blood of PPMS patients compared to other MS patients and healthy individuals. We next revealed that methylation is under the control of genetic variation both in the blood and brain. Several genetic variants also affected the expression of proximal genes (CHD1L, PRKAB2, and FMO5) in the brain and displayed evidence of the association with the risk of developing PPMS, suggesting a genetic-epigenetic-transcriptional interplay in PPMS pathogenesis. We next addressed the causal link between DNA methylation and gene expression using reporter systems and dCas9-TET1-induced demethylation of CpGs in the identified region, which resulted in upregulation of CHD1L and PRKAB2 genes in SH-SY5Y neuron-like cells. Independent exploration using unbiased correlation network analysis confirmed the

putative implication of CHD1L and PRKAB2 in brain processes in PPMS patients.
Conclusions: We provide several lines of evidence suggesting distinct molecular changes in 1q21.1 region, known to associate with brain development and disorders, associated with a genetic predisposition to high methylation in PPMS patients that regulates the expression of genes within the extended locus.

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Pathology and pathogenesis of MS - Immunology

P146
Cellular immune profiling reveals effector memory CD8$^+$CCR5$^+$ T-cell effect of ocrelizumab in early relapsing-remitting multiple sclerosis

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Introduction: Ocrelizumab, a humanized anti-CD20 monoclonal antibody is highly efficient in relapsing-remitting multiple sclerosis patients.
Objectives: We assessed early cellular immune profiles and their association with disease activity before treatment start and under therapy.
Aims: This study may provide new clues on the mechanisms of action of ocrelizumab and on the disease pathophysiology.
Methods: A first group of 42 patients with an early relapsing-remitting multiple sclerosis (RR-MS), never exposed to disease-modifying therapy, was included in 11 centres participating to an ancillary study of the ENSEMBLE trial (NCT03085810) to evaluate the effectiveness and safety of ocrelizumab. Phenotypic immune profile was comprehensively assessed by multi-parametric spectral flow cytometry at baseline, after 24 and 48 weeks of ocrelizumab treatment on cryopreserved peripheral blood mononuclear cells and analyzed in relation to disease clinical activity. A second group of 13 untreated RR-MS patients was included for comparative analysis of peripheral blood and cerebrospinal fluid. Transcriptomic profile was assessed by single-cell qPCRs of 96 genes of immunological interest.
Results: Using an unbiased analysis, we found that ocrelizumab impacted four clusters of CD4$^+$ T-cells: one corresponding to naïve CD4$^+$ T-cells was increased, the other clusters corresponded to effector memory CD4$^+$CCR6$^-$ T-cells expressing homing and migration markers, two of them also expressing CCR5 and were decreased by the treatment. Interestingly, one CD8$^+$ T-cell cluster was decreased by ocrelizumab corresponding to effector memory CCR5-expressing T-cells with high expression of the brain homing markers CD49d and CD11a and correlated with disease activity at baseline. These effector memory CD8$^+$CCR5$^+$ cells were enriched in the CSF of relapsing-remitting Multiple Sclerosis patients and corresponded to activated and cytotoxic cells.
Conclusion: Our study reports new insights into the anti-CD20 Ocrelizumab mode of action: it decreases a particular subset of effector memory CD8 T-cells expressing CCR5. These cells are able to infiltrate brain and their number correlates to disease activity, strongly suggesting their involvement in MS pathology.

Disclosure
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B cells infiltrating the MS brain: from local maturation to targeting by evobrutinib

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Introduction: Recently, our group demonstrated that IFN-γ and infectious factors such as TLR9 ligand and Epstein-Barr virus are important triggers for the development of $CXCR3^+$ B cells and their recruitment to the CNS in MS patients. How such B cells locally, in the periphery or CNS, evolve into effector populations and can be suppressed by BTK inhibitors is unclear.
Objectives: To study B-cell maturation in the CNS of MS and control brain donors, how this corresponds to immunoglobulin (Ig) production, T-cell presence and lesion formation and whether this can be a target of BTK inhibitor evobrutinib.
Aims: To define B-cell maturation in the CNS and yield new insights into the mechanism of action of next-generation BTK inhibitors in MS.
Methods: Flow cytometry was used to characterize *ex vivo* B cells and antibody-secreting cells (ASCs) in postmortem blood, CSF, meninges and white matter from 28 MS and 10 control donors. Laser capture microdissection and microarrays were performed to determine Ig gene expression in perilesional areas and rims of MS lesions. IHC/IF was used to analyze B and T cells in MS lesions. Phosphorylated and total BTK levels were screened in different blood B-cell subsets from several MS and control groups (n=15-30). Human B-cell differentiation under T follicular helper (T_{FH})-like circumstances and migration through the blood-brain barrier were assessed *in vitro* with and without evobrutinib.
Results: ASC/B-cell ratios were increased in all CNS compartments of MS brain donors, especially in white matter lesions. IgG gene expression was mainly upregulated in the rims of active MS lesions compared to normal-appearing and control white matter. ASC/B-cell ratios and CXCR3 expression on B cells in the CSF positively correlated with intrathecal IgG synthesis. In MS lesions, such ratios corresponded to $CD4^+$/$CD8^+$ T-cell frequencies and not age, which was supported by the proximity of B cells to T_{FH} cells *in situ*. Finally, we found that BTK activity was elevated and associated with CXCR3 expression levels in blood B cells from relapsing MS patients and that evobrutinib targeted these cells *in vitro* by hindering T_{FH}-dependent class switching, transmigration and maturation into ASCs.
Conclusions: Our work reveals that $CXCR3^+$ B cells preferentially mature into ASCs after entering the CNS and that the development of this pathogenic subset is a promising target of next-generation BTK inhibitor evobrutinib in both the periphery and CNS in MS.

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Reduced Treg suppressive capacity exacerbates B cell dysfunction in multiple sclerosis

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Introduction: Research strongly indicates the multi-factorial role of self-reactive B cells in driving pathophysiological processes in

Multiple Sclerosis (MS). In MS, B cell clones expressing autoreactive B cell receptors (BCRs) are able to escape tolerance checkpoints that maintain self-tolerance under normal physiological conditions. Incomplete elimination of self-reactive B cells may in part be mediated by dysfunctions in the suppressive capacity of regulatory T cells (Treg). In addition, B cell fate is to a large extent regulated by BCR stimulation-induced calcium signals and the downstream activation of distinct, calcium-dependent transcriptional programmes that either result in B cell apoptosis, or survival and expansion.

Objectives / Aims: To assess whether calcium responses and their downstream signalling cascades in B cells differ between healthy donors and MS patients, and whether MS patient-derived Treg differently affect B cells.

Methods / Results: Using a single-cell calcium imaging setup, in vitro proliferation assays, and transcriptomics, we showed that in both healthy donors and MS patients, BCR stimulation resulted in a significant increase in intracellular calcium, NFAT (nuclear factor of activated T cells) nuclear translocation, B cell proliferation, and an upregulation of mitosis-related genetic programmes. Treg derived from healthy donors significantly suppressed these hallmarks of B cell activation. MS patient-derived Treg, however, reduced BCR stimulation-induced B cell activation and proliferation to a lesser extent than their healthy counterparts. Mixed co-cultures with cells derived from healthy donors and MS patients revealed that this alteration in B cell proliferative capacity was solely due to dysfunctional Treg suppressive capacities in MS, and not due to inherent changes in B cell activation status. Furthermore, we were able to show that Treg suppressive effects on B cells were dependent on direct cellular contact.

Conclusions: We report an altered B cell activation in MS that is largely due to a reduction in Treg suppressive capacity, while B cell responses to BCR triggering remain intact.

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COVID-19 severity and vaccination effect in persons with MS treated with alemtuzumab

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Introduction: While there is evidence that persons with MS (pwMS) treated with anti-CD20 are at higher risk of severe COVID-19 and lower levels of antibodies after vaccination, there was no emerging evidence of an effect of alemtuzumab on COVID-19 severity and response to vaccine. However, small samples were analysed.

Objective/Aim: To evaluate COVID-19 severity, disease characteristics, and response to SARS-CoV-2 vaccination of pwMS treated with alemtuzumab.

Methods: We evaluated the subgroup of pwMS treated with alemtuzumab enrolled in the nationwide MuSC-19 and CovaXiMS studies. MuSC-19 was a retrospective study of pwMS with suspected or confirmed COVID-19 and CovaXiMS was a prospective study evaluating the antibody levels pre- and post-vaccination in pwMS.

Results: Forty-four pwMS treated with alemtuzumab (mean age 36 years, 71% female, 91% relapsing-remitting MS, mean interval since last infusion 730 days) had COVID-19 between March 2020 and December 2021. Seven (16%) were asymptomatic and the rest had mild disease, with no hospitalization nor ventilation required. In the CovaXiMS study, 34 pwMS (mean age 38 years, 74% female, 100% relapsing-remitting MS, mean interval since last infusion 784 days) were last treated with alemtuzumab before the two doses of mRNA vaccine (26 Pfizer, 8 Moderna). Of these, 23 (68%) received their last infusion < 2.5 years before vaccination. The antibody level 4 weeks after the second dose was high (median=4203 U/mL, range=484–8662) and comparable to levels achieved in pwMS treated with other DMTs except anti-CD20 and fingolimod. Antibody levels were not correlated to the time since last alemtuzumab infusion ($r=0.14$, $p=0.42$). All had 6 months of follow-up and no breakthrough infections were observed.

Conclusions: There is no evidence of any increased risk for severe COVID-19 in pwMS treated with alemtuzumab. In these patients, humoral response to anti-SARS-CoV-2 vaccine was high and comparable to those treated with other DMTs or untreated.

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Longitudinal COVID-19 immune trajectories in autoimmune patients on anti-CD20 therapy

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Introduction: B cell depleting therapies have been successfully utilized over the past decade to treat neuroimmune diseases. However, during the COVID-19 pandemic, these therapies pose a clinical concern, as patients may not be able to mount a sufficient antibody-mediated immune response to SARS-CoV-2 infection and vaccinations.

Objectives: Studies to-date have reported conflicting results on the degree of antibody production post-SARS-CoV-2 infection and vaccinations and have focused primarily on short-term follow up immune profiling. Our objective was to perform a longitudinal follow up of immune responses post-SARS-CoV-2 infection and vaccination in a cohort of COVID-19 B cell depleted autoimmune patients (n=5), COVID-19 non-B cell depleted autoimmune patients (n=15), COVID-19 immunocompetent patients (n=117), and healthy controls (n=6) for a total of 259 samples in 137 participants.

Aims: B cell depleted patients and controls were followed prospectively for 12 months and were evaluated at multiple time points for spike antibody titers, B and T cell composition, and frequency of T cells specific for SARS-CoV-2 spike, nucleocapsid, membrane, and envelope antigens.

Results: Four out of five B cell-depleted patients developed detectable anti-spike SARS-CoV-2 antibodies, which were boosted by vaccinations in two out of four patients. While SARS-CoV-2 spike antibodies were associated with presence of $CD20^{+}$B cells, very few B cells were required. In contrast, patients who primarily had $CD19^{+}CD20^{-}$B cells during acute COVID-19 disease or vaccination did not seroconvert. Interestingly, circulating B cells in B cell depleted patients were significantly $CD38^{high}$with co-expression of CD24 and CD27, indicating that B cell depletion may directly impact B cell-signatures and activation patterns. Additionally, all patients post COVID-19 mounted a sustained T-cell response to SARS-CoV-2 antigens, regardless of B cell depletion status and seroconversion. Specifically, all patients had responding naïve, central memory, effector memory, and effector memory RA+ T-cells, suggesting intact T-cell memory conversion in B cell depleted patients compared to COVID-19 controls.

Conclusions: We present the longest COVID-19 immune profiling analysis to date in B cell depleted patients, demonstrating that both humoral and cellular immune responses can be generated and sustained in this patient population for up to 12 months in response to SARS-CoV-2 infection and vaccination.

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NK-like CD8+ T cells with high cytotoxic properties are the reservoir of clonal cells and related to disease activity in multiple sclerosis

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Memory CD8 T cells are key players in multiple sclerosis (MS) as they predominate at the lesion sites of the central nervous system (CNS), with an oligoclonal distribution in the periphery and lesions, but the CD8 T cells driving autoimmune inflammation have not been identified yet. We hypothesized that cells able to provoke damage in the CNS might have a specific phenotypic and functional pattern.

To identify a cell subtype involved in MS, we used a high dimensional single-cell profiling of blood memory CD8 T cells combined with TCRβ sequencing on a cohort of MS patients, healthy controls (HC) and patients with other inflammatory diseases of the CNS (OID). The involvement of a cell subtype in MS was confirmed by flow cytometry (FC) and their infiltration into the CNS determined by immunofluorescence (IF). We then deepened the knowledge of the identified cells with RNA sequencing and FC phenotyping and, we analyzed their function with *in vitro* assay.

With single-cell analysis, we identify a subset of effector memory (EM) CD8 T cells expressing many markers associated with NK cells (including CD94) and cytotoxicity which was increased in MS patients compared to HC and OID patients. FC data on another cohort also confirmed this observation. Interestingly, IF on brain tissues demonstrated an infiltration of these CD8+CD94+ T cells in MS lesions and more particularly in active lesions. Focusing on the disease process, we found that these cells were increased during disease relapse. Moreover, based on a third cohort of treatment-naive MS patients, we confirmed the correlation between the frequency of these cells and the delay from the last relapse. Identification of clonal cells using bulk and single cells TCR sequencing allow us to show that these cells belong to a reservoir of peripheral oligoclonal cells. A better characterization of these cells by RNAseq and FC defined the cells as NK-like CD8 T cells. Finally, functional assays showed that the NK-like CD8 T cells exert a cytotoxic activity against the K562 cell line independent of any TCR involvement, although they display a reactive TCR.

Taken together, our data are the first to describe EM CD8 T cells with NK-like properties specific to MS patients, belonging to an oligoclonal reservoir of peripheral T cells and mobilized in the periphery during inflammation to enrich lesions of the CNS. These NK-like CD8 T cells exert cytotoxicity against target cells independent of any involvement of the TCR.

Disclosure

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Brain-specific T cells from multiple sclerosis patients have a T central memory phenotype and express adhesion molecules and chemokine receptors necessary for migration to brain

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Introduction: We recently developed a method to stimulate peripheral blood mononuclear cells (PBMC) with human brain

homogenate. Culture of PBMC with brain elicits modest proliferation with a mean stimulation index of 3.8 and no significant difference in proliferation between MS and controls. A pilot experiment with RNA-Seq suggested that the responding cells in MS patients had more pathogenic potential than those from controls, based on expression of mRNA for cytokines, chemokine receptors, and adhesion molecules.

Objectives: To measure the memory phenotype and the expression of adhesion molecules and chemokine receptors in T lymphocytes specific for brain antigens, comparing MS to healthy controls.

Methods: We obtained blood samples from newly presenting, untreated MS patients and healthy controls. We isolated PBMC, labeled them with CFSE, and stimulated them with brain homogenate, influenza, and other antigens. After 6 days, we collected the viable cells, and stained with viability stain and antibodies to CD3, CD4, CD8, CD45RA, CD49d (VLA4), CD62L (SELL), CD196 (CCR6), and CD197 (CCR7). Cells were analyzed on a BD FACS ARIA II flow cytometer. We gated on the viable, CFSE low, CD3+ cells (responding T cells). We defined T central memory (Tcm) as CD45RA-, CD62L+, CD197+. We defined T effector memory (Tem) as CD45RA-, CD62L-, CD197-. We considered cells expressing both CD49d and CD196 capable of entering the CNS.

Results: The responding cells from MS patients had a higher fraction of Tcm than controls, mean 49.6% with standard deviation (sd) 23.5% in MS compared to 21.5% with sd 8.7% in controls, p=0.019, t test. The expression of CD62L did not differ, but the expression of CD197 was significantly higher in MS; median 69.8% with interquartile range (IQR) 27.0 to 97.8% in MS versus median 24.7% with IQR 17.8 to 29.8% in controls, p=0.026, rank sum test. Similarly, the fraction of responding T cells expressing both CD49d and CD196 was higher in MS, median 42.3% with IQR 37.7 to 57.3%, compared to controls, median 21.5% with IQR 16.5 to 28.9%, p=0.002, rank sum test. The expression of CD49d was not different, but the expression of CD196 was higher in MS, p=0.007, t test.

Conclusions: The brain responding cells from MS patients have a higher fraction of Tcm phenotype and higher expression of surface molecules required for entry into the brain than those from controls. The increased expression of the chemokine receptors CD196 and CD197 in MS is notable.

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Evaluation of the clonal architecture of T-cell repertoire in multiple sclerosis patients experiencing relapses

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Introduction: Relapses are the distinctive feature of multiple sclerosis (MS) and represent the clinical manifestation of a damage in the central nervous system induced by a burst of autoimmune inflammatory insult. The study of global characteristics of the immune repertoire during relapses is an innovative approach to characterize this phenomenon.

Aims: *T*o investigate characteristics of the immune repertoire in MS patients experiencing relapses.

Methods: T-cell receptors (TCR) CDR3 sequences were obtained from DNA extracted from whole blood collected from 144 untreated relapsing-remitting MS subjects according to the ImmunoSEQ hsTCRB kit (Adaptive Biotechnologies). Among them, patients were classified as: "relapsing patients" if they experienced a clinical relapse at the time of blood sampling (considering a window of ±30 days from sampling) (n=12) or "relapse-free patients" when no clinical relapses occurred within ±1 year (n=16). Repertoire architecture was evaluated through the construction of CDR3 sequences networks using the Levenshtein distance to define connections. Analyses were performed with *immunarch* and R packages. Target prediction of the relevant clonotypes was performed with TCRMatch.

Results: We observed a reduced degree of connection in relapsing patients compared to relapse-free patients (P = 0.036 including age, sex and productive clones as covariates, median = 0.167 and 0.184 respectively in "relapse" and "relapse-free" groups). Focusing on highly shared clonotypes in relapsing individuals (shared among >50% of the relapsing individuals and absent in all the relapse-free group), we identified 5 clonotypes showing a potential ability to bind viral proteins, mainly Epstein-Barr virus and Cytomegalovirus, as well as to human antigens such as MBP (Myelin Basic Protein).

Conclusions: The similarity landscape of CDR3 amino acid sequences constitutes the clonal architecture of the immune repertoire and reflects its antigen recognition breadth. Our results suggest that the immune repertoire undergoes changes during a clinical relapse toward a repertoire that is more prone to recognize more antigens. Preliminary analyses on target prediction suggest shared clonotypes among relapsing patients targeting viral and myelin antigens.

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Quantitative proteomics reveals protein dysregulation during T cell activation in multiple sclerosis patients compared to healthy controls

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Introduction: Multiple sclerosis (MS) is an autoimmune, neurodegenerative disorder with a strong genetic component that acts in a complex interaction with environmental factors for disease development. $CD4^+$ T cells are pivotal players in MS pathogenesis, where peripherally activated T cells migrate to the central nervous system leading to demyelination and axonal degeneration.
Objectives and aims: Through a proteomic approach, we aim at identifying dysregulated pathways in activated T cells from people with MS (pwMS) as compared to healthy controls (HCs).
Methods: $CD4^+$ T cells were purified from peripheral blood from pwMS and HCs by magnetic separation. Cells were left unstimulated or stimulatedin vitro through the T cell receptor and costimulatory CD28 receptor for 24 hours prior to sampling. Electrospray liquid chromatography-tandem mass spectrometry was used to measure protein abundances.
Results: Upon T cell activation the abundance of 1,801 proteins was changed. Among these proteins, we observed an enrichment of proteins expressed by MS-susceptibility genes. When comparing protein abundances in T cell samples from HCs and pwMS, 18 and 33 proteins were differentially expressed in unstimulated and stimulated $CD4^+$ T cells, respectively. Moreover, 353 and 304 proteins were identified as proteins exclusively induced upon T cell activation in HCs and pwMS, respectively and dysregulation of the Nur77 pathway was observed only in samples from pwMS.
Conclusions: Our study highlights the importance of $CD4^+$ T cell activation for MS, as proteins that change in abundance upon T cell activation are enriched for proteins encoded by MS susceptibility genes. The results provide evidence for proteomic disturbances in T cell activation in MS, and pinpoint to dysregulation of the Nur77 pathway, a biological pathway known to limit aberrant effector T cell responses.

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The other authors declare that they have nothing to disclose.

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Re-visiting αβ-crystallin: EBNA1 antibody cross-reactivity and CRYAB-specific T cell responses in multiple sclerosis

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Introduction: Epstein-Barr virus (EBV) is linked to MS development and molecular mimicry between autoantigens and viral proteins has been hypothesised to drive central nervous system (CNS) attack. EBNA1 antibodies have been the focus of cross-reactivity studies due to their elevation in MS sera, and αβ-crystallin (CRYAB) has been suggested for many years as an autoantigen in MS but its role in disease has been hotly debated.
Aims: To investigate adaptive immune responses to EBNA1 and CRYAB in MS patients
Methods: Overlapping peptide pools from CRYAB and EBNA1 were used in a multiplex bead assay to quantify IgG responses in population-based control (n=713) and persons with MS (pwMS) (n=720) plasma. Individuals' IgG levels above 75thpercentile among controls were defined as positive. Competition assays were used to determine whether homologous peptides from EBNA1 and CRYAB could reciprocally block peptide binding

peptide to IgG. Peripheral blood mononuclear cells (PBMC) from controls, individuals with other neurological disease (OND) and pwMS were stimulated using full-length EBNA1 and CRYAB antigen-coupled beads. Responding T cells were analysed by FluoroSpot and flow cytometry.
Results: Sequence alignment showed homology between peptide sequences in EBNA1 (aa399-415) and CRYAB (aa8-27). pwMS IgG antibody responses to overlapping peptides with one amino acid change showed an increased MS odds ratio (OR) for CRYAB peptides aa3-17 (OR=2) and aa121-172 (OR=2.8). Reciprocal blocking experiments showed that spike in of EBNA1 peptides with CRYAB homology blocked antigen-specific IgG binding and vice versa, whereas addition of an EBNA1 peptide with no homology to CRYAB was not able to block binding. FluoroSpot analysis of CRYAB- and EBNA1-specific T cells in PBMC showed a higher frequency of IFNγ, IL-17A and IL-22 cytokine production in pwMS compared to control groups.
Conclusion: We detected increased anti-CRYAB antibody levels in pwMS and reciprocal blocking experiments demonstrated antibody cross-reactivity between EBNA1 (aa399-415) and CRYAB (aa8-27). Investigation of cellular immunity showed CRYAB to elicit a strong T cell response in pwMS, and further investigation of these cells is warranted to determine their relevance in MS disease pathology. However, due to literature stating a possible protective role for CRYAB in MS, more research is warranted to elucidate the complex role of antibody and T cell responses to this protein in CNS autoimmunity.

Disclosure
HG is the founder and co-owner of the company NEOGAP Therapeutics AB, which holds patents and pending patents regarding bead-based antigen processing. MB and HG are inventors of said patents.GGholds apositionat NEOGAP Therapeutics AB. TO has received unrestricted MS research grants and/or lecture/advisory board honoraria from Biogen, Novartis, Genzyme, Merck, and Roche, of which none are applicable to this study. R.M. received unrestricted grants from Biogen and Novartis and personal compensation for lecture or advisory board functions from Biogen, Merck, Novartis, Roche, Sanofi Aventis, Teva, Cell-Protect, Neuway, and Third Rock Ventures. He is a cofounder and co-owner of Cellerys, a startup company of the University of Zürich. He is a coinventor and patent holder on patents related to antigen-specific tolerisation, treatment/vaccination of PML, and the use of daclizumab as a treatment of MS. IK has support in the form of research grants from Swedish Brain Foundation, Swedish research council (2020-01638), EU Horizon 2020 (MultipleMS, project nr 733161 and EU-STANDS4PM, project nr 825843) and Region Stockholm. KT was supported by a grant from Swedish Brain Foundation.

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Investigating the T cell response to Anoctamin-2 and Epstein-Barr virus nuclear antigen 1 in multiple sclerosis using antigen-coupled beads

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Introduction: Antibody responses to anoctamin-2 (ANO2) have previously been shown to be increased in frequency in plasma from persons with multiple sclerosis (pwMS), with ANO2 IgG also shown to be able to bind a small homologous peptide from Epstein-Barr virus nuclear antigen 1 (EBNA1). ANO2 has not previously been investigated as a target of cellular immunity in MS, and we sought to determine whether T cell responses to this antigen could be detected in pwMS from Sweden and Switzerland.
Aim: To determine whether ANO2 is a target of T cell responses in MS
Methods: Peripheral blood mononuclear cells (PBMC) from two cohorts were stimulated in a FluoroSpot assay with paramagnetic beads coupled to protein fragments from ANO2, EBNA1 and the control CMV antigen pp65. The first cohort consisted of healthy controls (HC), individuals with other neurological disease (OND) and untreated pwMS (MS-Un), the second cohort with HC and natalizumab-treated pwMS (MS-Nat). Production of IFNγ, IL-17A and IL-22 were used to determine the frequency of antigen-specific T cells. Addition of human leukocyte antigen (HLA)-blocking antibodies to FluoroSpot wells was used to determine HLA class I or II signalling, and spectral flow cytometry was applied to analyse the phenotype of ANO2-specific T cells.
Results: T cell reactivity to the short region of ANO2 (ANO2s) containing the EBNA1 homologous epitope was significantly higher in MS-Un and MS-Nat groups compared to controls as measured by FluoroSpot (cohort 1 IFNγ MS-Un:HC *p=0.0015*,cohort 2 IFNγ MS-Nat:HC *p=0.0004* Mann-Whitney). T cell responses to further regions of ANO2 were also increased in MS patient groups compared to controls, flow cytometry analysis detected both IFNγ- and TNFα-producing CD4+ and CD8+ T cells to ANO2 in MS patients.
Conclusions: ANO2-specific T cells were more frequent in pwMS and responses were not restricted to the ANO2s region, suggesting epitope spreading beyond the sequence which is the focus of cross-reactive autoantibody responses in MS. Further investigation of these ANO2-specific T cells is needed to establish their relevance to CNS disease.

Disclosure
OT nothing to disclose. HG is the founder and co-owner of the company NEOGAP Therapeutics AB, which holds patents and pending patents regarding bead-based antigen processing. MB and HG are inventors of said patents. GG,CCQ, AK, and ON hold positions at NEOGAP Therapeutics AB. TO has received unrestricted MS research grants and/or lecture/advisory board honoraria from Biogen, Novartis, Genzyme, Merck, and Roche, of which none are applicable to this study. R.M. received unrestricted grants from Biogen and Novartis and personal compensation for

lecture or advisory board functions from Biogen, Merck, Novartis, Roche, Sanofi Aventis, Teva, Cell-Protect, Neuway, and Third Rock Ventures. He is a cofounder and co-owner of Cellerys, a startup company of the University of Zürich. He is a coinventor and patent holder on patents related to antigen-specific tolerization, treatment/vaccination of PML, and the use of daclizumab as a treatment of MS.

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Novel CD20+ innate lymphoid cells show increased killing capacity and are related to multiple sclerosis prognosis

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Introduction: Although CD20 is known as a B cell marker, T cells that express low levels of CD20 are also present. In this study, we have identified and characterized a novel fraction of $CD3^-CD56^-$ innate lymphoid cells (ILCs) and $CD3^-CD56^+$ natural killer (NK) cells that also express low levels of CD20.
Objectives: To investigate the presence of $CD20^+$NK and ILCs in blood and cerebrospinal fluid (CSF), identify the relationship between $CD20^+$ILCs and MS and obtain insight into the immunological properties of $CD20^+$NK cells.
Methods: $CD20^+$T, NK and ILCs were analyzed in the peripheral blood mononuclear cells (PBMC) and CSF samples of 31 people with multiple sclerosis (pwMS), eight inflammatory demyelinating disorders (IDD), 12 other inflammatory neurological disorders (OIND), 15 non-inflammatory neurological disorders (NIND) and PBMC samples of 14 healthy controls (HC). Functional properties of $CD20^+$NK cells were analyzed in the PBMC from 10 HCs and 12 pwMS. Stimulated PBMCs and MACS sorted $CD56^+$ cells were analyzed for the expression of CD107a, NKp46, IFN-γ, GM-CSF, TNF-α and IL-10. Killing assay with the K562 cells were performed with $CD20^+$and $CD20^-$NK cells to determine NK cell cytotoxicity, and supernatants were collected to determine the concentrations of TNF-α, sFas, sFasL, IFN-γ, Granzyme A/B, Perforin and Granulysin. Correlation analysis with EDSS was also performed.
Results: A positive correlation with disease severity was observed between EDSS scores and $CD20^+$T, NK and ILC populations in PBMCs and CSF of pwMS. We also found that the percentage of $CD20^+$T, NK and ILCs were higher in pwMS compared to controls and these cells were more abundant in the CSF compared to blood. CD20+ NK cells were enriched in the CD56bright population. Stimulation studies showed that CD107a and cytokine expressions and cytotoxic molecule concentrations were significantly higher in the $CD20^+$NK cells compared to $CD20^-$NK cells. We have also observed increased apoptosis in K562 cells cocultured with $CD20^+$NK Cells.
Conclusions: In this study, we identified a novel subset of $CD20^+$NK cells and ILCs. The ratio of these cells was increased in pwMS and showed a positive correlation with EDSS. Similar to their T cell counterparts, $CD20^+$NK cells showed a more active profile than $CD20^-$NK cells. Additionally, increased apoptosis was observed in K562 cells cocultured with $CD20^+$NK cells. These data suggest that $CD20^+$innate lymphocytes may also play in MS pathogenesis and treatment response.

Disclosure
Nothing to Disclose

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Single-cell RNA sequencing of peripheral CD8+ T cells of MS-discordant monozygotic twins reveals disease-associated alterations in immune signaling

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Introduction: In multiple sclerosis (MS), genetic predisposition and environmental conditions both contribute to disease initiation, but their effects are hard to untangle. Using a cohort of monozygotic twins discordant for MS enabled us to control for both early environmental effects and the genetic background and decipher the disease-associated immunological alterations. For this purpose, we have collected peripheral blood mononuclear cells (PBMCs) and cerebrospinal fluid (CSF) from the MS TWIN STUDY, a worldwide unique cohort of monozygotic twin pairs discordant for MS.
Methods: The discovery cohort included 6 monozygotic twin pairs discordant for MS and 6 twin pairs, in which the corresponding clinically unaffected co-twin presented with signs of subclinical neuroinflammation (SCNI, detected on MRI and/or CSF) as a correlate for prodromal MS. The validation cohort included samples of 13 untreated patients with early MS and 5 patients with idiopathic intracranial hypertension (IIH) as non-inflammatory controls. We sorted out the antigen-experienced CD8+ T cells from the PBMCs and subsequently generated the transcriptomic and T-cell receptor libraries. For the data analysis, we applied unbiased bioinformatics pipelines using gene and pathway enrichment tools. To focus our analysis on those CD8+ T cells actively involved in the disease process, we selected those clusters containing T cell clones present in both compartments (PBMC and CSF).
Results: Our unbiased bioinformatics analysis of disease-associated CD8+ T cell clusters revealed dysregulation of interleukin-2 (IL-2), TNF-alpha, and interferons signalling cascades. Subsequently, we identified single components of each cascade significantly upregulated in the SCNI and the MS-group. The SCNI group showed overexpression of *IL-2 receptor, JAK3*, and various transcription factors (*JUNB, XBP1*). The MS group was

characterised by upregulation of proteasomal subunits (*PSMB1, PSME1*), *CD74, CD27* and*CD69*. The subsequent unbiased analysis of the validation cohort showed significant enrichment of the pathways described above.
Conclusions: The exact identification of factors possibly leading to early immunological activation (*IL2R, JAK3, JUNB*) and establishment of MS (proteasomal subunits, antigen presentation (*CD74*) and excessive activation through *CD69* and *CD27*) enhance our understanding of the pathogenesis of the disease and enables us a new prospect for novel diagnostic and therapeutic strategies of MS.

Disclosure
VK, LM, KE have nothing to disclose.
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TK has received speaker honoraria and/or personal fees for advisory boards from Novartis Pharma, Roche Pharma, Alexion/Astra Zeneca and Biogen. The Institution she works for has received grant support for her research from Bayer-Schering AG, Novartis and Chugai Pharma in the past
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P160
Characterization of immunosenescence trajectories in diverse adults and patients with multiple sclerosis

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Introduction: Immunosenescence (ISC) is the physiologic aging of the immune-system, involving gradual changes in immune-cell proportions and functions. Whereas in multiple sclerosis (MS), ISC is thought to occur prematurely and older age at disease onset is associated with a poor prognosis. Genetic variation, sexual-dimorphism and viral infections may influence the ISC profile. To date, there are few large-scale studies of multi-modal ISC trajectories, and they profiled mostly individuals of European ancestry.
Objective: To define reference trajectories of ISC in healthy individuals to better understand the relation of ISC to the neurodegenerative component of MS.
Aim: To establish trajectories of ISC in diverse reference populations, and compare to MS.
Methods: To assess ISC-associated phenotypic changes on PBMCs of control adults (n=268, age 20-84 years) and untreated RRMS (n=21, age 50-74 years), we used multiparametric cytometry with a pool of 15 antibody markers to capture all major PBMC populations.
Results: Standard bi-dimensional FlowJo analysis uncovered 15 age-associated cell-subsets. First, we confirmed previous findings: decrease in naïve CD8 ($p=2.14x10^{-17}$), CD20 B cells ($p=1.6 x 10^{-4}$) and increase of CD8 TEMRA ($p= 3.05x10^{-10}$) with advancing age among African American, Hispanics & Caucasians. However, only Hispanics displayed a significant increase of effector memory (EM) CD4 and CD8 T cells with age ($p=4.6 x 10^{-3}$, p=0.01). Frequencies of NKT cells also increased with age ($p=9.7x10^{-4}$), which was driven by Hispanics and Caucasians. CD11c+B cells appear as ISC markers ($p=6.81x10^{-4}$). RRMS patients exhibit a comparable ISC profile to controls, although central memory (CM) CD8 T cells were higher in MS (p=0.03).
To complement standard FlowJo analysis, we used PhenoGraph to empirically cluster ~ 4 million PBMCs with 15-dimensional cytometric data into 39 discrete cell-subsets. This effort uncovered several novel cell-subsets, including a $CD16^+CD56^+PD1\text{-}L^+NK$ cell-subset in MS participants which increases with age (p=0.01). We have also established an "immunological age" for each individual and contrast this to their chronological age.

Conclusions: We confirmed well-established senescent cell subtypes. Signatures of ISC included NKT-cells and CD11c^{+}B cells, and a novel NK cell-subset in older Caucasian RRMS, that may contribute to disease progression. The immunological age could help predict MS progression, and further guide interventional therapies.

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Pathology and pathogenesis of MS - Microbiology and virology

P161
Computational prediction of molecular mimicry in chronic, neurotropic, and commensal pathogens as a link to autoimmunity

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Introduction: Molecular Mimicry is a mechanism used by pathogens to evade immune detection by "mimicking" human peptide motifs in viral proteins. While protective for pathogens, molecular mimicry has been demonstrated to cause neurological autoimmunity. One of the strongest viral connections with neurological autoimmunity is Epstein-Barr virus which can trigger production of cross-reactive antibodies and T-cells. However, there is less known about the contribution of molecular mimicry among different pathogens preceding neurological autoimmunity.
Objectives: Identify predicted molecular mimicry in silico for the most prevalent human pathogens consisting of various chronic, acute, neurotropic, pathogenic, and commensal bacterial taxa and viruses.
Aims: In this study, we executed one of the largest in silico molecular mimicry evaluations to date to identify predicted molecular mimicry and compare its frequency between chronic and acute pathogens, neurotropic and non-neurotropic pathogens, taxa from the gut microbiome and pathogenic bacteria, and pathogens with reported infections preceding neurological autoimmune disorders.
Methods: Pathogen protein sequences were referenced to the human proteome using suffix array kernel smoothing to identify amino acid (AA) sequences of either 12 or 18 AA long sequences with less than 33% mismatches to AA sequences in the Homo sapiens proteome. The rate of molecular mimicry in pathogen proteomes, the match rate of each mimic, and the evolution of the pathogen mimics overtime were compared between the different pathogen groups to identify possible pathogen strategies associated with higher rates of molecular mimicry. Mimicked human proteins were evaluated for reported expression in the central nervous system to identify mimics with possible implications in neurological autoimmunity.
Results: Chronically infecting pathogens demonstrate higher rates of protein molecular mimicry, with chronically infecting neurotropic viruses and herpesviruses having some of the highest rates among all evaluated species.
Conclusions: Pathogens use molecular mimicry as a survival mechanism, which can result in autoimmunity. In this study, we identified classes of pathogens with higher rates of predicted molecular mimicry, and present specific predicted molecular mimics for proteins highly expressed in the central nervous system. These findings will help to continue to unravel the contribution of viral infections to neurological autoimmunity.

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P162
Epstein-Barr virus and multiple sclerosis in a spanish cohort. A two-years longitudinal study

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Introduction: Although the etiology of multiple sclerosis (MS) is still unknown, there are increasing evidences that a number of environmental factors could be important in the disease. Thus, the infection by certain viruses have been linked with the development of MS, especially the Epstein-Barr virus (EBV) that could be the leading cause of MS.

Objectives: 1. To analyze the prevalence and levels of anti-EBNA-1 and anti-VCA IgG antibodies in a Spanish cohort of MS patients and their interactions with other environmental (smoking habit and vitamin D) and genetic (HLA-DRB1*15:01) risk factors. 2. To analyze the association of the evolution of the anti-EBNA-1 and anti-VCA IgG antibody titers with the clinical response to different disease modifying therapies (DMTs) after two-years of follow-up.
Methods: We recruited 325 MS patients (217 females; mean age: 36.0) without DMT (serum samples were collected 1-3 months before starting a therapy) and 295 healthy controls (HC) (115 females; mean age: 39.0). For each patient we also collected serum samples 6, 12, 18 and 24 months after starting the DMT (interferon beta, glatiramer acetate or natalizumab). EBNA-1 and VCA IgG titers were analyzed by ELISA; 25(OH)D levels were analyzed by immunoassay; HLA DRB1*15:01 allelic variant was analyzed by Taqman technology.
Results: 1. 97.8% (318/325) vs. 87.1% (257/295) positives for EBNA-1 in MS patients and HC, respectively ($p<0.0001$; O.R.=6.7); 99.7% (324/325) vs. 94.6% (279/295) for VCA in MS patients and HC, respectively ($p=0.0001$; O.R.=18.6). All MS patients were positive for EBNA-1 and/or VCA IgG antibodies vs. 280/295 (94.9%) HC ($p<0.0001$). IgG titers were also significantly higher in MS patients than in HC. After stratification by other predisposing factors for MS, EBNA-1 and VCA IgG prevalences and titers remained significantly higher in MS patients than in HC. 2. We did not find any statistical correlation in the variation of the EBNA-1 and VCA IgG titers between baseline and 24 month visits with the number of relapses, progression, clinical response, NEDA-3 condition or therapeutic failure to any of the DMTs included in the study.
Conclusions: These results confirm that MS occurs rarely in absence of EBV. Although other predisposing factors could be involved in MS pathology, prevalences and titers remained significantly higher in MS patients than in controls after stratification by them. Similar studies with B-cell–targeted therapies should be performed.

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P163
Oral microbiome characterization in multiple sclerosis patients

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Context: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system. There has been growing evidence of the microbiota's involvement in the regulation and development of the immune and nervous systems through the gut–brain axis. With extensive research being carried out to characterize gut microbiome composition in MS, several relevant associations have been pointed out. However, oral microbiome, which has the ability to shape B-cell repertoire in tonsils, remains uncharacterized in MS. Thus, we aim to characterize oral microbiome in MS and assess whether previously found associations in the gut can also be found in saliva.
Methods: We collected saliva samples from 14 MS patients and 21 healthy volunteers (HV). Within this set of individuals, 12 MS and 11 HV feces samples were also available. The oral and fecal microbiota compartment was characterized using 16S rRNA sequencing. We then performed an *in silico* bacterial metabolite inference by Flux Balance Analysis (FBA) and bacterial pathways analysis using Picrust2 algorithm. We created a logistic regression discrimination model based on the inferred metabolites and validated it on an independent German cohort.
Results: Oral microbiota from MS patients showed signs of dysbiosis with decreased alpha-diversity and Shannon diversity indices compared to healthy volunteers. We found 12 oral taxa and 31 gut taxa differentially present between MS and HV (FDR<0,1). *Dialister* abundance was decreased in both saliva and gut of MS patients. *Streptococcus* abundance which was decreased in saliva was increased in gut of MS patients. An *in silico*FBA analysis indicated that microbiome-derived metabolites myo-inositol and fructose were decreased, whereas L-lactate was increased in MS patients' saliva. Amino-acids metabolites were also disturbed. Our discrimination model suggest a microbiome-derived metabolites signature found in the saliva of MS patients.
Conclusion: This is the first study to assess oral microbiome in a MS cohort.Our data reveal a specific MS signature in both oral and fecal microbiome with a lower diversity for salivary microbiota suggesting the oral compartment as another site for immune regulation.

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Léo Boussamet: nothing to disclose

P164
Short-chain fatty acids (SCFAs): propionate, butyrate, and acetate are associated with clinical, radiological, and immunological parameters in multiple sclerosis patients

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Background: Different environmental factors could be involved in multiple sclerosis (MS) pathophysiology, such as viruses or sun exposure. Recently, the gut microbiota has been added to this list. Short-chain fatty acids (SCFA) are microorganism-derived molecules that could have a role in the microbiota gut-brain axis; the most abundant are butyrate (BA), propionate (PA), and acetate (AA) (95% of SCFA).
Objective: To study the levels of AA, BA, and PA in MS patients compared to those of healthy donors (HDs), and their association with demographic and immunological parameters in these two populations. To assess the association of these previous factors with different clinical and radiological parameters in MS patients.
Methods: In this cross-sectional study participated 161 untreated MS patients and 130 HDs. Patients were selected according to their score in the EDSS (MS2: 113 patients with EDSS <2.0 and MS4: 48 patients with EDSS >4.0). SCFA levels were studied in plasma samples by liquid chromatography-mass spectrometry. Blood mononuclear cells subpopulations were analyzed by flow cytometry, including the intracellular detection of IL-17, IFN-gamma, TNF-alpha and GM-CSF. The levels of the cytokine Activin A, and the IgG and IgM against EBV, HHV-6 and CMV, were measured by ELISA.
Results: Two logistic regression models were performed, including all variables that were statistically different between MS and HD: Activin, anti-EBNA IgG, anti-VCA IgG, anti-CMV IgG, certain cellular subpopulations, and the ratio PA/AA or the PA/BA. The two definitive/final models included: Activin, anti-EBNA IgG, percentage of dendritic cells, and one of the 2 ratios, being the ratios in each model, the variables with better OR [PA/AA: OR:0.026 (0.001, 0.581), PA/BA: (0.174 (0.066, 0.461), meaning the risk of being patient vs. being HD is 38.5 times higher among individuals with lower PA/AA and 5.8 times higher among those with lower PA/BA. The ratio PA/AA was significant higher in MS2 patients (0.22 ± 0.1) versus MS4 (0.16 ± 0.1) ($p = 0.002$), we obtained the same results for the ratio BA/AA (0.23 ± 0.08 vs 0.17 ± 0.1; $p = 0.001$). In MS4 patients, we observed a correlation between AA and the number of T2 lesions ($r=0.612$; $p=0.0001$).
Conclusions: Our results suggest that the SCFA PA, BA, and AA could be involved in MS pathology. Further studies are warranted to study their potential use as biomarkers for the diagnosis and prognosis of MS disease, and their utility as new therapeutic targets.

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P165
MS-associated gut microbiome in the Israeli population and inter-relationship with diet

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Background: The gut microbiome plays a major role in health in the human host and has been implicated in a range of disorders, including Multiple Sclerosis (MS), linked to both disease susceptibility and activity. Gut microbiota is modulated by both genetic and environmental factors including diet, and may differ among geographical regions and populations. This study aimed to characterize the MS-associated microbiota in the Israeli population, comprised of relatively defined ethnicities.
Methods: Stool was collected from57 treatment-naive relapsing remitting patients with MS (PwMS) (31Jewish and 26 Arabs) and 43 matched healthy controls. All participants completed a food frequency questionnaires (FFQ) and a Mediterranean Diet Score questionnaire (MDS), specifically adapted to the Israeli population. Microbial DNA was extracted from stool and 16S rRNA V3-V4 region sequenced (Illumina Miseq). Reads were clustered into Operational Taxonomic Units (OTUs) using CLC-Bio and statistical analysis performed using MicrobiomeAnalyst.
Results: 1295 OTUs were identified for analysis. There was no difference in α or b diversity between MS and controls at any taxonomic level. Analysis of relative abundance identified 4 families, 18 genera and 14 species with significant differences between MS and control. The differential abundance of genera such as Mitsuokella, Tyzzerella and Lachnospiraceae NK4A126 group and species such as Ruminococcus gnavus and Negativibacillus massiliensis was

detected both in the Jewish and Arab cohorts, while others were specific to an ethnic group. We found lower abundance in MS of several butyrate- and other short-chain fatty acids (SCFAs)-producing genera, including Lachnospiraceae NK4A136 group and Ruminococcaceae UCG 013.SCFAs like Butyrate may lessen inflammatory disease by inducing T regulatory cells. Ruminococcus gnavus showed increased abundance in MS patients, as has been reported in inflammatory bowel disease.
53% of PwMS and 58% of controls scored intermediate or high compliance to a Mediterranean diet, with no significant difference in MDS score between the groups. Correlations between disease duration and several nutrients including vitamins were found, suggesting that patients introduce changes in dietary habits following disease diagnosis.
Conclusions: This study provides novel candidates for biomarkers of MS etiology, and expand the comprehention of the role of the microbiota and diet in health and disease.

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Pathology and pathogenesis of MS - Environmental factors

P166
Modulation of the peripheral blood immune cell transcriptome by vitamin D supplementation in people with a first demyelinating event

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Introduction: Vitamin D deficiency is a risk factor for multiple sclerosis (MS). Both*in vitro* and animal studies suggest an immunomodulatory effect of vitamin D. It is currently unclear whether vitamin D supplementation can prevent recurrent disease activity in people who have had a first demyelinating event (FDE), and how supplementation alters immune cell activity.
Objectives: We aimed to investigate the effects of vitamin D supplementation on gene expression of peripheral immune cells in people with a FDE, and to identify the pathways modulated by vitamin D supplementation.
Methods: This was a substudy of PrevANZ, a Phase IIb randomised, double blind, placebo-controlled trial of vitamin D supplementation in people with a FDE. Participants were randomised to take 10,000, 5000 or 1000 IU daily of vitamin D3, or placebo. Peripheral blood was collected at baseline (within 120 days of FDE onset) and 3 months in PAXgene Blood RNA tubes. The transcriptome was assessed by RNA sequencing. Kallisto was used for pseudoalignment of reads to the reference transcriptome, edgeR for differential expression analysis, and clusterProfiler for gene set enrichment analyses.
Results: Samples from 55 participants were included. P-value histograms of differential gene expression analysis results showed anti-conservative right-skewed distributions for 5,000 and 10,000 IU groups and uniform distributions for 1000 IU and placebo groups, suggestive of modulated gene expression by higher supplementation doses. Combining the 5000 and 10,000 IU groups, we identified 2355 differentially expressed genes after supplementation ($P<0.05$). RNA processing and ribosome biogenesis pathways were significantly upregulated ($FDR<0.05$). Oxidative phosphorylation was downregulated. Inflammatory pathways were downregulated including TNF and IL-17 signalling. Gene set enrichment analysis did not identify significant pathways/gene sets modulated by 1000 IU or placebo.
Conclusions: Vitamin D supplementation for 90 days modulated the peripheral immune cell transcriptome of people with a FDE with an overall anti-inflammatory effect. Our results suggest a dose-dependent effect of vitamin D supplementation on gene expression.

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The impact of air pollution on COVID-19 severity among infected individuals in a population of italian MS patients

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Introduction: Studies have found associations between air pollution and pneumonia and air pollution is an established risk factors for common COVID-19 complications including pneumonia. Additionally, air pollutants have been identified as possible risk factors for MS onset and relapses. To our knowledge, only one study explored the impact of air pollution on Covid-19 severity specifically among MS patients but has only focused on PM2.5 exposures.
Aims: We aim to evaluate the association between long-term exposure to air pollution and COVID-19 severity, described as developing pneumonia in a population of COVID-19-positive MS patients.
Methods: Data on COVID-19 infection among MS patients were extracted from an Italian web-based platform (Musc-19). A case-control study was designed including patients with and without pneumonia at a case-control ratio of 1:2 and 615 patients were included. The included patients were asked to provide information on the geographical area where they had spent most time in the previous 5 years. When this information was missing, the address of the MS center was used as a proxy and evaluated in sensitivity analysis. Air quality was assessed as annual average particulate matter (PM2.5 and PM10) and Nitrogen Dioxide (NO2) ground-level concentrations derived from air quality model results as provided by the 'Copernicus Atmospheric Monitoring Service', and evaluated as categorical exposures (terciles). The association between pollutants and COVID-19 pneumonia was studied using logistic regression models, also adjusting for confounders (age, sex, BMI, comorbidities, EDSS, MS type, duration and treatments).
Results: Detailed exposure was obtained for 491 patients, of whom 34% had pneumonia. Higher concentrations of air pollutants were associated with increased odds of developing COVID-19 pneumonia in both unadjusted and adjusted models (Adjusted models estimates: PM2.5: 2nd vs 1st tercile OR(95% CI)=2.09 (1.20;3.65), 3rd vs 1st tercile OR(95% CI)=2.26(1.29;3.96); PM10: 2nd vs 1st tercile OR(95% CI)=1.83(1.05;3.20), 3rd vs 1st tercile OR(95% CI)=2.12(1.22;3.68); NO2: 3rd vs 1st tercile OR(95% CI)=2.12(1.21;3.69)). Results remained consistent in the sensitivity analysis.
Conclusions: Higher long-term concentrations of PM2.5, PM10 and NO2 were associated with COVID-19 pneumonia among MS patients. Urgent measures to reduce air pollution should be adopted especially to protect the most vulnerable population.

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The effects of different types of smoking on recovery from multiple sclerosis attack

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Introduction: Several studies demonstrated the association between tobacco smoking and the risk and progression of multiple sclerosis (MS).
Aims: Data about the effect of smoking on the recovery from MS attacks is limited. Furthermore, different types of tobacco exposures such as waterpipe and passive smoking are not well assessed.
Objectives: This study evaluated the effect of different types of smoke, cigarette and waterpipe, and also passive smoking on the function recovery of relapsing-remitting MS (RRMS) attacks
Methods: This cohort study evaluated the adult patients with RRMS and Expanded Disability Status Scale(EDSS) <5 in the attack phase. Patients were divided into two groups: smokers and

non-smokers, also, the smokers group was including cigarette, waterpipe, and passive smokers as subgroups for more analyses. EDSS was monitored after relapse and two months later. Change of EDSS considered as the criteria for functional recovery. Also, the correlation between the amount of consumption and disability level was assessed among smoker patients.
Results: 142 patients were evaluated. 79 (55.6%) were smokers (43% male) while 63 (44.4%) were non-smokers (36.5% male). There was a statistically significant difference in change of EDSS between smoker and non-smoker groups, which change of EDSS was higher in non-smoker groups (-2.62±0.90 non-smoker vs. -1.75±0.76 smoker, P<0.001). Also, only there was a significantly lesser decline in EDSS after two months in the cigarette smoker group in subgroups analyses (P<0.001). A correlation analysis revealed a significant positive correlation between the number per day of cigarette smoking and EDSS after relapse (r= 0.3, P= 0.03) and a significant positive correlation between minutes per month of smoking of water pipe and EDSS two months after relapse (r= 0.6, P>0.001).
Conclusion: Tobacco smoking especially cigarette smoking is associated with a negative effect on recovery from the attack in patients with RRMS.
Keywords: Cigarette smoking, Function recovery, Passive smoking, Relapsing-remitting multiple sclerosis, Water pipe smoking

Disclosure
The authors have nothing to disclose.

P169
Randomized clinical trial of intermittent energy restriction in people with multiple sclerosis

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Background: Intermittent fasting (IF) reduces inflammation in preclinical models and in people with Multiple Sclerosis (pwMS). Mechanisms could include increased adipokine levels, reduced systemic inflammation and changes in gut microbiota composition.
Methods: Participants with relapsing remitting MS were randomly assigned to an intermittent energy restriction (IER) regimen or a standard western diet (SWD) for 12 weeks. Blood, stool and urine samples were collected at baseline, 6 and 12 weeks and dual-energy X-ray absorptiometry (DEXA). Secondary outcomes were: peripheral blood metabolic (lipids, cortisol, adiponectin, leptin, β-hydroxybutyrate, insulin and IGF-1) and immunologic profiling, anthropometric and total body fat measures, gut microbiota richness and composition. Differences between IER and SWD were examined using a linear, repeated measures mixed model and adjusted for the change in total body fat from the DEXA. A subset of participants performed a brain MRI at baseline and 12 weeks. Brain MRI were analyzed for volumetric, diffusion basis spectrum imaging (DBSI) changes.
Results: Forty-two pwMS were randomized (22 IER and 20 SWD), 34 finished the study (17 IER and 17 SWD). Adiponectin was increased from baseline in the IF (difference in means, SE -610.59, 256.34; *p=0.02*), but not in the SWD cohort (difference in means, SE -112.00, 272.90, p=0.67). In a subgroup of 10 participants, IER was associated with increased cortical thickness in the bilateral medial orbitofrontal cortices (F:8.93, *p:0.014*), improved regional perfusion in the bilateral inferior temporal gyri (F:14.1, p:0.02, & F:34.9, p:0.004) and bilateral fusiform gyri (F:24.6, *p:0.008*, & F:51.4, *p:0.002*) and decreased DBSI-derived white matter cellular infiltration and edema in the bilateral inferior longitudinal fasciculi (*p=0.04* and *p=0.002*, respectively).
Conclusions: in our cohort of pwMS, IER was associated with changes in adipokine levels and alterations in brain's structure and function. An increase in adiponectin, an insulin sensitizing and immunoregulatory adipokine, was observed in the IER group. MRI analysis confirmed reduce tissue inflammation in pwMS undergoing IER compared to SWD.

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P170
Waterpipe and cigarette smoking and the risk of primary progressive multiple sclerosis: a population-based case-control study

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Background: Primary progressive multiple sclerosis (PPMS) is one of the main type of MS. It has unknown environmental risk factors. Smoking, exposure to passive smoking, and waterpipe have repeatedly been associated with increased MS risk but no study has been conducted for PPMS.
Objectives: We examined the association of waterpipe, smoking, and passive smoking with PPMS.
Methods: The present population-based case-control study recruited PPMS cases and healthy controls from the general population during 2019 to 2020 in Tehran, Iran. 146 PPMS cases and 294 controls were enrolled. Clinical diagnosis of PPMS was based on the 2017 McDonald criteria and confirmed by a neurologist. The standard random digit dialing (RDD) was used to select sex-matched control participants. Logistic regression analysis was used to estimate unadjusted and adjusted odds ratio (OR) (odds ratio) using Stata software 13.
Result: Totally 440 participants were assessed in the study. Mean ages (SD) for cases and controls were 47.0 (9.4) and 37.7 (6.1), respectively (P =0.001). Having ever smoked tobacco and being exposed to passive smoking were all significantly associated with PPMS (OR=2.48, (CI=1.44-4.27) and OR=2.20, (CI=1.34-3.62), respectively). However, having ever waterpipe smoking was not significantly associated with PPMS risk (OR=1.19, CI= 0.62-2.26). Those who had all three types of smoking had an odds that was 10.45 times higher than those without any type (OR: 10.45, 95% CI=3.5-31.2).
Conclusion: We identified cigarette smoking and being exposed to passive smoking as an important risk factors for PPMS. Based on the increasing prevalence of tobacco smoking, this finding emphasizes conducting interventional programs for the prevention of tobacco smoking.
Keywords: primary progressive multiple sclerosis (PPMS), tobacco, cigarette, waterpipe, risk factor.

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P171
Weight during childhood and adolescence is associated with multiple sclerosis risk and disease course in a cohort patients of the same age

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Introduction: Obesity during childhood or adolescence is associated with an increased risk of multiple sclerosis (MS) development. However, data about the effect of weight during childhood and adolescence on MS disease course remain scarce. Besides, previous studies based on patients from different birth years may have been confounded by dietary trends in different time periods.
Objective: To investigate the association of overweight or obesity during childhood and adolescence with MS risk, age of onset and disease course in MS patients of the same year of birth.
Methods: 363 patients (264 females; 99 males) and 125 healthy controls (HCs) were available from the Project Y cohort, a Dutch population-based cross-sectional cohort study which aimed to include all MS patients born in 1966 and age and sex-matched HCs. Sex-stratified associations of weight during childhood and adolescence (non-overweight vs. overweight or obese) with MS risk, age at symptom onset, expanded disability status scale (EDSS), time to EDSS $\geqslant$ 6, onset type and number of relapses were calculated. Analyses were adjusted for smoking, sun exposure, age of menarche, disease modifying therapy and onset type where appropriate.
Results: In female patients, overweight or obesity during adolescence was associated with an increased risk of developing MS (odds ratio= 2.48, 95%CI 1.01–6.12). In female patients who smoked before the age of 18 years, overweight during adolescence was significantly associated with a younger age of onset (β = -0.20, p=0.017), whereas female patients who never smoked showed no significant relation. Male patients with overweight during childhood had a lower EDSS at mean age 53 (β=-0.20, p= 0.040) versus non-overweight male patients. Of all 47 patients with a primary progressive onset type, only one patient (2.1%) had overweight during childhood, whereas 45 patients with a relapsing onset (14.3%) had overweight during childhood (p=0.017) and six HCs (4.8%). Finally, weight during childhood or adolescence had no effect on relapse frequency or time to EDSS $\geqslant$ 6 in both males and females.
Conclusion: In our cohort of MS patients and HCs of the same age, overweight or obesity during adolescence increases the risk of MS later in life in females and also associates with an earlier age of onset in female patients who smoked during adolescence. Whether childhood overweight in males may indeed lead to lower disability later in the disease course, as in our cohort, needs to be validated.

Disclosure
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P172
Dietary factors in childhood are associated with multiple sclerosis risk and age of onset

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Introduction: Emerging evidence support an association between the composition of diet and multiple sclerosis (MS) onset and course. However, studies on childhood diet and MS risk are inconsistent and currently no convincing data exist on the effects of childhood diet on age of first MS-related symptoms.

Objective: To examine the contribution of diet components in childhood on MS risk and age of first symptom onset.
Methods: 363 patients (264 females; 99 males) and 125 healthy controls all around the same age were available from the Project Y cohort, a population-based cross-sectional study including MS patients born in 1966 in the Netherlands and age and sex-matched controls. Dietary information and data on MS risk factors during childhood (age 10) were collected by means of questionnaires. Sex-stratified regression analyses were used to test associations between frequency of consumption of various food types during childhood and MS risk and age of first symptom onset. Analysis were adjusted for smoking, overweight, sun exposure, age of menarche and onset type, where appropriate.
Results: In female patients, a significant protective effect against adult-onset MS was observed with the consumption of whole grain bread (never vs. ⩾ 7 times a week) at the age of 10 years (odds ratio: 0.49; 95% CI 0.26 – 0.93). Moreover, in female patients, high consumption of red meat (never vs. ⩾ 5 times a week) during childhood was associated with an earlier age of onset ($\beta = -0.146$,$p = 0.035$). No associations were found for male patients.
Conclusion: In our unique population based cohort (all birth year 1966) and age-matched controls, we demonstrate that dietary factors during childhood are associated with MS risk and age of onset in females. This suggests that dietary adjustments during childhood are modifiable risk factors to reduce the risk of MS.

Disclosure

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Effect of *in silico* depletion of lymphocyte subpopulations on the immune gene regulatory networks in chronic active MS lesions

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Background: Halting chronic inflammation, as seen in chronic active lesions, has prognostic relevance in MS. A previous single-nucleus RNA-seq study reconstructed the glial interactome at the chronic active edge and highlighted the importance of a lymphocyte-microglia-astrocyte axis in sustaining chronic inflammation (Absinta et al., Nature 2021).
Objectives: Here we simulated the effect of targeting the upstream end of this axis by selectively depleting sparse lymphocyte subpopulations at the chronic active edge.
Methods: We generated multiple datasets by removing specific subsets of lymphocytes (CD20 B-cells, plasma cells, and T-cells, separately, or by performing the virtual knock out (KO) of the BTK gene. We built and compared Gene Regulatory Networks (GRN) using a machine learning tool for comparative single-cell network analysis (scTenifoldNet for comparing the effect of cell removal and scTenifoldKnk for the virtual KO). The simulated differentially regulated features in the GRN comparison were analyzed for functional enrichment analysis. Using PCA, we then measured the samples simulated distances by comparing the original immune dataset with the same dataset after removing specific cell populations or after KO of BTK.
Results: In all virtual lymphocyte-depletion conditions, most of the significantly affected genes were markers of microglia and dendritic cells. CD20 B-cell depletion specifically perturbed genes involved in iron/heme metabolism, mitotic spindle, hypoxia, and antigen presentation. Additional enriched terms were identified when plasmablasts or T-cells were selectively depleted, including fatty acid biosynthesis and degradation, ferroptosis, TNF via NFKB signalling, PPAR pathway, and RAP1 pathway. Interestingly, BTK virtual KO (affecting both microglia and B-cell lineage) is associated with enriched terms including angiogenesis, mTORC1 signalling, complement and coagulation cascade, fatty acid metabolism, and hypoxia.
When all the virtual conditions were directly compared to each other and to the basal condition, T-cell depletion was strongly affected the immune GRN at the chronic active edge, explaining more than 47% of the total variance.
Conclusions: This analysis suggests the potential effects of targeted lymphocyte depletion strategies at the chronic edge and helps rank hypotheses to be further tested in an experimental design and in vivo MRI-based clinical trials (using the resolving paramagnetic rim lesion biomarker).

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P174
Evaluating the effect of a Bruton's tyrosine kinase inhibitor in a murine experimental autoimmune encephalomyelitis model of multiple sclerosis

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Introduction: Inhibition of Bruton's tyrosine kinase (BTK) may slow disease progression in people with multiple sclerosis (MS) by targeting microglia-driven neuroinflammation throughout the central nervous system (CNS). We previously showed that a structural analogue of the BTK inhibitor tolebrutinib can reduce BTK-dependent inflammatory signalling in microglia in the mouse brain, using the cuprizone-mediated model of demyelination. Here, we expand our understanding of BTK inhibition in murine experimental autoimmune encephalomyelitis (EAE), an inflammatory model of MS.
Objective/Aim: To characterise a CNS-penetrant, tolebrutinib-like BTK inhibitor in EAE for its potential to modulate disease progression and the expression of genes linked to disease-associated microglia (DAM).
Methods: Female C57BL/6 mice were immunised with MOG35-55 peptide (250 µg/mouse; two subcutaneous injections in the lower back) to induce EAE. Animals were randomised to receive either vehicle (n=15) or orally administered BTK inhibitor (15 mg/kg; n=15), starting at a clinical score of 1.0–1.5. Treatment groups were blinded until after final data analysis. Cohorts were monitored daily for the development and severity of disease symptoms. After 10 days of treatment, samples were taken from the spinal cord for transcriptome analysis and plasma samples were taken for measurement of neurofilament heavy chain (NfH) concentration.
Results: BTK inhibition significantly reduced the clinical score in the EAE mice, with significant differences between treatment groups starting after two days of treatment and continuing until end of study (Day 10). BTK inhibition also significantly reduced plasma concentrations of NfH. A BTK-dependent transcriptional signature was identified, with BTK inhibition found to modulate pathways relevant to MS pathology. BTK inhibition modulated mRNA expression of genes that had previously been linked to DAM and/or are associated with BTK signalling.
Conclusions: We extended our previous *in vivo* findings from a demyelination model by demonstrating that dosing with a BTK inhibitor halted disease progression in an immune-mediated model of MS. This therapeutic benefit was accompanied by modulated expression of genes associated with activated microglia, which could abrogate microglia-driven neuroinflammation implicated in disease progression in MS.

Disclosure
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Ross C Gruber was an employee of Sanofi when this work was performed; currently employed by Takeda.
Anna S Blazier, Lan Lee, Sean Ryan, Agnes Cheong, Evis Havari, Timothy J Turner, and Dimitry Ofengeim are employees of Sanofi and may hold shares and/or stock options in the company.

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Chitinase-3 like 1 is neurotoxic in hiPSC-derived neuronal cultures

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Background: Chitinase-3 like 1 (CHI3L1) has been described as a prognostic biomarker in early phases of MS, and high cerebrospinal fluid levels have been associated with an increased risk of neurologic disability. Moreover, CHI3L1 has been related to cognitive decline in the context of neurodegenerative disorders. A previous study by the group reported neurotoxic effect of CHI3L1 on murine primary cortical cultured neurons, where CHI3L1 induced dendrite retraction and decreased neuronal viability.
Objectives: To investigate the potential neurotoxic effect of CHI3L1 on human induced pluripotent stem cells (hiPSC)-derived neurons.
Methods: hiPSC-derived neuronal cultures from MS patients were treated with human recombinant CHI3L1 *in vitro*, and then neuronal morphology and synaptic plasticity were evaluated by immunofluorescence and confocal microscopy after 24, 72 hours. About neuronal morphology analysis, neurons were immunostained for MAP2, and parameters as total dendrite tree length, neuronal area and branching were assessed. To evaluate synaptic plasticity, neurons were immunostained for MAP2, the pre-synaptic marker synapsin, and the post-synaptic marker PSD-95. The MAP2 restricted synapsin and PSD-95 puncta were analyzed and the co-localization of both synaptic markers was considered active synapse. The neuronal network dynamics were evaluated using calcium imaging techniques and NETCAL software after 4, 24, 48, 72 hours of CHI3L1 exposition, analyzing parameters such as the % of active neurons, mean activity of culture, inter-burst interval of network bursts (IBI), and the proportion of the network participating in collective events (GNA sizes).
Results: CHI3L1 induced a significant reduction of the total dendrite tree length ($p<0.05$), the number of dendrite segments after 24 ($p<0.01$), 72 hours ($p<0.05$), and the neuronal area after 72 hours ($p<0.05$). Concerning the synaptic plasticity study, CHI3L1 promoted a significant increment of PSD-95 at 24 hours ($p<0.01$) and a significant reduction in the number of active synapses at 72 hours ($p<0.01$). Besides, CHI3L1 induced significant alterations in the GNA sizes ($p<0.0001$) at different time-points, and in the IBI at 72 hours ($p<0.001$). A trend for decreased % of active neurons was also observed at 72 hours.
Conclusions: These results suggest that CHI3L1 has also neurotoxic effects on hiPSC-derived neuronal cultures *in vitro*, affecting neuronal morphology, synaptic plasticity and neuronal network dynamics.

Disclosure
R. Pinteac has nothing to disclose.
G. García-Díaz has nothing to disclose.
C. Matute-Blanch has nothing to disclose.

X. Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS

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CHI3L1 driven reactive astrocytes modulate OPC differentiation and myelination

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Background: We reported that high inflammation at disease onset induces specific reactive astrocytes driving neuronal damage. Here, we aimed to study whether reactive astrocytes induced by multiple sclerosis (MS) inflammatory microenvironment and chitinase 3-like 1 (CHI3L1) drive oligodendroglial damage.

Methods: Astrocyte cultures were challenged for 6h with medium (Basal), cerebrospinal fluid (CSF) from MS patients with high (MS-High, n=9) and low (MS-Low, n=9) inflammatory activity, non-inflammatory neurological disease controls (NINC, n=9), and CHI3L1 (600 ng/ml). Next, astrocyte secretomes were collected after 18h with medium. We assessed astrocyte secretomes and CHI3L1 (300 and 600 ng/ml) effect on oligodendrocyte precursor cell (OPC) cultures. Finally, we addressed whether CHI3L1 could be a potential driver of astrocyte-mediated damage *ex vivo*using organotypic brain slice cultures.

Results: Neither CHI3L1- and CSF-exposed astrocyte secretomes nor direct CHI3L1 treatment altered OPC viability or proliferation *in vitro*. Interestingly, high inflammatory secretomes (MS-High) promoted OPC differentiation into oligodendrocytes (p=0.03 vs. NINC). Similarly, OPC treated with secretomes from astrocytes exposed to CHI3L1 increased the number of oligodendrocytes ($p<0.0001$ untreated vs. Basal; p=0.011 Basal vs. CHI3L1-secretomes) as well as the total MBP area per well (p=0.001 vs. untreated). In contrast, direct CHI3L1 treatment did not influence OPC differentiation ($p>0.99$ vs. PBS). Despite this pro-differentiation effect *in vitro*, brain slices treated for 2 days with CHI3L1 showed impaired myelination (70% reduction, p=0.03 vs. PBS). In addition, CHI3L1 treated brain slices also showed increased axonal damage indicated by reduced neurofilament density (58% reduction, p=0.017 vs. PBS). To address whether CHI3L1 effect on myelination could be overcome, we treated brain slices with CHI3L1 for 2 days and let them recover untreated for an additional 5 days (2dt+5dr). Interestingly, CHI3L1-treated brain slices partially recovered myelination (3.9-fold increased myelination, p=0.008 CHI3L1: 2dt vs. 2dt+5dr; p=0.07 PBS vs. CHI3L1 at 2dt+5dr).

Conclusions: Secretomes from CHI3L1- or high-inflammatory-exposed astrocytes enhance OPC differentiation *in vitro* but lead to impaired myelination in organotypic cerebellar slices. These results suggest that the pro-differentiation effect observed *in vitro* is outweighed by the negative impact of CHI3L1 in neurons in cerebellar slices.

Disclosure

C Matute-Blanch, A Guzman de la Fuente, LM Villar, and DC Fitzgerald report no disclosures.

L Midaglia has received speaking honoraria from Roche and Luzan.

X Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, Excemed, MSIF and NMSS.

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IL-17-dependent modulation of the basal ganglia network: implications for multiple sclerosis

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Introduction: The basal ganglia (BG) network exerts a key role in integrating cortical inputs and underlies motor learning and the regulation of behavior, emotional responses, and cognitive functions.Little is known on how immune cells and soluble immune mediators influence BG activity. Interleukin-17A

(IL-17A) is under the spotlight because of its emerging role as neuromodulator of cortical synaptic transmission and plasticity in both physiological and pathological conditions, including multiple sclerosis (MS).
Aim: To investigate if the IL-17 axis is involved in the regulation of synaptic plasticity in the nucleus striatum, the gateway to the BG.
Methods: Electrophysiological recordings were performed in the striatum of wild-type (WT) mice, mice affected by experimental autoimmune encephalomyelitis (EAE), and mice lacking IL-17A or its receptor (IL-17RA). IL-17RA expression patterns were assessed through immune-histochemistry. Glutamatergic NMDA receptor (NMDAR) expression and subunit composition were assessed through western blot in post-synaptic fractions.
Results: The IL-17 axis contributes to the physiological expression of long-term potentiation (LTP) in medium spiny neurons. LTP induction was impaired in mice lacking IL-17A or IL-17RA ($p<0.05$). This effect might rely on an alteration of glutamatergic transmission, since synaptic expression of NMDAR subunit GluN2B is reduced in mice lacking the cytokine ($p<0.05$). The exposure to high IL-17A concentrations impairs LTP induction ($p<0.05$), mimicking EAE-related LTP loss ($p<0.05$), through a modulation of NMDAR currents ($p<0.05$). These results highlighted a dual effect of this cytokine on synaptic plasticity. Immune-histochemistry showed that striatal projecting neurons and interneurons highly express IL-17RA, suggesting a direct effect of the cytokine.
Conclusions: The IL-17 axis emerges as a key neuromodulator in the BG circuit, with potential implications for neuroinflammatory disorders such as MS.

Disclosure
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Characterizing the immunomodulation and remyelination efficacy of 20-αHydroxycholesterol in pre-clinical models of multiple sclerosis

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Introduction: Progress has been made towards developing novel therapies for multiple sclerosis (MS) patients. However, they are associated with significant health risks, tend only to manage disease symptoms, and do not reverse disease course.
Objectives: Characterize endogenous 20α-hydroxycholesterol (20HC) as a novel therapy to regulate immune response, promote remyelination and have a significant impact on correcting the mechanisms underlying the pathogenesis and progression of MS.
Aims: Use pre-clinical models of neonatal white matter injury and MS to understand the mechanisms underlying 20HC mediated immunomodulation and remyelination.
Methods: We have used a combination of *in vitro*immune profiling, stereology, and transgenic lineage tracing (PDGFRa-CreER^{T2};EYFP mice) to determine the efficacy of 20HC therapy. We have also used transmission-electron microscopy to assess 20HC mediated remyelination and immune modulation by immunoprofiling of leukocytes. Further, we used single nuclei profiling to understand the pathological processes associated with immunomodulation, cuprizone (CPZ) demyelination, and 20HC-driven remyelination in the corpus callosum, at the site of WMI repair.
Results: Our preliminary data establishes that prophylactic treatment with 20HC in the context of experimental autoimmune encephalomyelitis (EAE) decreases T Helper 17 (Th17) cell polarization in peripheral lymphoid organs and attenuates the clinical severity in EAE. We also show in a neonatal white matter injury model and a demyelinating CPZ model of MS that 20HC promotes oligodendrocyte progenitor cell differentiation into mature myelinating oligodendrocytes, which contributes to improved myelination. This is beyond the limited spontaneous regeneration that occurs during the MS disease course.
Conclusions: 20HC represents an exciting, novel, and safe approach to improving neurologic outcomes in MS.

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Stephanie Arvai – I have nothing to declare.
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Kelly Pegram – I have nothing to declare.
Agnes Chao – I have nothing to declare.
Glenn Matsushima – I have nothing to declare.
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Women have higher brain reserve against functional decline in MS than men

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Introduction: Sex differences in brain structure and function have been reported in multiple sclerosis (MS) patients. Here, we tested whether women are better able to maintain neurocognitive function in the face of MS disease neuropathology than men.
Methods: Participants were enrolled in MS PATHS, a cohort study of patients collected during routine care at 10 centers in 3 countries. All participants were scanned in Siemens 3T MRI and completed the MS Performance Test: Processing Speed Test (PST), Manual Dexterity Test (MDT), Contrast Sensitivity Test (CST). PCA was conducted on MRI metrics of brain parenchymal fraction, cortical gray matter fraction, deep gray matter fraction, white matter fraction, thalamic fraction, and cubed root of T2 lesion volume. The first component, comprised of negative loadings for volumetric variables and a positive loading for lesion volume, explained 58% of total variance and was labeled neurodegeneration. Linear mixed effects models were fit to assess our hypothesis. For each outcome (PST, MDT, CST), we entered age, sex, age-by-sex, current DMT status (yes/no), MS phenotype, education, total brain volume, and neurodegeneration. Sex-by-neurodegeneration terms tested the primary hypothesis of differential brain structure-function relationships between men and women.
Results: Models were tested in 10,286 patients (7,544 women, 2,742 men). Across all 3 outcomes, greater neurodegeneration was associated with worse performance in both men (b_{PST} = -0.38, b_{MDT} = -0.33, b_{CST} = -0.22) and women (b_{PST} = -0.33, b_{MDT} = -0.26, b_{CST} = -0.21). The magnitude of this association was significantly smaller for women compared to men in PST ($b_{W\text{-}M}$ = 0.05, 95% CI = [0.01, 0.08], p = 0.013) and MDT ($b_{W\text{-}M}$ = 0.06, 95% CI = [0.02, 0.10], p = 0.005); but not CST ($b_{W\text{-}M}$ = 0.01, 95% CI = [-0.05, 0.06], p = 0.74).
Conclusions: Our results show that women are better able to maintain cognitive and fine motor dexterity in the face of increasing MS neurodegeneration than men. This is the first demonstration of sex differences in reserve against neurofunctional decline in MS. These results highlight the need for further mechanistic studies of reserve, which could inform the development of personalized treatments and interventions.

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The effect of alemtuzumab treatment on neurodegeneration in relapsing remitting multiple sclerosis: real-world data from a five-year prospective one center study

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Introduction: Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease. The high efficacy of alemtuzumab (ALZ) in reduction inflammatory disease activity in relapsing-remitting MS (RRMS) is widely documented. Neurodegeneration in RRMS is an important therapeutic target as it causes irreversible disability progression, including long-term physical, and cognitive impairment. We investigated the effect from ALZ, an immunoreconstitution therapy (IRT), on biomarkers of degeneration, during 5 years of follow up.
Objectives: To assess ALZ possible effect on neurodegeneration.
Methods: RRMS patients (n = 51; female = 31), eligible for ALZ treatment, were consecutively included at the MS Centre, Sahlgrenska University Hospital, Gothenburg 2014-2016. Patients were assessed clinically, using Expanded Disability Status Scale (EDSS), occurrence of relapses, brain MRI, synthetic MRI to assess brain volume, optical coherence tomography (OCT) to assess retinal nerve fiber layer (RNFL) and ganglion cell - inner plexiform layer (GCL-IPL) thickness, glial fibrillary acidic protein (GFAP), and neurofilament light (NFL), at baseline, and then annually throughout 5 years of follow-up.
Results: Mean brain parenchymal fraction (BPF) at baseline was 0.86 (95% confidence interval 0.84-0.88) and no annual significant reduction in BPF was observed during 5 years of follow-up. While patients with no evidence of disease activity (NEDA-3, n=16) had unchanged thickness of RNFL and GCL-IPL during follow-up, there was an annual significant reduction in RNFL thickness in the evidence of disease activity (EDA-3, n=33, $p < 0.05$) group, and a trend towards a significant reduction in GCL-IPL thickness (p = 0.052). There were no significant differences in serum or cerebrospinal fluid (CSF) GFAP levels between baseline and after 24 months of ALZ treatment. However, CSF NFL levels were significantly lower at 24 months, compared to baseline levels (p = 0.005), though this could not be confirmed in serum.
Conclusions: Increased neurodegeneration including increased rate of brain atrophy is expected in active RRMS. In this

prospective observational study of ALZ treated patients, measures of degeneration were essentially unchanged or improved after 5 years of follow-up. However, OCT revealed further degeneration of RNFL in patients with clinical or MRI signs of disease activity. Thus, IRT may show long-term effects on both inflammatory disease activity and degeneration.

Disclosure

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Pathology and pathogenesis of MS - Repair mechanisms

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Intranasal administration allows rapid transport of anti-Nogo-A antibody and cell signaling modulation in the CNS of EAE mice

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Background and aim: We have previously reported that nose-to-brain transfer of a Nogo-A-neutralizing antibody (11C7) attenuates experimental autoimmune encephalomyelitis (EAE). In this context, the mechanisms underlying the therapeutic effect of intranasally-administered 11C7 have not been elucidated. The aim of the present study was to study the distribution and signaling effects of intranasally-administered 11C7 in the mouse CNS.

Materials and Method: In healthy C57BL/6JRj female mice, the concentration of 11C7 was assayed in different CNS regions by capture ELISA, 30 min to 24 h after a single intranasal administration of antibody. In other mice, the distribution of the antibody was observed by fluorescence microscopy on whole head cryosections. In separate groups of mice, EAE was induced with myelin oligodendrocyte glycoprotein (MOG_{35-55}). Mice received daily intranasal administrations of 60 µg 11C7 or control IgG for 30 days. Motor deficits were monitored every day using a 0-3 scoring system. The protein levels of *growth-associated protein 43* (GAP43), a marker of neuronal plasticity, phosphorylated-cofilin (P-cofilin), an intracellular component of Nogo-A signaling, and Nogo-A were followed by Western blotting (WB).

Results: By capture ELISA, 11C7 was detectable in the thoracic and lumbar spinal cord as early as 30 min post-administration, suggesting fast mechanisms of uptake and transport in the CNS. One hour after its administration, the antibody was observed by fluorescence microscopy in the olfactory mucosa and in neuronal cells. WB analyses and capture ELISA measurements revealed a strong correlation between the level of Nogo-A and the amount of 11C7 detected in the cerebellum ($n=5$, $p<0.0005$). Preliminary data suggest a correlation between the level of Nogo-A protein and clinical scores in 11C7-treated mice. P-cofilin was downregulated in the cerebellum of mice treated with 11C7 ($n=5$, unpaired t-test, $p<0.05$). In 11C7-treated mice, the level of GAP43 tended to be higher ($n=5$, unpaired t-test, $p=0.1129$). Further experiments are required to confirm these results.

Conclusion: The intranasal route of administration allows the rapid and widespread distribution of 11C7 in the CNS of naïve and EAE mice where it may locally downregulate Nogo-A signaling activation.

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Cognitive reserve modulates the impact of frontal lobe damage on executive functioning in multiple sclerosis

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Introduction: Early-life enriching experiences may influence frontal lobe maturation and may preserve executive function (EF) integrity in multiple sclerosis (MS).
Objectives and Aims: In this study, we investigated the interaction between cognitive reserve, frontal gray matter (GM) atrophy and white matter (WM) tract microstructural abnormalities and their associations with EF in MS patients.
Methods: Frontal GM volumes, lesional volume, fractional anisotropy, mean diffusivity, intracellular volume fraction and orientation dispersion index of frontal WM tracts were quantified in 93 MS patients and 27 matched healthy controls (HC). Cognitive reserve index (CRI), Wisconsin Card Sorting Test (WCST) and Word List Generation (WLG) of the Rao's battery were assessed. Interaction of structural MRI measures and CRI on cognitive performance were explored.
Results: MS patients vs HC showed diffuse frontal GM atrophy and WM tract microstructural abnormalities ($p \leqslant 0.046$) and worse performances in categories and total errors of WCST and WLG ($p \leqslant 0.034$). In MS, higher CRI was correlated with better WLG performance, WCST-categories, frontal gyri volumes and diffusivity measures of frontal WM tracts (r from -0.212 to 0.455; $p \leqslant 0.046$). The combination of demographic, clinical and MRI measures of frontal lobe structural damage significantly explained EF (WLG: $R^2=0.44$; p=0.022; WCST categories: $R^2=0.33$; p=0.010). Higher CRI explained a further portion of variance in WLG (WLG: $R^2=0.50$; p=0.002; $\Delta R^2=0.07$; p=0.003).
Conclusions: In MS, CRI is associated with higher frontal GM volumes and better frontal WM tract microstructural integrity. CRI may contribute to preserve semantic verbal fluency and cognitive flexibility, possibly moderating the effect of frontal lobe structural damage on cognitive performance.

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Gene expression profiling of MS lesions for identification of pro-remyelinating factors

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Introduction: Approaches to restore damaged axons and myelin are a clinically unmet need in multiple sclerosis (MS).
Objectives: The objective is to develop a new, non-invasive regenerative gene therapy for MS using viral vector technology to deliver pro-remyelinating factors in the central nervous system.
Aims: We aim to identify pro-remyelinating factors through gene expression profiling of remyelinated and actively remyelinating tissue of MS donors with high remyelinating potential of the MS autopsy cohort of the Netherlands Brain Bank (NBB).
Methods: To identify MS lesion types reflecting early remyelination, we correlated proportions of white matter MS lesion types (i.e. remyelinated, active, mixed active/inactive, and inactive lesions, including microglia morphology subscores[1]) with clinical information in the NBB autopsy cohort (n=189). Lesions with foamy microglia, unlike those with ramified microglia, were previously also known to be related to axonal damage[2]. Therefore, type 2.1 lesions and type 6 lesions were selected to identify pro-remyelinating factors and type 2.3 lesions to compare with. To identify MS donors with increased remyelinating potential, we selected non-progressive relapsing MS donors (R-MS, n=7), previously identified as having a higher proportion of remyelinated lesions and a lower lesion load compared to donors with progressive MS[1]. Secondly, we selected MS donors with a high proportion of type 6 lesions (H6, n=7) and donors with a low proportion of type 6 lesions (L6, n=7). We will compare different MS donors (R-MS, H6, and L6) and MS lesions (type 6 (n=7), type 2.1 (n=7), and type 2.3 (n=7)) with NAWM. MS tissue dissection was guided by HLA-PLP, Klüver, Sudan Black B, and thionine stainings in adjacent sections, and RNA sequencing is currently in progress.
Results: We found a positive correlation between the proportion of remyelinated lesions (type 6 lesions) and the proportion of active lesions with ramified microglia (type 2.1 lesions) but not with active lesions with foamy microglia (type 2.3 lesions).
Conclusions: Pro-remyelinating factors associated with 2.1 and 6 lesions will be identified from our donor and tissue selection for putative development of new regenerative therapeutic approaches.
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2. van den Bosch et al.,*Neurol Neuroimmunol neuroinflammation*., 2022

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Galectin-4: a novel target to promote remyelination in MS lesions?

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Introduction: The quiescence of oligodendrocyte progenitor cells (OPCs) is one of the major impediments to remyelination failure in multiple sclerosis (MS). Potent negative regulators of OPC differentiation in MS lesions are neuronal-derived molecules and extracellular matrix (ECM) components. Previously, we have shown that neuronal galectin-4 act as a negative soluble regulator in the timing of OPC differentiation, indicating that the persistent presence of (re) expressed galectin-4 on demyelinated axons in MS lesions may impair remyelination. Given its bivalency, galectin-4 is predestined to bridge counterreceptors, a property that is essential in its role as a regulator of OPC differentiation. Manipulating or competing with galectin-4 oligodendroglial counterreceptors may be therapeutic approaches to improve OPC-based remyelination in MS lesions.
Objectives and aims: Identify and validate therapeutic agents that specifically interfere with galectin-4 binding to oligodendrocytes and that may serve as attractive candidates for promoting remyelination in MS.
Methods: Primary oligodendrocytes and organotypic cerebellar slice cultures were used for functional assays designed to study the effect of galectin-4 on (re)myelination in a micro-environment that mimic the ECM composition of MS lesions. Affinity-based pull-down assays followed by mass spectroscopic identification were performed to identify proteins that may act as functional counterreceptors for galectin-4 on the surface of oligodendrocytes.
Results: Rather unexpectedly, and in contrast to their individual activities, simultaneous presence of galectin-4 and the ECM protein fibronectin, effectively promoted myelin membrane formation*in vitro*and remyelination *ex vivo*. UGT8, an enzyme required for the biosynthesis of galactosylceramide, and contactin-1, an adhesive protein involved in the onset of MBP expression, were identified as the major galectin-4 counterreceptors at the surface of the proximal part of primary processes of immature oligodendrocytes.
Conclusions: Modulating galectin-4-mediated signalling in oligodendrocytes based on interference with its binding to its major cell surface counterreceptors, UGT8 and contactin-1, may be an attractive novel approach to promote remyelination in MS lesions. To accomplish this more insight in the post-binding effects of the bivalent galectin-4 is essential, as well as in a functional role of galectin-4 under inflammatory conditions.

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The authors have nothing to disclose

Imaging and non-imaging biomarkers - MRI & PET

P185
Diagnostic performance of central vein sign versus oligoclonal bands for multiple sclerosis

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Introduction: Oligoclonal bands (OCB) in cerebrospinal fluid (CSF) are commonly used as a diagnostic biomarker in multiple sclerosis (MS) and can serve to meet the requirement for dissemination in time (DIT) in the 2017 McDonald Criteria. The central vein sign (CVS) is a novel neuroimaging biomarker for MS that may improve diagnostic accuracy and reduce the need for CSF testing.
Objectives: To determine the diagnostic performance for MS of CVS in comparison to CSF-specific OCB.
Aims: To compare the sensitivity and specificity of standalone simplified CVS methods (Select-3* and Select-6*) to standalone OCB for the diagnosis of MS.

Methods: This is a retrospective analysis of participants in the CVS in the diagnosis of MS (CAVS-MS) pilot study who also underwent CSF analysis. Post-gadolinium FLAIR* images were used for determination of Select-3* or Select-6* (counting up to 3 or 6 CVS positive lesions per scan) by local raters. The diagnosis of MS at baseline was adjudicated by 3 investigators (neurologists and neurologist/neuroradiologist) based on the 2017 McDonald Criteria. Diagnosis was reassessed at 12 months. Contingency tables were used to determine relative sensitivity and specificity of the CVS and OCB, as standalone tests, for predicting MS diagnosis (chi-square or Fisher's exact test). The positive predictive values (PPV) for the presence of CVS or OCB, or their combination, were calculated.

Results: 53 participants were included in the analysis; 24 (45%) met 2017 McDonald MS Criteria at baseline and 27 (51%) at 12-month follow-up. In participants with OCB (n=25), 65% (standard error, SE=7%) of lesions were CVS positive versus 32% (SE=6%) in those without OCB ($p<0.001$). At baseline, sensitivity was 75% [53%, 90%] for OCB, 83% [62%, 95%] for Select-3*, and 71% [49%, 87%] for Select-6*. Specificity was 76% [56%, 90%] for OCB, 48% [29%, 67%] for Select-3*, and 86% [68%, 96%] for Select-6*. No significant differences were found for sensitivity/specificity between CVS methods and OCB. Of the 27 participants who met MS criteria at month 12, 5 (18.5%) had required OCB to meet DIT; among these, Select-3* was positive in 4 and Select-6* in 3. PPV of OCB was 84%, [64%, 95%], of Select-6* 95%, [76%, 99%], and of combined Select-6* and OCB 100% [80%, 100%].

Conclusions: As standalone tests, the diagnostic and predictive performance of simplified CVS methods was similar to that of OCB for meeting MS diagnostic criteria.

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3 Tesla T_1 / T_2 ratio imaging improves cortical lesion contrast in multiple sclerosis

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Introduction: Cortical demyelinated lesions are prevalent in multiple sclerosis (MS) and associated with disability; their presence

on MRI has recently been incorporated into MS diagnostic criteria. Presently, advanced ultra-high-field MRI — not routinely available in clinical practice —are the most sensitive methods for detection of cortical lesions, and approaches utilizing MRI sequences obtainable in routine clinical practice remain an unmet need.

Objectives: To assess the sensitivity of the ratio of T_1-weighted and T_2-weighted (T_1/T_2) signal intensity for focal cortical lesions using 3-tesla (3T) images in comparison to other established, sensitive, advanced, and high-field imaging methods.

Methods: 3T and 7T MRI collected from 10 adults with MS participating in a natural history study at the National Institutes of Health were included in the study. T_1/T_2images were calculated by dividing 3T T_1w images by 3T T_2w fluid-attenuated inversion recovery (FLAIR) images for each participant. Cortical lesions were identified using 7T T_2*w and T_1w images and corresponding voxels were assessed on registered 3T images. For each participant, ratios derived from the median signal intensity of nonlesional tissue in the cortical region of the lesion and the median lesional voxel intensity were computed. These values were compared across 3T imaging sequences, including the calculated T_1/T_2image, as well as T_1w, T_2w FLAIR, and Inversion Recovery Susceptibility Weighted Imaging with Enhanced T_2 weighting (IR-SWIET) images.

Results:614 cortical lesions were identified on 7T images. 3T T_1/T_2images demonstrated a larger contrast between median nonlesional cortical signal intensity and median cortical lesion signal intensity (median ratio = 1.29, range 1.19 – 1.38) when compared to T_1w (1.01, 0.97 – 1.10, $p<0.002$), T_2w FLAIR (1.17, 1.07 – 1.26, $p<0.002$), and IR-SWIET (1.21, 1.01 – 1.29, $p<0.03$).

Conclusion: 3T T_1/T_2 images are sensitive to cortical lesions. Approaches incorporating T_1/T_2 could improve the accessibility of cortical lesion detection in research settings and clinical practice.

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Myelin water fraction of the corpus callosum is a robust measure of remyelination in a double-blind placebo-controlled clinical trial

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Introduction: Myelin repair is an unrealized therapeutic goal in the treatment of multiple sclerosis. Despite success identifying promising candidates capable of inducing OPC differentiation and consequent remyelination, uncertainty remains about the optimal techniques for assessing therapeutic efficacy and imaging biomarkers are required to measure and corroborate myelin restoration. We previously completed the first double blind-placebo controlled remyelination trial (REBUILD) meeting its primary outcome (Green, 2017).

Objectives/Aims: To assess myelin content using dedicated magnetic resonance imaging obtained in the REBUILD trial.

Methods: In this secondary analysis of the REBUILD clinical trial data, we analyzed the myelin content dedicated magnetic resonance imaging within brain regions rich in myelin. 50 subjects (average age ± SD of 40.1 yrs ± 10.0, average EDSS ± SD 2.1 ± 1.0, and average disease duration ±SD of 5.1 yrs ± 5.0) underwent 3T MRI at time 0 (T0), month 3 and 5. 25 subjects were randomly assigned to group 1 (G1) and received treatment from T0 through 3 months, whereas the other 25 subjects (G2) received treatment from month 3 to month 5. We computed the myelin water fraction (MWF) changes occurring in the normal appearing and lesional white matter of corpus callosum, optic radiations and corticospinal tracts.

Results: MRI-derived WMF improved in the normal appearing white matter of the corpus callosum, in correspondence with the administration of remyelinating treatment with clemastine. At 3 months, G1 mean MWF increased from 0.087, 95% CI [0.080, 0.095] to 0.092 [0.084, 0.100], while G2 mean WMF decreased from 0.088 [0.081, 0.096] to 0.082 [0.074, 0.090], p=0.012 for difference in change from T0. At 5 months G1 mean MWF continued to increase to 0.094 [0.087, 0.102], while G2 mean MWF increased up to 0.086 [0.078, 0.094], p=0.032. Unequivocal treatment-related changes were instead not detected within lesions or within the normal appearing white matter of the optic radiations and corticospinal tracts.

Conclusions: This study provides the first direct, biologically-validated imaging-based evidence of medically induced myelin repair. Moreover, our work strongly suggest that significant myelin repair occurs outside of lesions. This novel finding has the potential to shift the focus of scientific and clinical-translational

interest beyond the lesion and enable the more rapid development of therapeutics capable of myelin regeneration.

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Effect of ibudilast on slowly-evolving lesions in progressive multiple sclerosis

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Background: Chronic active lesions (CALs) are considered a contributing mechanism of clinical worsening in multiple sclerosis (MS). Slowly-evolving lesions (SELs) have been proposed as an in vivo biomarker for CALs and have been associated with disability worsening. Ibudilast was investigated in progressive MS in a phase II multi-center clinical trial (SPRINT-MS), and ibudilast's inhibition of phosphodiesterase suggested a potential effect on CALs.
Objective: To evaluate the effect of ibudilast on SELs.
Methods: SPRINT-MS involved brain MRIs every 24 weeks for 96 weeks. Inclusion criteria were either primary or secondary progressive MS according to 2010 criteria and EDSS 3.0-6.5. For this analysis, at least 4 MRIs without scanner change from baseline MRI were required. The analysis involved nonlinear registration of all follow-up MRIs to subject's baseline MRI to obtain maps of Jacobian determinant. For SEL detection, we performed voxel-wise linear regression over time within the baseline T2 lesions. The cutoff between 7.5 and 20%/year was used to determine the SELs. Finally we measured the volumes of voxels meeting these cutoffs. We determined the effect of ibudilast on SEL volume using linear regression with covariate adjustment of baseline T2 lesion volumes (T2LV). We further evaluated the treatment effect in subtypes (PPMS vs SPMS) by interaction term as well as stratified models. Disability progression was evaluated using Cox proportional hazard and log-rank tests with dichotomized and quartiles of SEL volume. R software with survival package was used.
Results: Of 255 randomized patients in the core study, 33 dropped out, 1 had only 3 scans, and 26 had a change in scanner. The remaining 195 patients were analyzed. The mean SEL volumes were 1.08 ml (SD=1.32) in ibudilast and 1.49 (2.00) in placebo. After the baseline T2LV adjustment, ibudilast was associated with a 26% decrease in SEL volume (p=0.004). The interaction between treatment and MS subtype was not significant (p=0.58), and stratified models showed similar treatment effects of in PPMS (30%) and SPMS (21%). There was no significant difference between SEL categories for disability progression in any of the time to event analyses.
Conclusion: We observed a significant treatment effect of ibudilast on SEL. This was consistent with proposed mechanism of action (microglia inflamed in MS) and adds to the efficacy profile of ibudilast in progressive MS.

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Investigating normal appearing white matter using intensity scaled T1-weighted magnetic resonance images in multiple sclerosis

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Introduction: In multiple sclerosis (MS), damage of white matter, which can occur in regions of normal appearing white matter (NAWM), is supposed to play a role in disease progression and to go along with decent intensity changes in conventional MRI, which have not been quantifiable so far. For this purpose, we implemented a scaling method that uses extracerebral reference regions as they are not directly affected by MS. The goal of this project was to reduce technical variance due to instability of acquisition parameters, but to preserve the biologically induced intensity

variance, and, finally, to compare NAWM intensities of healthy controls (HCs) and patients with MS for biological validation.
Methods: 3 Tesla T1w images were used to investigate brain MRI data of HCs and patients with MS. 3917 images were pre-processed and averaged to identify extracerebral regions with lowest variance in intensity. Brain T1w intensities were scaled by the intensities of the identified reference regions. NAWM intensities were compared between age- and gender-matched groups (HCs: 115, MS: 112). Group differences in mean NAWM intensity were analyzed by two sample t-test.
Results: Orbital fatty tissue, neck muscles, temporal fatty tissue, and temporal muscles showed the least variance and were chosen as reference regions. After intensity scaling, the variation of NAWM intensities was reduced (median-normalized interquartile range before/after scaling: 9.1%/5.5%). Comparing raw images of HCs and MS subjects yielded no significant difference in mean NAWM intensities ($p>0.05$), whereas scaled image intensities differed significantly ($p<0.001$).
Conclusions: Scaling T1w images using extracerebral reference regions reduces technical variance while preserving biological variance, i.e., the difference between HCs and MS patients, making it an attractive candidate method for the investigation of NAWM in MS.

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Lesion evolution on MRI in multiple sclerosis with separation of myelin and iron

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Introduction: The evolution of MS lesions may yield both paramagnetic ($\chi+$) iron-laden microglia and diamagnetic ($\chi-$) myelin fluctuations spatiotemporally. Quantitative Susceptibility Mapping (QSM) enables measurement of the in-vivo magnetic susceptibility (χ) distribution in each voxel, but until recently QSM was unable to separate diamagnetic and paramagnetic contributions, providing only the net sum. Here we used recently-introduced magnetic susceptibility separation (χ separation), which relies on QSM and transverse relaxation (T2, T2*) measures, to follow lesion evolution over 1 year in relapsing-remitting MS (RRMS).
Aim: To evaluate χ separation for distinguishing MS lesion evolution of paramagnetic iron ($\chi+$) and diamagnetic myelin ($\chi-$).
Methods: 18 subjects with RRMS (mean age [SD] 42.4 [9.5] yrs, 12 females) underwent two MRI scans with 14 months interval (14.2 [2.1] months) in between. The MRI protocol included three methods from which χ separation was derived: dual-echo based T2 mapping and 3D multiple gradient echo for T2* mapping and QSM. In addition, FLAIR imaging was used for manual lesion segmentation. Serial images of each individual were registered and changes were quantified with each measure.
Results: A total of 115 lesions were found. Mean changes for all lesions over 14 months were: QSM increase of 49% (3.3 [11.5] to 4.9 [12.4] ppb), $\chi+$ decrease of 6% (19.4 [16.4] to 18.2 [9.5] ppb), and $\chi-$ decrease of 15% (16.4 [15.3] to 13.9 [6.2] ppb). Among 36 lesions with both T2* and QSM increase, 97% showed decrease in $\chi-$, representing demyelination. For 22 lesions with both T2* and QSM decrease, all showed increase in $\chi-$, reflecting a remyelination-driven evolution. For 28 lesions with increased T2* and decreased QSM, 93% had $\chi+$ reduction, corresponding to iron loss. For the remaining 29 lesions with decreased T2* and increased QSM, 97% exhibited a $\chi+$ increase, corresponding to iron gain, likely from iron-laden microglia.
Conclusions: χ separation for lesion evolution allows discrimination of demyelination, remyelination, iron gain and iron loss. Combined with relaxometry methods, this technique may produce

more insightful pathological and clinical interpretation of lesion evolution.

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Characterization of brain T2 lesions suggestive of demyelination in presymptomatic patients: the radiologically isolated syndrome cohort

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Introduction: Since the first published 2009 Radiologically Isolated Syndrome (RIS) diagnostic criteria, our consortium has collected cases with incidental findings on the brain or spinal cord MRI suggestive of demyelinating disease without Multiple Sclerosis (MS) signs and symptoms.
Objectives: The cohort has many objectives, but the main aim of this work is to present an inventory of the RIS cohort and emphasize all RIS 2009 criteria, whether imaging or clinical criteria.
Aim: The aim is to analyze all files centralized as RIS and collect clinical, biological, and imaging data to promote research.
Methods: We collected prospectively all cases addressed for suspicion of RIS in 41 MS clinics, a double-blind MRI reading agrees for RIS status on imaging and patient medical history. These cases are classified into 3 groups: (1)RIS subjects fulfilling RIS 2009 criteria (at least 3 out of 4 criteria for Dissemination in Space (DIS)); (2)Subjects with lesions suggestive of demyelination but fulfilling only 1 or 2 criteria for DIS; (3)Subjects with lesions not suggestive of demyelination: NON-RIS.
Results: This cohort contains 812 files in April 2022: 589 (72.5%) Women, Mean age at the inclusion of 37.9 years [7 -71]. MRI motives were headache for 34%, neurological follow-up for 21%, ENT for 16%, mood disorders or ophthalmological for 7%, and trauma for 5.5%.
On the 500 confirmed RIS cases at the index scan: during the mean follow-up of 42.1 months [0.1-275], 142 (29%) have converted clinically. Meantime for the seminal event: 38.9 months [1.5– 196.9].
On the 252 subjects with lesions suggestive of demyelination but not fulfilling RIS criteria: during the mean follow-up of 55.5 months [0.1-325], 72 (28.6%) have converted clinically.
Of the 180 (71.4%) subjects with lesions suggestive of demyelination but not fulfilling RIS criteria who have not converted clinically, 84 (48%) have MRI DIT and eventually fulfilled the RIS criteria, and 91 (52 %) are still not classified as RIS.
60 cases were classified after adjudication as NON-RIS for either suggestive history of demyelinating disease (14), abnormalities suggestive of another condition (8), or non-specific lesions (38).

Conclusion: This cohort demonstrates that 1/Some RIS subjects can rapidly present clinical events 2/Subjects with lesions suggestive of demyelination but notfulfilling 2009 RIS criteria can evolve either to RIS or to MS 3/Misdiagnosis is possible, and criteria sensibility should not overrule specificity.

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Networks of myelin covariance in relapsing-remitting multiple sclerosis

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Introduction: Myelination, a key microstructural feature of gray matter tissue, changes concurrently among spatially distant brain regions to form characteristic networks of myelin covariance(Myelin-Nets). These processes and their topological organization may be altered in Multiple Sclerosis(MS) patients.
Objectives: To investigate the extent of Myelin-Nets impairment in Relapsing-Remitting MS(RRMS).
Methods: We included 98 RRMS patients (age:37.91±11.16y, mean±SD, males=33); and 101 healthy controls(HC, age:38.09±12.87y, mean±SD, males=46).
A 3T MRI was performed, including 3D RF-spoiled gradient-echo acquisitions with predominantly Magnetization Transfer-weighted, Proton Density-weighted, and T1-weighted images to estimate Magnetization Transfer saturation maps (MTsat) as a surrogate measure of myelination.
The synchronized co-variations in myelination between all pairs in a group of 112 gray matter regions were estimated by computing the Pearson's correlation coefficient across subjects. The correlation matrices represent the Myelin-Nets for RRMS and HC.
Based on the graph theory framework, we explored the topological organization of the Myelin-Nets. We focused on global network properties: clustering index, characteristic path length, global and local efficiency, global connectivity, and connectivity between homologous brain regions.
To examine differences in network properties between groups, we performed the following steps: a) construction of the empirical bootstrapped distribution of differences by subtracting the corresponding bootstrap samples between groups; b) definition of the statistical significance level: a 95% biased corrected percentile bootstrap confidence interval(CI) of the distribution of the empirical difference is estimated; c) hypothesis testing: a significant difference between groups is accepted if CI does not contain zero.
Results: Significant group differences (HC vs. RRMS) were found for clustering index(CI: [0.073377,1.5038]), global connectivity(CI: [0.0025675,0.18821]) and connectivity between

homologous regions(CI: [0.015605,0.10627]). Specific differences in myelination correlation were found in 34 pairs of regions in all brain lobes comprising hub regions like precuneus and posterior cingulate.

Conclusions: The gray matter myelination/demyelination processes in RRMS showed different topological organization as compared to HC. RRMS-Myelin-Net showed a global reduction in myelination synchronization between homologous regions.

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The impact of adult-onset multiple sclerosis on intracranial volume: results from an MRI study in clinically discordant monozygotic twins

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Background: Intracranial volume (ICV) represents the maximal brain volume for an individual and remains constant throughout life after reaching a maximum before late adolescence. ICV is not affected by brain disorders and reflects pre-morbid brain size and acts as a surrogate marker for the integrity of brain growth.

Objectives: The influence of neuroinflammation on brain growth is highlighted by past studies on pediatric-onset MS, where affected children showed low ICVs.

Aim: It remains an open question how adult-onset multiple sclerosis (MS) and prodromal subclinical neuroinflammation impact brain growth.

Methods: We investigated a unique monozygotic twin cohort with discordance for MS (MS-TWIN STUDY; N = 54 twin-pairs, 42.45±11.98 years, 80 females), with the unique advantage to control genetic and environmental risk factors and to evaluate effects of prodromal changes in this high risk cohort. ICV scores, derived from 3D T1-weighted MRI images, were compared between within twin pairs. As a reference we used standardized ICV z-scores of a healthy reference cohort (Human Connectome Project, N = 731; including 109 monozygotic and 69 dizygotic twins). To control for scanner-related effects a local control cohort of healthy adults (N=35) was added.

Results: ICV scores was overall very similar within the twin pairs. In 45 (83%) of twin-pairs, both clinically affected and healthy co-twins showed negative ICV z-scores, meaning ICVs lower compared to the average in the healthy reference cohort (M = -1.53±0.11, $P < 10^{-5}$). Importantly, younger age at MS diagnosis was strongly associated with lower ICVs (t = 3.76, P = 0.0003). Stratifying the twin-pairs according to age at MS diagnosis in the affected co-twin (< 30 years versus > 30 years) yielded lower ICVs in those twin pairs with younger age at diagnosis (P = 0.01). Moreover, comparing ICV within individual twin-pairs identified a lower ICV in the MS affected co-twins with younger age at diagnosis compared to their corresponding healthy co-twins (P = 0.003).This discrepancy in ICV on the twin-pair level was even more pronounced looking at twin-pairs without any signs of subclinical neuroinflammation in the healthy co-twin ($P < 10^{-4}$; N=23) compared to those with detected subclinical neuroinflammation reflecting prodromal MS in this high-risk cohort (N=13, screened via MRI and/or CSF).

Conclusion: Our findings suggest a possible link between adult-onset MS and lower ICV. The impact of adult-onset MS on this surrogate marker of brain growth seems to be more pronounced with younger age at MS diagnosis, which points to early neurodegeneration during prodromal phases in MS temporally closer to critical neurodevelopmental stages.

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Toward a joint automated assessment of cortical and paramagnetic rim lesions with 7T MRI

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Background: Cortical lesions (CL) and paramagnetic rim lesions (PRL) are imaging biomarkers that contribute to MS progression. Our understanding of their relationship is limited (Treaba et al., Brain Comm, 2021). Manually annotating these biomarkers is extremely tedious, and some automated methods have been proposed to facilitate this task (La Rosa et al., arXiv, 2022).
Objectives: First, we evaluate the agreement between the manual and automated assessment of CL and PRL, respectively, on the same 7T magnetic resonance imaging (MRI) dataset. Second, we investigate the monotonic correlation between CL and PRL count depicted either manually or by automated techniques.
Methods: We retrospectively analyzed the MRI of 20 MS patients (13 RRMS/7 PMS, 15 female/5 male, age range [25-66] years, EDSS range [0-7.5]) imaged with a 7T research scanner (MAGNETOM 7T, Siemens Healthcare, Erlangen, Germany). The protocol included MP2RAGE (0.7 mm isotropic), and T2*-weighted dual-echo gradient echo (0.2x0.2x1.0 mm). A neurologist visually identified 208 PRL (median 6.5, range [1,42]). RimNet (Barquero et al., Neuroimage Clin, 2020) was then applied to automatically detect PRL from T2*-GRE phase images. A pre-trained convolutional neural network (CLaiMS) was used (La Rosa et al., NMR Biomed, 2022) to segment CL from MP2RAGE images. A second neurologist, blinded to the PRL assessment, manually corrected the automated CL masks, discarding false positives and adding false negatives.
Results: CLaiMS achieved a CL detection rate of 68% with 12% of false positives (mostly juxtacortical lesions). A fair correlation was observed between the manual and automated CL count (Lin's correlation coefficient ρ=0.79). Setting a false positive rate of 5%, RimNet achieved a PRL sensitivity of 55% and specificity of 95%. Manual and automated PRL counts showed a modest correlation (ρ=0.65). CL and PRL number moderately correlated according to both the manual and automated assessment (Spearman's rank correlation coefficient=0.56 and 0.41, respectively).
Conclusions: Automated approaches provide an accurate assessment of both CL and PRL biomarkers, but room for improvement remains. As in previous work (Beck et al, MSJ, 2022), CL and PRL counts were moderately correlated when analyzed manually and a similar relationship was observed for their automated assessment. Future work will involve larger cohorts of patients and explore the correlation between automated findings and disability measures.

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Voxel-wise multimodal MRI reveals specific patterns of brain damage in the main multiple sclerosis phenotypes

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Introduction: Advanced magnetic resonance imaging (MRI) techniques can be used to detect demyelination and neurodegeneration affecting gray (GM) and white matter (WM) in multiple sclerosis (MS).
Objectives: In this study, we applied a multimodal MRI approach to investigate in vivo the heterogeneous pathological processes occurring in the main MS clinical phenotypes.
Methods: Fifty-seven MS patients (42 relapsing-remitting [RR], 15 secondary progressive [SP]) and 47 healthy controls (HC) underwent brain 3T MRI. Voxel-wise differences of brain GM and WM atrophy, T1weighted (w)/T2w-ratio, quantitative susceptibility mapping (QSM), neurite density index (NDI) and magnetization transfer ratio (MTR) maps in the main study groups were investigated.
Results: Compared to HC, RRMS showed significantly lower MTR of posterior periventricular and infratentorial WM, deep GM and frontal cortex, widespread lower T1w/T2w-ratio, atrophy of deep GM, insular cortex and WM, widespread lower NDI in supratentorial WM and cerebellum, small GM/WM clusters with either significantly increased or decreased QSM ($p<0.001$). Compared to RRMS, SPMS patients showed significantly lower MTR of periventricular WM, deep GM and cerebellum, lower T1w/T2w-ratio of fronto-temporal regions, widespread cortical atrophy, widespread lower NDI of WM, increased QSM in the pallidum and striatum and increased T1w/T2w-ratio of the pallidum ($p<0.001$).
Conclusions: By combining advanced MRI techniques, we found that demyelination and irreversible neuro-axonal loss are already present in RRMS and become more severe and widespread in SPMS. Higher T1w/T2w-ratio and QSM in pallidum and striatum, possibly reflecting iron accumulation and neurodegeneration, may represent relevant MRI markers able to discriminate SPMS from RRMS.

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An in-vivo ultrahigh-resolution window into the infratentorial MS brain

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Introduction: Susceptibility-weighted ultrahigh field MRI of the supratentorial brain shed light into the pathological processes involved in multiple sclerosis (MS), including the presence of the central vein sign (CVS), an imaging biomarker of MS, and the presence of paramagnetic rim lesions (PRL), a marker of chronic inflammation and disease severity. In the infratentorial brain, there is signal loss at 7T associated with susceptibility-induced distortions and inhomogeneities of the static magnetic field (B_0), most evident near air-bone interfaces. Navigator-guided motion and B_0 correction substantially improves the overall supratentorial image quality of T_2^*weighted MRI at 7T.
Objective: To determine if motion and B_0 correction of T_2^*-weighted images at 7T can improve infratentorial brain image quality, detect PRL, and help assess CVS.
Aims: To assess the CVS and PRL in the infratentorial brain.
Methods: We included 7T brain MRI from adults with MS acquired between July 2021 and May 2022. 3D-T_2*weighted GRE images (0.5 mm isotropic) in 4 partially overlapping scans, reconstructed using motion and spatially linear B_0 correction, whole brain 3D-MP2RAGE (0.7 mm isotropic), and whole brain 3D-EPI (slice thickness 0.6 mm) were acquired. Infratentorial lesions were identified in MP2RAGE. The proportion of lesions showing CVS and PRL was determined in corrected 3D-T_2* weighted GRE images (magnitude and phase, respectively). Signal to noise ratio (SNR) was calculated.
Results: Ten adults with MS were consecutively scanned: 7 women, 3 men; 7 with relapsing-remitting MS, 3 with secondary-progressive MS; mean age, 47 years (range, 22-66); mean disease duration, 16 years (range, 4-35); Expanded Disability Status Scale score range, 1.5–6. A total of 55 infratentorial lesions were identified on MP2RAGE, 96% were CVS-positive. 50% of the patients had infratentorial PRL (range 1-6), all of whom had supratentorial PRL (range 5-32). Infratentorial SNR was: T1map 12.7, T_2^*weighted GRE 12, T_2*wEPI 9.7.
Conclusions: The microscopic anatomy of the infratentorial MS brain can be depicted using T_2*-weighted images with navigator-guided motion and B_0 correction. Like the supratentorial brain, most infratentorial lesions are perivenular, and PRL are present in 50% of the cases.

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Upper cervical spinal cord atrophy in early-stage relapsing-remitting multiple sclerosis

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Introduction: Disease progression and severity in multiple sclerosis (MS) vary between individuals. Accurate predictors of disease progression at an early stage of MS are required for more effective treatment stratification and evaluation of efficacy for individual patients. Previous research has shown that spinal cord atrophy is associated with clinical disability in MS and may thus be a relevant magnetic resonance imaging (MRI) marker of disease progression.
Objectives: This study assesses whether cervical spinal cord atrophy is already present in early relapsing-remitting MS (RRMS), and if atrophy rates differ between patients with stable and increasing clinical disability.
Aims: To establish whether spinal cord atrophy, as measured with MRI, can be used as a biomarker of early neurodegeneration in RRMS and aid targeted treatment development.
Methods: 268 participants (204 female, mean age 38.1y±10.1) with a recent diagnosis of RRMS (<6 months) underwent 3T MRI at baseline and 12-month follow-up, as part of the Scottish multi-centre 'FutureMS' study. Spinal cord cross-sectional area (SCCSA) was segmented from brain T1-weighted images at cervical levels 2 and 3 (C2-3), using in-house software. Disability was assessed using the expanded-disability status scale (EDSS), and participants with 12-month change in EDSS<1 or EDSS=>1 were grouped as stable or increasing, respectively. Multi-level regression was applied (R v4.0.2) to compare longitudinal SCCSA-C2-3 change between disability groups.
Results: Mean SCCSA-C2-3 for stable disability (N=200) was $64.8mm^2 \pm 7.8mm^2$ at baseline and $62.5mm^2 \pm 8.0mm^2$ at follow-up, with $64.7mm^2 \pm 6.6mm^2$ and $62.8mm^2 \pm 6.6mm^2$ respectively, for increasing disability (N=68). SCCSA-C2-3 decreased over time for both groups ($p_{stable}<0.0001$, $p_{increasing}=0.043$) but did not differ over time ($p>0.05$) between groups. SCCSA-C2-3 was not different ($p>0.05$) between disability groups at either time point.
Conclusions: Upper cervical spinal cord atrophy is evident in early-stage RRMS, indicating detectable spinal neurodegeneration from point of diagnosis, and suggesting a role for quantitative spinal cord MRI in disease evaluation. Atrophy rates were similar for stable and increasing disability. This may reflect clinically-silent spinal atrophy, limitations to EDSS as an index of clinical disability, or confounding effects of clinical improvement following the acute inflammatory episode that prompts initial MS diagnosis. Our future research on spinal cord atrophy as biomarker of early neurodegeneration will therefore include longitudinal MRI and additional measures of clinical disability over a five-year period in the same cohort.

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Detection of lesions in the optic nerve with magnetic resonance imaging using a 3D convolutional neural network

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Introduction: Optic neuritis is the first manifestation of multiple sclerosis (MS) in around 20% of patients. Detecting optic nerve lesions using magnetic resonance imaging (MRI) could be a relevant diagnostic marker in patients with MS, but there are no available tools for automatic or semiautomatic identification of lesions. Moreover, MRI interpretation by radiologists does not always coincide, due to scan quality, observer expertise or clinical knowledge of the patient by the radiologist, among other factors.
Objectives: The aim of this study was to create an automated, interpretable
method for optic nerve lesion detection from MRI scans.
Material and methods: A 3D convolutional neural network (CNN) model that detects optic nerve lesions based on axial T2-weighted fat-saturated MRI scans was implemented. The proposed approach includes a data processing step to select the area around the optic nerve, and the generation of saliency maps, which highlights the areas of the image that are more important for the decision. The approach was validated on two different datasets from two different 3T scanners (MAGNETOM TRIO n=107 and MAGNETOM PRISMA n=62). Both cohorts were labelled by compiling their medical records and written report of an expert radiologist, to discern if optic nerve lesions were present in the scan. Support Vector Machine (SVM) and Random Forest (RF) approaches were also implemented as alternative approaches.
Results: The CNN model showed good performance (69.68% balanced accuracy, 68.24% specificity, 71.11% sensitivity) that generalizes to unseen data (68.21% balanced accuracy, 68.60% specificity, 65.14% sensitivity). Saliency maps generated showed that the CNN focuses its attention to areas that correspond to lesions in the optic nerve. Accuracies for the SVM and RF were around 50%, and for the unseen data, specificity fell below 50%.
Conclusions: The CNN approach proposed shows robustness and, when using only imaging data, its performance is comparable to trained radiologists. Given its speed and performance, the developed methodology could potentially be translated into a clinical setting.

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Using The Virtual Brain to study the relationship between structural and functional connectivity in people with multiple sclerosis: a multicentre study

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Introduction: The relationship between structural (SC) and functional (FC) connectivity as well as their interaction with disability and cognitive impairment is not well understood in multiple sclerosis (MS). The Virtual Brain (TVB) is a numerical approach that creates personalized models reflecting the coupling between SC and FC. An usual methodology in TVB is to use an average SC based on healthy controls (HCs).

Objectives: We propose to assess this approach in MS and compare it to individualized models.

Methods: The dataset included 7 centers, composed of 219 HC and 518 people with MS (pwMS). The disability (EDSS) and the score obtained in the Single-Digit Modality Test (SDMT) were also collected. The corresponding SC and FC matrices were generated following established pipelines. Then, simulated FC was generated from the SC using the reduced Wong-Wang model in TVB. The fitting of the numerical model was based on maximizing the similarity between the simulated and the acquired FC, providing an estimation of the coupling (G) between structural and functional connectivity. Two approaches were compared, one using an average SC based on the HCs of each center, and one using the individual data. Corresponding absolute differences (Delta_G = G_average - G_individual) were computed. Associations between G and MRI measures (lesion and regional volume fractions, regional fractional anisotropy and radial diffusivity) and cognitive status were assessed with partial correlations (age, sex and center as covariates).

Results: For the average approach, no significant differences were found between HC and pwMS, while for the individual, a significant decrease in G was found in pwMS compared to HC ($t=2.905$, $p=3.78e-3$). Within pwMS, those with EDSS$>=3$ showed a significant increase in G compared to those with EDSS<3 ($t=2.093$, $p=0.036$). No significant associations were found between G and MRI measures, EDDS nor SDMT scores in none of the approaches. Delta_G was found to be significantly higher for pwMS compared to HC ($t=4.28$, $p=2.1e-5$), and poor significant associations ($r<0.10$, $p<0.05$) were found between delta_G and MRI measures. No significant associations were found between delta_G and SDMT nor EDSS.

Conclusions: Results suggest that the coupling between SC and FC in pwMS is independent of their brain affectation, disability or cognition. In MS, TVB should incorporate individual SC information to better account for the specific stage of the person.

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Filippi M is Editor-in-Chief of the Journal of Neurology and Associate Editor of Human Brain Mapping; received compensation for consulting services and/or speaking activities from Almiral, Alexion, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Novartis, Roche, Sanofi, Takeda, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

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P200

Correspondence between gray matter atrophy and neurotransmitter maps is relevant in multiple sclerosis

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Introduction: In multiple sclerosis (MS), clinically-relevant gray matter (GM) atrophy progresses in a non-random manner, possibly due to the preferential involvement of specific neurotransmitter networks, which has not been fully evaluated yet.
Objectives: To investigate the associations among regional GM atrophy, neurotransmitter distributions and clinical manifestations in a large group of patients with MS (PwMS).
Methods: Brain 3.0 T MRI scans were acquired from 286 PwMS and 172 healthy controls (HC). Regional GM volume differences, cross-correlations between regional GM atrophy and nuclear imaging-derived neurotransmitter maps and their associations with disease duration (DD), clinical disability, cognitive impairment, fatigue and depression were investigated using voxel-based morphometry and Juspace toolbox.
Results: Compared to HC, PwMS showed a widespread cortico-subcortical GM atrophy being spatially correlated with serotonergic, dopaminergic, opioid, noradrenergic, cholinergic and glutamatergic maps (false discovery rate, [FDR]-p≤0.004). PwMS with a DD ≥5 vs <5 years had a significant GM atrophy in several deep GM, cortical and cerebellar regions being spatially correlated with a higher distribution of serotoninergic and dopaminergic receptors (FDR-p≤0.03). Compared to mildly-disabled PwMS, those with Expanded Disability Status Scale (EDSS)≥3.0 or ≥4.0 had significant cortical, subcortical and cerebellar atrophy, which was associated with serotonergic and dopaminergic maps (FDR-p≤0.04). A significant spatial correspondence with opioid and cholinergic maps was also found for PwMS with EDSS≥4.0 vs <4.0 (FDR-p≤0.04). Cognitively-impaired vs cognitively-preserved PwMS had a widespread GM atrophy being spatially correlated with serotonergic, dopaminergic, noradrenergic, cholinergic and glutamatergic maps (FDR-p≤0.04). PwMS with vs without fatigue had significant cortical, subcortical and cerebellar atrophy, which were associated with serotonergic, dopaminergic, opioid and glutamatergic maps (FDR-p≥0.07). No significant GM atrophy and associations with neurotransmitter maps were found according to depression.
Conclusions: GM atrophy in regions belonging to specific neurotransmitter systems may contribute to explain part of MS clinical manifestations, including locomotor disability, cognitive impairment and fatigue.

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Comparison between microscopic and tensor diffusion anisotropy measures to quantify lesion volume across white matter bundles

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Introduction: Advanced biophysical multi-compartment models of diffusion imaging enable the characterization of complex fiber configurations at a smaller spatial scale than diffusion tensor imaging (DTI). Thus, they could better depict the presence of white matter lesions (WM) in multiple sclerosis (MS).
Objectives & Aim: This study aims to compare the ability of the anisotropy measures derived from multi-compartment models with the ones from DTI to quantify MS lesions in several WM tracts using an Automated Fiber-Tract Quantification (AFQ) method.
Methods: Cross-sectional study with 76 MS patients [78% females; age: mean (standard deviation) 54.84 (10.76) years; Expanded Disability Status Scale: 2.0 (range 1.0-7.0)] that underwent a brain MRI. MS lesions were manually delineated in the 3D-T1 and 3D-FLAIR sequences. Multi-shell diffusion-weighted images were processed using FSL and MRtrix tools to estimate fractional anisotropy (FA) values. Subsequently, microscopic anisotropy (μFA) measures were obtained using the spherical mean technique model. The AFQ method was employed to analyze the anisotropy metrics of the bundle's profiles from 9 WM bundles for each hemisphere and to quantify the presence of regional damage according to the division of these bundles in 100 segments. We correlated the mean FA and μFA from each bundle and from each division with the lesion load. Finally, the anisotropy measures were used to quantify the MS lesion volume in specific locations of the WM bundles.
Results: μFA from the whole bundles showed a higher correlation with lesion volume (r=0.71) than FA (r=0.46). Similarly, the bundle profiles analysis, which allows not only the quantification of the lesion volume but also the localization of the lesion across the bundle, displayed a better performance of μFA over FA values (mean bundle profiles: r=0.67 and r=0.28 respectively). Microscopic anisotropy outperformed conventional FA metric to predict the presence of MS lesions in specific segments across the bundles, scoring an R-Squared nearly three times greater (r2 = 0.218 for FA and r2 = 0.535 for μFA).
Conclusions: Multi-compartment diffusion models have larger sensitivity than classical diffusion tensor models to depict the presence of focal MS damage in the white matter tracts.

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Disclosure
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Quantification of thalamic volume in multiple sclerosis: from the multicenter INNI dataset towards the clinical application

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Introduction: The thalamus is a structure of particular interest in multiple sclerosis (MS). Thalamic atrophy has been found since the earliest phases of MS and is clinically relevant. However, this measure is still not included in clinical practice, due to the time-consuming manual segmentation and technical challenges.
Aims: Aim of this study was to obtain a reliable segmentation of the thalamus in MS by comparing existing automatic methods.
Methods: 141 relapsing-remitting MS patients and 69 healthy controls (HC) with baseline and 1-year 3D T1-weighted, T2-weighted and diffusion weighted (DW) MRI acquisitions were collected from the Italian Neuroimaging Network Initiative repository. From DWI, fractional anisotropy (FA) maps were derived to be used with T1-weighted MRI, as input for multimodal thalamic segmentation for the FSL-MIST. The other automatic approaches applied were FSL-FIRST v5.0.9 and Freesurfer v6.0, both at baseline and at follow-up. The agreement among the results of the pipelines and the effect sizes in differentiating between MS and

HC were assessed. In patients, correlations with age, disease duration, EDSS and T2-hyperintense lesion volume (LV) were also evaluated.
Results: At baseline, FIRST and MIST (R=0.87, p<0.001) showed the highest significant agreement in the results of thalamic volume, with the highest effect size in differentiating MS and HC found for MIST (Cohen's d=1.11). At baseline, FIRST showed the highest significant correlations with age (-0.36, p<0.001), EDSS (R=-0.3, p<0.001, adjusted for age), T2-hyperintense LV (R=-0.4, p<0.001) and disease duration (R=-0.2, p=0.02). At follow-up, MIST showed the lowest variability in estimating thalamic volume changes (TVC) for HC (standard deviation=1.07%) in comparison to the other pipelines, and a better capability to significantly differentiate between MS and HC (Cohen's d=0.21). In MS patients, only MIST TVC showed a significant correlation (adjusted for age) with T2-hyperintense LV change (R=-0.22, p=0.01).
Conclusions: We found that the inclusion of FA contrast increased robustness of the results and a better capability to detect small longitudinal variations of thalamic volumes, as shown by MIST results. The advantage of a multimodal approach is also shown by the results of correlations with LV changes at follow-up for MIST.

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Spinal cord myelin imaging in patients with multiple sclerosis using [^{11}C]MeDAS PET

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Introduction: In multiple sclerosis (MS) remyelination of lesions in brain and spinal cord is essential for repair of function after a relapse. Development of remyelinating therapies is hampered by the lack of a quantitative myelin imaging method. Myelin quantification in the brain using PET seems promising but many clinical relevant lesions reside in the spinal cord.
Objective: To evaluate [^{11}C]MeDAS as a PET tracer for myelin imaging in the human spinal cord.
Methods: Six controls (HC) and 11 MS patients were subjected to T2-weighted and proton density-weighted magnetic resonance imaging (MRI) and [^{11}C]MeDAS PET. Eight MS patients underwent a second [^{11}C]MeDAS PET after a one week interval to test reproducibility. Lesion detection and identification was performed on MRI. Subsequently, regions-of-interest (ROIs) with various diameters were drawn on the PET images for sections of the spinal cord corresponding to vertebrae C5 to T6. Best results were obtained whenROIs of the spinal cord covered 40% of the diameter of the spinal canal. The spinal cord ROIs were then normalized to the activity in the blood pool of the aorta ($SUVR_{aorta}$), the heart, the neck muscle, or the injected dose and body weight (SUV_{mean}).
Results: Tracer uptake was higher in the cervical spinal cord than in the thoracic spinal cord using both visual and quantitative assessment (SUV_{mean}: C5-C7 1.41±0.29; T1-T3 0.92±0.18; T4-T6 0.83±0.15; p=0.004, $SUVR_{aorta}$: C5-C7 1.55±0.15; T1-T3 1.02±0.18; T4-T6 0.93±0.20; p>0.001), which correlates well with the known physiological gradient in myelin density. The tracer uptake in MS patients was lower compared to HC (SUV_{mean}: C5-C7 1.41±0.29 HC vs. 0.86±0.15 MS; T=4.09; p=0.001, T1-T3 0.92±0.18 HC vs. 0.58±0.18 MS; p=0.014). Reproducibility was moderate to good (test-retest variability=6.5-17.7%), depending on the quantification method ($SUVR_{aorta}$=11.68%±9.78%; SUV_{mean}=17.7±13.6%). After extensive analysis, correction of spinal cord uptake for radioactivity in the blood pool of the aorta seems to be the most optimal normalization procedure, due to detection of physiological myelin gradient and reproducibility. These pilot $SUVR_{aorta}$data resulted in a good sensitivity (84%) and

negative predictive value (91%) for the detection of MS lesions in a specific section of the spinal cord.
Conclusions: [^{11}C]MeDAS PET shows the potential to quantify myelin density in the spinal cord, which warrants further evaluation.

Disclosure
The authors declare no conflict of interest

P204
An evaluation of the impact of MRI field strength and contrast delay on visualization of meningeal enhancement in multiple sclerosis

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Background: Gadolinium (Gd)-based meningeal enhancement (ME) on post-contrast FLAIR MRI is an investigational biomarker in multiple sclerosis (MS), possibly linked to meningeal inflammation or lymphatic drainage. ME was first noted on post-contrast 3T FLAIR, but subsequent data suggested greater sensitivity with post-contrast acquisition delays and 7T MRI.
Aim: To perform a comparison of field strength and acquisition delay on ME in an MS cohort to provide direct evidence of the impact of these protocol differences.
Methods: 84 patients with MS underwent a 7T brain MRI. The 7T MRI protocol included a FLAIR acquisition at 0.5 x 0.488 x 0.488 mm^3 resolution before, immediately after (early 7T FLAIR), and approximately 23 minutes after Gd injection (delayed 7T FLAIR). 54 subjects also underwent a 3T brain MRI within 30 days. The 3T MRI protocol included a FLAIR acquisition at 1.0 mm^3 resolution, which was acquired before and approximately 23 minutes after Gd injection (delayed 3T FLAIR). All images were co-registered to a common space and subtraction images were reviewed for the presence of ME. Enhancement patterns were characterized as leptomeningeal (LME) or perivascular/dural (PDE).
Results: LME was detected in 53.6% (95% CI: 43.7 – 64.5) of participants on delayed 7T FLAIR compared to 45.2% (34.4 – 56.1) on early 7T FLAIR ($p = 0.180$) and 20.4% (9.27 – 31.5) on delayed 3T FLAIR ($p < 0.001$). PDE was detected in 98.9% (96.4 – 101.1) of participants on delayed 7T FLAIR compared to 85.7% (78.1 – 93.4) on early 7T FLAIR ($p < 0.001$) and 64.8% (51.6 – 78.0) on delayed 3T FLAIR ($p < 0.001$). The mean number of LME foci found on delayed 7T FLAIR was 1.27 (95% CI: 0.85 – 1.70) compared to 0.92 (0.60 – 1.23) on early 7T FLAIR ($p = 0.031$) and 0.31 (0.12 – 0.50) on delayed 3T FLAIR ($p < 0.001$). The mean number of PDE foci found on delayed 7T FLAIR was 8.90 (7.52 – 10.29) compared to 4.52 (3.60 – 5.44) on early 7T FLAIR ($p < 0.001$) and 2.85 (1.80 – 3.90) on delayed 3T FLAIR ($p < 0.001$).
Conclusions: The number of foci and proportion of participants with ME were significantly greater on delayed 7T FLAIR than on early 7T FLAIR and both were more sensitive than delayed 3T FLAIR. These data validate the hypothesis that a delay after contrast administration and higher field strength maximizes the sensitivity of this imaging biomarker. These data should inform future studies investigating the clinical significance and potential treatment response of ME in MS.

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Serum neurofilament light associates with increased TSPO-PET measurable microglial activation in multiple sclerosis brain

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Introduction: Innate immune cell activation is central for promoting neuroaxonal damage in multiple sclerosis (MS) and other neurodegenerative diseases. Neurofilament light (NfL) on the other hand, is a biomarker released from damaged neurons. 18-kDa translocator protein – positron emission tomography (TSPO-PET) and NfL report on brain pathology, but their potential association has not yet been studied in MS *in vivo.*
Objectives: To evaluate the association between serum NfL and TSPO-PET-measurable microglial activation in the brain of clinically stable patients with MS.
Methods: Microglial activation was detected using PET and the TSPO-binding radioligand [^{11}C]PK11195 in 44 patients with MS (40 relapsing-remitting and 4 secondary progressive) and in 24 age and sex matched healthy controls (HC). Distribution volume ratio (DVR) was used to evaluate specific [^{11}C]PK11195-binding in several region of interests. The 80th percentile of the HC brain DVR (1.2052) was used as a cut-off value to define patients with unaltered or increased microglial activation. T1 hypo lesions were classified based on DVRs within the lesion core and rim. Serum levels of NfL were measured using single molecule array (Simoa). The associations between TSPO-PET related parameters and NfL were evaluated using correlation analyses and stepwise multiple regression modelling.
Results: Nearly half of the patients (43 %, n=19) had increased microglial activation in the brain compared to HC. These patients had higher EDSS, and more rim-active lesions compared to patients with brain DVR values comparable to HC ($p=0.047$, $p<0.001$, respectively). In the patient group with elevated brain DVR, increased serum NfL levels correlated with higher DVR in the normal appearing white matter (Pearson correlation coefficient [r]=0.5, p=0.04), T1 hypolesions (r=0.5, p=0.03), lesion rim (r=0.6, p=0.008) and perilesional white matter (r=0.6, p=0.009). Moreover, increased NfL correlated with higher number and larger volume of

rim-active lesions (Spearman correlation coefficient, [ρ]=0.46, p=0.045 and ρ=0.62, p=0.006, respectively) and with smaller proportion of inactive lesions (ρ= -0.64, p=0.003). In patients with unaltered brain DVR no such associations were observed.
Conclusions: Our demonstration of a strong association between TSPO-PET-measurable microglial activation and elevated serum NfL emphasizes the significance of smoldering inflammation for progression-promoting pathology in MS.

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P206
Quantitative susceptibility mapping demonstrates the significance of thalamic pathology in patients with secondary progressive multiple sclerosis: baseline analysis from the MS-STAT2 randomised controlled trial

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Introduction: Deep grey matter (DGM) abnormalities are a key driver of disability in people with MS (pwMS). Quantitative susceptibility mapping (QSM) is an advanced MRI technique sensitive to both iron and myelin.
Objectives: To investigate differences between DGM mean regional susceptibility (χ) in people with secondary progressive multiple sclerosis (pwSPMS) and controls; to examine relationships between DGM χ and clinical and imaging measures of disease severity.
Methods: Baseline data from the MS-STAT2 trial (simvastatin vs. placebo in SPMS, NCT03387670) were included. Patients underwent clinical assessments and an advanced MRI protocol at 3T. A cohort of age-matched healthy controls underwent the same MRI protocol. QSM data were acquired using a multi-echo 3D gradient-echo sequence and processed using iterative Tikhonov regularization (https://xip.uclb.com/product/mri_qsm_tkd). Regions of interest (ROIs) were segmented using Geodesic Information Flows from 3D T1-weighted images, and lesions segmented from 3D FLAIR using NicMSlesions. Linear regression was used to compare χ from ROIs in the DGM between cases and controls, adjusting for age and sex, and to examine associations with clinical and imaging measures of MS severity.
Results: 149 pwSPMS and 33 age-matched controls were included. Mean (SD) age and disease duration were 53 (7) and 24 (9) years, respectively. Median (IQR) EDSS was 6.0 (4.5-6.0).
Thalamic χ was significantly lower in pwSPMS compared to controls: mean (SD) was 39.3 (12.7)ppb in controls and 28.6 (12.8) ppb in pwSPMS (regression coefficient -12.1 [95% confidence interval: -17.2 to -7.1]ppb, $p<0.001$).
In pwSPMS, a 10ppb lower thalamic χ was associated with a +0.13 [+0.01 to +0.23] point higher EDSS ($p<0.05$), a -1.95 [-3.30 to -0.61] point lower SLOAN low contrast acuity, 2.5% (p=0.005) and a -2.34 [-3.73 to -0.94] point lower symbol digit modality test (SDMT, p=0.001).
A 10ppb lower thalamic χ was also strongly associated with a +6.14 [+4.16 to +8.12]mL higher T2 lesion volume ($p<0.001$) and lower normalised whole brain, DGM and thalamic volumes (all $p<0.001$).
Significant results for other DGM ROIs will also be presented.
Conclusions: Thalamic susceptibility is lower in pwSPMS compared to controls and is strongly associated with measures of SPMS severity. Advanced imaging measures, such as QSM, are promising biomarkers of the pathophysiology of SPMS and should be further investigated as biomarkers of neuroprotective treatment response.

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The effect of natalizumab, fingolimod and first-line treatment on brain atrophy in patients with multiple sclerosis

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Introduction: Natalizumab (NTZ) and fingolimod (FTY) are high efficacy disease modifying treatment (DMT) options for patients with relapsing remitting multiple sclerosis (RRMS). In contrast to the strong anti-neuroinflammatory and clinical effects, the effects on neurodegeneration of these compounds remain largely unknown.
Objectives: To investigate the effect of NTZ and FTY on brain atrophy compared to lower efficacy DMT in a real-world clinical setting using 3D-FLAIR scans.
Methods: Treatment history, Expanded Disability Status Scale (EDSS) and clinical 3D-FLAIR exams were retrospectively collected from 67 patients starting with NTZ and 43 patients starting with FTY. These groups were matched based on sex and disease duration to 90 patients starting lower efficacy DMT (interferon beta, glatiramer acetate, dimethyl fumarate and/or teriflunomide). Evolution of atrophy was analyzed between 1 year after DMT group initiation (i.e. after the pseudo-atrophy period) and an average follow-up of 4.1 years. 3D-FLAIR images were segmented with SynthSeg to obtain brain, ventricle, white matter (WM), cortical gray matter (GM), deep GM and thalamus volumes. In addition, data driven patterns of GM atrophy were obtained by applying source-based morphometry. Volume and GM pattern loading changes over time were compared between the three DMT groups, corrected for age, sex and disease duration using linear mixed models.
Results: EDSS and brain volumes at baseline were similar between DMT groups. Worse EDSS was associated with lower

brain (β=-0.18, p=0.021), deep gray matter (β=-0.23, p=0.008) and thalamic volumes (β=-0.25, p=0.002). Ventricle growth rates were lower in patients treated with NTZ compared to lower efficacy DMT (β=0.36, p=0.043) and similar to FTY therapy (β=0.02, p=0.935). Thalamus volume was lower in the NTZ group compared to lower efficacy DMT group (β=0.84, p=0.041), but did not show a different atrophy rate over time. Four GM patterns correlated with EDSS at baseline (Spearman's ρ<-0.2, p<0.05); one of these patterns (cingulate gyrus) had a lower atrophy rate in NTZ compared to first-line therapy (β=-0.02, p=0.005) and a similar rate compared to FTY (β=-0.01,p=0.130).

Conclusion: In a real-world clinical setting, RRMS patients treated with high efficacy DMT had slower ventricular expansion and cingulate atrophy rates compared to lower efficacy DMT. However, thalamus volumes were lower in the high efficacy group, suggesting more severe damage at baseline.

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Feasibility of detecting atrophy relevant for disability and cognition on 3D-FLAIR

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Introduction: Disability and cognitive impairment are related to brain atrophy in multiple sclerosis (MS), but high resolution 3D-T1 imaging required for brain volumetrics is often unavailable in clinical protocols, unlike 3D-FLAIR.

Objectives: This study investigated the agreement between 3D-T1 brain volumetrics and 3D-FLAIR volumetrics. Additionally, the feasibility of detecting atrophy relevant for disability and cognition on 3D-FLAIR was assessed.

Method: 3T-MRI data of 293 MS patients and 48 controls from two centers were included in this study. Disability was measured with the expanded disability status scale (EDSS) and cognitive assessments were based on an expanded BRB-N. Brain segmentation was performed on 3D-FLAIR with SynthSeg and SAMSEG and compared to segmentation performance in the same subjects on 3D-T1 (FreeSurfer, SynthSeg and SAMSEG) by calculating the intraclass correlation coefficient (ICC) for consistency. The relation between brain volume measures and clinical outcome measures was assessed with univariate linear regression analysis.

Results: Volumes derived from 3D-FLAIR showed good to excellent absolute agreement with those derived from FreeSurfer on 3D-T1 for total brain, ventricle, cortical and deep grey matter (DGM) volumes (ICC>0.75) in MS patients and controls. For thalamus segmentation on 3D-FLAIR the ICC was moderate for SAMSEG (ICC=0.63), but good with SynthSeg (ICC=0.87). Higher disability was associated with lower brain volumes using FreeSurfer on 3D-T1 (β=-0.51, R^2=0.15, p<0.001), SAMSEG on 3D-FLAIR (β=-0.57, R^2=0.14, p<0.001) and SynthSeg on 3D-FLAIR (β=-0.58, R^2=0.17, p<0.001). Similar associations with EDSS were found for cortex, ventricle and DGM using both 3D-T1 and 3D-FLAIR-based segmentation. Worse cognition was associated with atrophy of brain and grey matter structures using all methods (p<0.001). Using 3D-FLAIR, SynthSeg showed a higher relation between thalamus volume and cognition compared to SAMSEG (β=0.47 vs. β=0.40), but lower relation for cortical volumes (β=0.23 vs. β=0.41).

Conclusion: 3D-FLAIR can be used to detect global and regional atrophy relevant for disability and cognitive dysfunction, which could enable monitoring of neurodegeneration in a clinical setting.

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Assessing the performance of an automated decision-support system for detecting active T2 lesions on non-standardized MRI systems and field strengths

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Introduction: Quantification of new T2 lesions using an automated software is usually challenging due to the requirement for strict standardization of image acquisition protocols (MRI systems, pulse sequences, and acquisition parameters).
Objective: To assess the performance of an automated decision-system trained only with data from a 3T Siemens scanner to detect new T2 lesions in brain MRI of five different 1.5T Philips scanners with different acquisition parameters.
Methods: The study was composed of 80 treated MS patients with two MRI exams. MRI data was acquired on five 1.5T scanners from two Spanish MS reference centers (2 Philips Achieva, 2 Philips Intera and 1 Philips Ingenia) following the same image protocol (3D-FLAIR, and T2-weighted sequences). A supervised convolutional neural network (CNN) based approach, which was already trained on 3T MRI data (Siemens Trio Trim) to detect the presence of new T2 lesions in the follow-up image, was used to automatically compute the lesion masks on the 1.5T MRI data of the 80 patients. The outcome of the visual standard radiological report used during clinical routine (O1) was compared with the outcome of the CNN method (M1) and with the radiological report resulting of using the automated decision-system during the visual analysis (O1+M1).
Results: The visual standard report (O1) detected 32 lesions in 11 patients (40% sensitivity, 100% specificity) while the automated (M1) method alone detected 60 lesions in 15 patients (75% sensitivity, 78% specificity). In contrast, the combination of the (O1+M1) detected 80 new T2 lesions in 22 patients, which represents a 60% increase of the sensitivity with respect (O1) and a 25% increase with respect to (M1) alone with a 100% specificity. The sensitivity of the (O1+M1) method detecting patients with at least one lesion was 50% higher than the (O1) method (11 patients) and 32% higher than the (M1) method (15 patients).
Conclusions: The adoption of the CNN based automated decision-system during the standard visual report significantly increased the capability (50%) of detecting active patients even though the images were acquired on different MRI machines, field strengths and acquisition parameters than the ones used to train the CNN method. The results of this study show that the automated decision-system have the potential to be used as an aid to the radiological visual assessment without a strict standardization of the image acquisitions.

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Predominantly spinal cord MRI phenotype of multiple sclerosis

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Background: A possible new entity of spinal multiple sclerosis (MS) which may represent a distinct phenotype within the MS disease spectrum has been described in few studies.

Objectives: To retrospectively review magnetic resonance imaging (MRI) of brain and spinal cord (SC) of patients with clinically definite MS, identify patients with focal lesions limited to SC and extract demographic and clinical data of the group from iMED database.

Aims: To define the frequency, clinical characteristics and course of spinal MS.

Methods: 2739 MS patients underwent MRI of the brain and SC between January 2016 and December 2018. Selection criteria were: at least one SC lesion, absence of longitudinally extensive transverse myelitis, presence of maximum one brain lesion (<2mm), positive oligoclonal bands in cerebrospinal fluid and negative antibodies against aquaporin-4 and myelin oligodendrocyte glycoprotein. To assess the short-term course, we included patients with at least 3 years of clinical and MRI follow-up. Progression was defined as an increase in EDSS ⩾1.5 from an EDSS of 0, ⩾1.0 from an EDSS of 1.0–5.5 or ⩾0.5 from an EDSS ⩾6.0. SC volume was measured by using an automatic segmentation tool and compared to normative data based on 102 healthy individuals.

Results: Spinal MS was diagnosed in 49 patients (1.8%) out of 2739 patients (40 women, 9 men). One male patient with primary progressive MS and 2 relapsing-remitting (RRMS) patients were lost to follow-up and thus excluded from the analysis. 43 patients had RRMS and 3 secondary progressive MS (SPMS) at the time of MRI. All 3 SPMS patients were active with progression based on Lublin's clinical phenotype classification. The mean age was 33.9±6.3 years, disease duration 5.0±5.1 years. The median Expanded Disability Status Scale (EDSS) was 1.5(0-5.0) at the time of the MRI and 1.5(0-6.5) at follow-up. 14 patients had at least one documented optic neuritis. Progression was documented in 14 patients (12 women), of which 11 were active RRMS patients and 3 patients progressed from RRMS to SPMS (one patient was non-active with progression and two were active with progression). 8 patients had SC atrophy.

Conclusions: Spinal MS is a rare occurrence. In our cohort, female patients significantly predominated and the disability progression was not due to primary progressive disease course as in the previously described smaller group by Nociti et al., but rather due to active progressive disease course in RRMS and SPMS.

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Hypodiamagnetism on χ-separation: a potential marker for the differential diagnosis between MS and NMOSD

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Introduction: χ-separation imaging can provide surrogates for iron and myelin that are closely related to the pathologic changes in multiple sclerosis (MS) lesions.

Objectives: To evaluate the appearances of MS and neuromyelitis optica spectrum disorder (NMOSD) brain lesions on χ-separation maps.

Aims: To explore their diagnostic value in the differentiation between the two diseases.

Methods: This prospective study included 32 MS and 15 NMOSD patients. Using local frequency shifts and R_2' (= R_2^*- R_2), positive (χ_{pos}) and negative susceptibility (χ_{neg}) were separately estimated. For each type of lesion, the presence of the central vein sign (CVS) and paramagnetic rim sign (PRS) were assessed. Signal characteristics on the χ_{neg} maps were classified into hypointense (hypodiamagnetic), isointense, and hyperintense. On the χ_{pos} maps, the presence of a paramagnetic rim and signal characteristics were assessed. The characteristics of MS and NMOSD lesions were compared. For each subject, the proportion of lesions with CVS, PRS, and hypodiamagnetic lesions was calculated, and the diagnostic performances of these proportions were assessed using receiver operating characteristic (ROC) curve analysis.

Results: In total, 661 MS and 225 NMOSD brain lesions were analyzed. On the χ_{neg} maps, 80.2% (490/611) of the MS lesions were categorized as hypodiamagnetic versus only 14.2% (32/225) of the NMOSD lesions ($P<0.001$). On the other hand, the lesion appearances on the χ_{pos} maps were not significantly different between the two diseases. In the per-patient analysis, the MS patients showed a significantly higher proportion of

hypodiamagnetic lesions (0.83, interquartile range [IQR] 0.72-0.93) than the NMOSD patients (0.06, IQR 0.00-0.14, $P<0.001$). The proportion of hypodiamagnetic lesions achieved an excellent diagnostic performance (area under ROC curve 0.961, 95% confidence interval 0.907-1).

Conclusions: On negative χ-separation susceptibility maps, MS lesions tend to be hypodiamagnetic, which can serve as an important hallmark for differentiating MS from NMOSD.

Disclosure

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P212

Predicting cognition from structural disconnectivity metrics and estimated functional connectivity networks

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Brain connectivity analysis provides a promising tool with which to map the effect of multiple sclerosis (MS)-related pathology on physical and cognitive impairment. Advanced imaging techniques such as diffusion and functional MRI are commonly used to quantify structural connectivity (SC) and functional connectivity (FC) networks; however, they are expensive and time-consuming. Our recent study showed that the SC and FC networks estimated using deep learning and lesion masks extracted from conventional MRI can predict disability as well as SC and FC networks derived from advanced MRI. However, how well the estimated connectivity networks can predict cognition is unknown. Therefore, the aims of this study are to predict cognitive scores using 1) regional structural dysconnectivity (called ChaCo scores), estimated by identifying white matter pathways in a normative database that intersect a patient's lesion mask, 2) estimated FC (eFC) derived using a pre-trained deep learning model, and 3) both ChaCo scores and eFC together using machine learning. One hundred fifty-eight MS patients (female: %72, mean age: 42.40) were included in our study. Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Test (BVMT) were used to assess cognition. Spearman's correlation (r) between observed and predicted cognitive scores for a hold-out set of test subjects was used to assess the models' prediction performances. The model based on ChaCo scores outperformed other models in predicting SDMT ($r=0.39$, $p<0.01$ for all comparisons) and CVLT ($r=0.42$, $p<0.01$ for all comparisons). However, the eFC outperformed other models in predicting BVMT ($r=0.38$, $p<0.01$ for all comparisons). Structural disconnectivity in subcortical regions, specifically the putamen and thalamus, was associated with poorer cognitive scores in all models. Increased eFC in visual-related regions was associated with better cognitive scores, in particular with BVMT which measures visual memory. Lower eFC in the thalamus and the frontal pole was associated with poorer cognitive scores in all models. Our modeling approach that predicts cognition in MS performed similarly to the highest accuracy in previous models in the literature. Our work demonstrates that lesion masks, coupled with our approach to estimating structural dysconnectivity and FC using them, can be a viable alternative to collecting advanced MRI, bringing the connectome one step closer to the clinic.

Disclosure

No conflict of interest to disclose. Ceren Tozlu received a postdoctoral fellowship from the National MS Society in the United States.

P213

Structural disconnection due to chronic active lesions may occur relatively earlier in disability progression in multiple sclerosis than structural disconnection due to inactive lesions

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In multiple sclerosis (MS), chronic active lesions which constitute approximately 5-10% of all lesions present a rim-shaped accumulation of microglia and or macrophages at their borders. Chronic active (rim+) lesions have recently been found to be larger and structural dysconnectivity (i.e., white matter pathways damaged by MS lesions) due to rim+ was found to be better associated with disability compared to structural dysconnectivity due to rim- lesions (Tozlu et al., 2021). However, how rim+ vs rim- lesions differentially impact clinical disability through their structural disconnection is still unknown. Event-based modeling (EBM) is a data-driven approach used to estimate the order of biomarker abnormalities that drive disease progression using cross-sectional data. The aim of our study is to investigate the sequence of structural dysconnectivity due to rim+ vs rim- lesions in different brain networks for the transition from "no disability" to "disability" in MS patients using EBM. Ninety-six MS patients (female=67%, mean age: 38) were included. The Expanded Disability Status Scale (EDSS) score was used to classify patients into no disability (EDSS<2) and disability (EDSS≥ 2) groups. Quantitative susceptibility mapping was used to identify rim+ lesions. Fifty-six patients had at least one rim+ lesion. For the subjects who had both rim+ and rim- lesions, two different lesion masks were created. Then, the network modification tool (Kuceyeski et al., 2013) was used to estimate the structural disconnections due to rim+ vs rim- lesions for an anatomical atlas of 86 gray matter regions. Structural disconnections due to rim+ lesions occur relatively earlier compared to structural disconnections due to rim- lesions as disability progresses. The structural disconnections due to rim+ lesions occur first (in terms of disability progression) in regions of the limbic, frontoparietal, subcortical, default mode, and cerebellar networks, followed by structural

disconnections due to rim- lesions in the subcortical regions and cerebellum. Our results show that the structural dysconnectivity due to rim+ lesions occurs relatively earlier compared to structural dysconnectivity due to rim- lesions for the transition from no disability to disability group. Our study demonstrates that rim+ lesions, which were known to be larger compared to rim- lesions, are more detrimental to structural connectivity, therefore earlier appearance of rim+ lesions may drive disability in MS.

Disclosure
No conflict of interest to disclose. Ceren Tozlu is funded by the National MS Society in the United States.

P214
Longitudinal fixel-based white matter damage predicts cognitive decline in multiple sclerosis

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Background: During the course of multiple sclerosis (MS), many patients experience cognitive deficits which are not easily related to lesion load or location. This discrepancy could be driven by an inability of current imaging methods to consider the full complexity of white matter (WM) structure both at a macro- and microstructural level.
Objective: To use a novel fixel-based approach to investigate specific patterns of WM degeneration, the evolution over time, the manifestation across different stages of the disease and their role in cognitive impairment.
Methods: Cognitive and 30-direction diffusion weighted MR data were included from 327 MS patients (mean age=48.34 years, 221 female) and 95 healthy controls (HCs; mean age=45.70 years, 55 female). Of those, 233 patients and 61 HCs had follow-up assessments five years after. Patients scoring 1.5SD or 2SD below HCs on at least 2 cognitive domains (BRB-N) were classified as mildly cognitively impaired (MCI) or cognitively impaired (CI), respectively, or otherwise cognitively preserved (CP). Fixel-based analysis of diffusion data was used to calculate fiber-specific measures (fiber density [FD], reflecting microstructural diffuse axonal damage; fiber cross-section [FC] reflecting macrostructural tract atrophy) within atlas-based WM tracts at each visit.
Results: At baseline, all fixel-based measures were significantly abnormal in MS compared to HCs ($p<0.05$). All measures showed a similar pattern, with SPMS patients having the most severe damage, followed by PPMS and RRMS. Similarly, damage was least severe in CP (n=177), more severe in MCI (n=63), and worst in CI (n=87; $p<0.05$). Microstructural damage was most pronounced in the cingulum, while macrostructural alterations were most pronounced in the corticospinal tract (CST), cingulum and superior longitudinal fasciculus (SLF). Over time, WM alterations worsened most severely in progressive MS ($p<0.05$), with WM atrophy progression mainly seen in the CST and microstructural axonal damage worsening in cingulum and SLF. Both cognitive decline and clinical disability at follow-up could best be predicted by baseline fixel-based measures (R^2 ranging from 0.36 to 0.45, $p<0.001$).
Conclusion: These results indicate that fixel-based approaches can have powerful predictive value in MS for both physical and cognitive disabilities. Longitudinal deterioration was worst in progressive MS, indicating that degeneration in WM remains important to study further in this phenotype.

Disclosure
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P215
Spinal cord atrophy predicts silent progression in relapse-onset multiple sclerosis

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Introduction: A major challenge in multiple sclerosis (MS) research is the understanding of insidious disability worsening termed silent progression that occurs early in MS in a subset of patients. As such, brain and cord atrophy from MRI volume changes might be useful predictors of clinically silent disease progression.
Objectives: To develop predictive biomarkers that could facilitate early patient stratification for therapeutic strategies.
Aims: Using a novel method to accurately capture upper cervical cord area from legacy brain MRI scans we aimed to study spinal cord and brain atrophy as predictors of silent clinical progression.
Methods: From a single-center observational study, all relapsing remitting (RR) MS (n=360) and secondary progressive (SP) MS (n=47) patients and 80 matched controls were evaluated. Silent progression was defined as onset of irreversible EDSS worsening, confirmed over 12 months and independent from relapses. RRMS patients who silently progressed (n=159) were compared to clinically matched RRMS patients remaining stable (n=147) during the 12-year observation period. From brain MRI, we assessed the value of global and regional brain measures and spinal cord area at C1 vertebral level (C1A) to predict silent clinical progression.
Results: In survival analyses, spinal cord atrophy was the strongest predictor of silent clinical progression: a 1% faster spinal cord atrophy rate was associated with 69% ($p<0.0001$) shorter time to silent clinical progression. Ventricular enlargement was the second strongest MRI metric and the strongest brain measure to predict silent progression, with each 1% enlargement of the lateral ventricles being associated with a 16% shorter time to silent clinical progression ($p=0.007$).
Conclusions: Using a novel method to accurately capture C1A from legacy brain MRI scans we show that silent clinical progression is predominantly associated with cervical cord atrophy. This atrophy is often present from the earliest disease stages and predicts the speed of silent progression.

Disclosure
AB reports travel fees from Actelion. RMB has received research support from the National Multiple Sclerosis Society, Hilton Foundation, California Initiative to Advance Precision Medicine, Doris Duke Award, Sherak Foundation, and Akili Interactive; and has received personal compensation for medical legal consulting and for consulting or serving on the advisory boards of F. Hoffmann-La Roche Ltd, Sanofi-Genzyme and Novartis. JMG reports research support for clinical trials from Genentech/Roche and Vigil Neuroscience; consulting for Biogen; medical legal consulting; service on trial steering committees for Roche/Genentech. DSG has participated as principal investigator in several clinical trials in MS and has given many public lectures regarding the epidemiology of MS and/or its treatment. These clinical trials and many of these lectures have been sponsored by various pharmaceutical companies including Biogen Idec, Bayer Schering, Novartis, EMD Serono, Genzyme, and Teva pharmaceuticals. JSG reports personal fees from BMS, personal fees from Alexion, personal fees from Novartis, personal fees from Genentech, grants from Biogen and END Serono. EW has not received any pharmaceutical company honorarium. She is site PI for Novartis and Roche multicentre trials. She volunteers on an advisory board for a Novartis trial. She is a non-remunerated advisor for clinical trial design to Novartis, Biogen-IDEC, Sanofi, Genentech, Serono, Celgene, Emerald Health Pharmaceuticals and DBV. She has funding from the NMSS, PCORI and the Race to Erase MS and receives compensation as the section editor for Annals of Clinical and Translational Neurology, and co-Chief editor for MSARD. MRW receives research support from Roche/Genentech and philanthropic support from the Rachleff Family. AJG reports personal fees from Inception Sciences and Mylan, Pharmaceuticals and grants/awards from the National Multiple Sclerosis Society, Novartis, UCSF CTSI, and That Man May See as well as philanthropic support from the Rachleff Family and the Robert Dale Family. He also reported serving on end point adjudication committees for Biogen and Medimmune. He serves on trial steering committees for Novartis and Scientific Advisory Board for Bionure. BACC has received personal compensation for consulting from Akili, Alexion, Biogen, EMD Serono, Novartis and TG Therapeutics. SLH currently serves on the Scientific Advisory Board of Alector, Annexon, Bionure, Molecular Stethoscope, and Symbiotix, and on the Board of Trustees of Neurona. He also has received travel reimbursement and writing assistance from F. Hoffman-La Roche Ltd. and Novartis Pharma AG for CD20-related meetings and presentations. RGH has received grants from Stem Cells Inc, Hoffmann La Roche, and Sanofi Genzyme outside the submitted work, and advisory board honoraria from Abbvie, Roche, and Novartis. SLH currently serves on the Scientific Advisory Board of Alector, Annexon, Bionure and Molecular Stethoscope, and on the Board of Trustees of Neurona. He received travel reimbursement and writing assistance from F. Hoffman-La Roche Ltd. and Novartis Pharma AG for CD20-related meetings and presentations. RGH received grants from Hoffmann La Roche outside the submitted work, and consultancy honoraria from Abbvie, Roche/Genentech, Sanofi/Genzyme, Atara, Celgene, QIA, Medday, and Novartis. SSZ has served as a consultant and received honoraria from Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals, Inc., and has served on Data Safety Monitoring Boards for Lilly, BioMS, Teva and Opexa Therapeutics. He receives research grant support from the NIH, NMSS, Weill Institute, Race to Erase MS and the Maisin Foundation. NP, AK, AR, GK, JMM, XZ, CA, SS, TJG, CZ, WAS, EC, YZ, RG, NRR, AS, AHZ, JJ, CJB, ElC, and JRO have nothing to disclose.

P216
Distribution of cortical lesions across functional networks is non-random and related to cognitive impairment

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Background: Cortical lesions (CL) burden and functional organization of the brain are important features of Multiple Sclerosis (MS) and, both relate to cognitive impairment.
Objectives: The relationship between CLs and functional networks has not been studied yet.
Aims: To investigate the localization and extent of CLs within functional networks in MS and assess their relationship with cognitive impairment.
Methods: 177 MS patients (*M*age 54±9 years,*M*disease duration 16.7±5.7 years) from the Amsterdam MS cohort underwent neuropsychological testing (expanded BRB-N), resting-state functional and structural 3T MRI, including double inversion recovery. Patients were categorized as cognitively preserved (CP;*N*=83) and impaired (CI;*Z*-score −1.5 on ⩾2 out of 7 cognitive domains,*N*=94), based on 48 matched healthy-controls. The Brainnetome atlas was used to parcellate the brain into 210 regions of interest (ROI) and grouped in 7 functional literature-based networks: visual, sensorimotor (SMN), ventral attention (VAN), dorsal attention (DAN), default mode (DMN), frontoparietal (FPN), limbic network. Network function quantified with eigenvector centrality (ECM), a measure of regional network importance, was quantified per network. Median CLs volume/fraction per network and ROIs was calculated and Mann-Whitney test was used to compare the groups.
Results: In the total MS group, largest CLs volumes and fractions were found in DMN (volume [IQR] mm^3/fraction %; 51.4[166.4]/0.05),limbic (44.2[155.3]/0.08) and VAN (23.1 [70.9]/0.11). The most affected ROIs were in the superior temporal gyrus part of the limbic network (in 41.8% of patients) and the insular gyrus part of VAN (31.0% of patients). Comparing networks with to those without lesions, ECM was higher only in FPN (p=0.027). Looking at CI compared to CP, higher total lesion volume and fraction ($p<0.001$) were seen in all networks, with highest effect sizes in the DMN (Eta squaredη^2=0.09;CP 31.0[78.4]; CI 90.3[176.3]), SMN (η^2=0.09;CP 7.9[48.1]; CI 62.3[140.4]) and FPN (η^2=0.08;CP 0.0[30.9]; CI 29.7[109.4]).
Conclusions: CLs volume in MS was highest in the DMN, limbic network and VAN, the last reporting the highest CL fraction, whereas the relationship with cognition was strongest in the DMN, SMN and FPN. The relevance of FPN was further underlined as more CL volume was related to stronger functional embeddedness of the FPN, possibly indicating reduced inhibition due to focal grey matter damage.

Disclosure
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P217
Thalamic node strength connectivity is altered in cognitive impaired MS patients

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Introduction & Objectives: The thalamus is a critical node in networks supporting cognitive functions. In this work, we assessed the relationship between the strength of thalamic connectivity with different nodes (cortical, subcortical and cerebellar) and information processing speed, attention, and visual scanning functions in MS patients.
Methods: We included 68 MS patients (median age: 49 (+/-14,4), 42 females, median EDSS: 2,5) and 92 controls (median age: 31 (+/-12,9), 48 females) that performed the Symbol Digit Modalities

Test (SDMT) and 3T MRI, including multishell diffusion (dMRI), 3D FLAIR, and MP2RAGE. We obtained whole-brain probabilistic tractography using dMRI and parcellated the grey matter in 85 regions using MP2RAGE image. Connectomes were weighted using the Intra Neurite Volume Fraction map from the Spherical Mean Technique. We extracted the local strength of the thalamic nodes using brain connectivity toolbox. Automatic lesion segmentation was performed using an in-house tool.
MS patients were subdivided into cognitively impaired (CIMS, n=18, cutoff at -1.5 SD) and cognitively preserved (CPMS, n=50) using the SDMT z-score. Between-group comparisons were computed with linear models – using age, gender and education as covariates - and adjusted by Holm correction.
Results: Left thalamic node strength connectivity was lower in both CPMS (p=0.001) and CIMS (p=0.0078) when compared to controls, but was not different between CIMS vs CPMS patients (p=0.087). The strongest connection strength between the thalamus and connected nodes in MS patients was found between the left thalamus and left hippocampus (Cohens d= 0.335; adjusted p-value: 6.53e-10). This connection was found to be much weaker in CIMS compared with CPMS (p= 1.52e-13, F-value: 0.6704). In all MS patients, leukocortical white matter lesion volume and periventricular lesion volumes influenced the relationship between the connectivity strength of the left thalamus and SDMT ($p<0.05$ for both).
Conclusion: Disrupted node strength connectivity between the thalamus and the hippocampus was found in cognitively impaired but not in cognitive preserved MS patients. Focal lesions nearby the ventricles and adjacent to the cortex significantly affected the relationship between thalamic connectivity and information processing speed.

Disclosure
All authors have nothing to disclose.

P218
Predictors of paramagnetic rim lesion formation following gadolinium-enhancing lesions

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Introduction: Paramagnetic rim lesions (PRLs) are an emerging MRI biomarker to identify a subset of probable chronic active lesions in multiple sclerosis (MS). They have been associated with greater MS disease severity and disability accumulation. Previous work [Absinta 2016; Wenzel 2022] has suggested that PRL formation may be modulated/predicted by acute steroid treatment as well as MRI features including lesion size, gadolinium (Gd)-enhancement patterns and diffusion/T2* features of the lesion rim.
Objectives/Aims: We aimed to evaluate the effect of steroid treatment and other initial MRI characteristics as predictors for the development of chronic PRLs following an initial Gd-enhancing lesion.
Methods: We reviewed the electronic records of patients with MS participating in a longitudinal observational study. Inclusion criteria were (1) having an MRI demonstrating $\geqslant 1$ Gd-enhancing lesion and (2) information on steroid treatment, and (3) follow-up 3T MRI within 7 years including a standardized susceptibility-sensitive imaging protocol. We used logistic regression to determine whether any of the following variables were associated with evolution of the Gd-enhancing lesion into a PRL: age, MS phenotype, use of acute steroid treatment, Gd lesion size, pattern of Gd-enhancement, and a hypointense (restricted diffusion) rim on apparent diffusion coefficient imaging.
Results: Thirty patients had at least one MRI demonstrating $\geqslant 1$ Gd-enhancing lesions; a total of 18 patients (mean age=35 ± 10, 15 relapsing and 3 progressive) were included for final evaluation after excluding incomplete clinical records or MRI susceptibility artifacts (average time to follow-up: 3 years). Ten patients received IV steroids within 30 days of the enhancing lesion; 8 did not. Seven of the 18 Gd lesions evolved into PRLs; steroid administration was not significantly predictive (p=0.39). Larger initial Gd lesion size strongly associated with outcome: a Gd lesion cutoff diameter >8.2mm predicted PRL formation with 100% accuracy. The pattern of enhancement (ring vs nodular) was also associated (OR=5.9, p=0.10) with PRLs formation, but did not reach significance. A restricted rim on ADC was not associated with PRL formation, although diffusion protocols were heterogeneous.
Conclusion: Gd lesion diameter was a dominant factor in predicting PRL formation from this limited cohort; the pattern of enhancement may also aid in prediction.

Disclosure
MA received consultancy fees from GSK and Sanofi-Genzyme.
MAM received consultancy fees for Genentech

P219
Comparison of two high resolution MRI techniques in optic neuritis

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Introduction: 2D T2 weigthedMRI is highly sensitive in optic neuritis (ON). High spatial resolution of the normal anatomy and pathological features can increase diagnostic sensitivity and specificity.
Objective: To demonstrate the feasibility and usefulness of coronal oblique high resolution fat suppressed MRI perpendicular to each optic nerve separately to reduce partial volume effects from CSF or bone, in an attempt to improve demonstration of normal anatomy and pathological features in ON. This was compared to standard coronal images.
Methods: We performed high resolution MRI of the anterior visual pathways examinations of 10 normal controls and in 53

patients with optic neuritis with 2D fat suppressed T2w. In addition to i) coronal views ii) coronal-oblique MRI perpendicular to the optic nerve was performed for each optic nerve separately from the globe to the optic tract in order to visualise the nerve, the CSF and the surrounding sheath on intraorbital slices with high resolution fat suppressed T2w MRI.

Results: In normal controls the following features were demonstrated: The nerve showed sharp borders to CSF or the bony structures, very homogenous white matter intensity, the shape of the nerve changes from a round structure to an oval shape in the optic canal and intracranially before joining at the optic chiasm. On standard coronal MRI the common partial volume phenomena were seen resulting in slight loss of sharpness of the optic nerve at the CSF-nerve interface on all slices compared to the coronal-oblique slice positioning. In ON T2 hyperintensity was seen in the affected nerve in 52/53 cases on coronal images. The symmetrical demonstration of the healthy and affected site on coronal images allowed the identification of pathology by comparison to the healthy side in 4/53 cases that only showed mild hyperintensity in the affected optic nerve, while this was questionable/negative when optic nerves were evaluated separately. Cross-sectional lesion extent/swelling was seen in more detail on oblique coronal images.

Conclusions: The reduction of partial volume effects allows a more detailed visualisation of the optic nerve and intrinsic lesions, however the direct comparison to the healthy side is useful to determine the abnormality in cases with only mild signal change. The combination of the 2 planes appears useful whenever optic nerve lesions needs to be visualised with high resolution and best possible anatomical detail.

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P220

Cross-sectional robustness of 6 freely available software packages for brain volume measurements in multiple sclerosis

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Introduction: Brain atrophy measurement using magnetic resonance imaging (MRI) is an important way to assess disease progression in multiple sclerosis (MS). However, brain volumetry is still challenging, e.g. due to differences in scanners, acquisition protocols and analysis software. These differences are more present in multi-center trials and especially in the clinical setting. Quantifying measurement error will provide an improved understanding of the resulting variability in atrophy measures, and inform mitigation strategies.

Objectives: Here we perform a comparison of reliability and repeatability between three different MR-scanners applying six freely available brain volume segmentation techniques. Additionally, we analyze the effect of lesion-filling on robustness in MS-brain volumetry.

Methods: 21 people with MS underwent a scan and rescan on three 3T MRI scanners (GE MR750, Philips Ingenuity, Toshiba Vantage Titan). 3D T1-weighted images were acquired as well as an additional 3D FLAIR on GE. Both lesion-filled and un-preprocessed 3D T1 images were segmented with FreeSurfer, FSL, SAMSEG, FastSurfer, CAT-12 and SynthSeg. Brain, white matter, (deep) gray matter volumes were segmented. Both repeatability and reproducibility were assessed for each of the (regional) volumes using the intra-class correlation coefficient (ICC) for absolute agreement and for consistency, respectively. Reproducibility was additionally assessed with repeated measures ANOVA and Friedmann test with post-hoc testing.

Results: The overall between-scanner ICC for consistency was good to excellent (>0.7, range:0.4-1) for all the segmentation packages, except for some small structures such as nucleus accumbens. For the same software and brain structure ICCs (for absolute agreement) between repeats were higher than ICCs (for consistency) between scanners (range: 0.65-1 vs. 0.41-1). However, systematic differences in volume measurements between-scanners are found across segmentation outputs for both gray and white matter ($p<0.05$). Lesion filling resulted in higher WM volumes but did not significantly improve ICC values for any structure.

Conclusions: Although both between and within ICCs are high, systematic differences between scanners are present for every software, suggesting the need for standardization for between-scanner volume-measurements. This implies that in a clinical setting or a cross-sectional multi-center/multi-scanner study, scanner effects need to be accounted for.

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P221

The effect of ocrelizumab versus oral highly active immunotherapies on white matter microstructure in relapsing remitting multiple sclerosis

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Introduction: Data regarding the effect of intravenous (ocrelizumab, OCR) and oral highly active immunotherapies (fingolimod, FINGO and cladribine, CLAD) on tissue repair as evaluated by microstructural diffusion analysis and brain atrophy in relapsing remitting (RR) multiple sclerosis (MS) are still sparse.
Aims: To compare the impact of different immunotherapies (OCR vs FINGO/CLAD) on white-matter microstructure and brain volumes in a cohort of RRMS patients.
Methods: In this ongoing study, RRMS patients underwent 3T-MRI at the time of treatment start and at 12-months follow-up (FU). Changes in percentage-brain-volume-change(PBVC) and multi-compartment spherical-mean-technique(SMT) diffusion metrics of the normal-appearing-white-matter (NAWM) were evaluated with repeated measures ANCOVA adjusted for sex, age, disease duration, baseline EDSS.
Results: A total of 83 patients were included in the analysis, [55 OCR and 28 FINGO/CLAD; females: 61%; mean age, disease duration, ARR previous year: 37.8+10.7, 8.6+8.5 years, 0.6+0.7; median (range) EDSS: 2 (0-6)]. At 1-year FU, 3/55 (5.4%) in OCR group had new/gadolinium-enhancing lesions vs 5/28 (17.8%) in FINGO/CLAD group. EXTRAMD (extracellular water) and EXTRATRANS (myelin damage) decrease, together with INTRA (fiber integrity) increase, was more pronounced in the NAWM of OCR treated patients with respect to FINGO/CLAD group ($p<0.001$ for all metrics). A trend was noted in PBVC between the two groups (-0.46%OCR vs -0.85% FINGO/CLAD; p=0.065).
Conclusions: we observed a more pronounced effect in reducing CNS inflammation and axonal damage and in promoting myelin repair within the NAWM in OCR group as compared to FINGO/CLAD treated patients. A beneficial trend on brain atrophy was observed in OCR group but it has to be confirmed in further analysis.

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P222

Evaluating Central Vein Sign accuracy in pediatric onset multiple sclerosis (POMS) diagnosis

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Background: The central vein sign (CVS) has been proposed as a marker of CNS demyelinating lesions. Its role in the diagnosis of MS is still debated. To date no study has investigated the diagnostic accuracy of CVS in pediatric onset multiple sclerosis (POMS) patients.
Aim: To compare the performance of CVS in a cohort of 10 POMS and 12 sex and disease duration-matched adult onset (AOMS) patients.
Methods: In this ongoing study, POMS patients underwent 3T-MRI and were compared with 12 AOMS patients. CVS assessment was performed according to the current guidelines and white matter lesion were classified according to their location. Differences in terms of lesion volumes and numbers were assessed with ANOVA analysis while the difference in terms of patients fulfilling the CVS 40% threshold was evaluated with Chi-square test.
Results: 10 POMS patients [(female: 60%; mean (SD) age and disease duration: 13.5 (1.7) and 1.6 (1.7), median (range) EDSS 1 (1-2)] and 12 sex and disease duration- matched AOMS [(female: 58%; mean (SD) age at disease onset and disease duration at MRI: 38.5 (15.2) and 1.7 (1.3), median (range) EDSS 1 (0-6.5)] patients were included in the analysis. No significant differences were found in FLAIR lesion number ($p = 0.84$) and FLAIR lesion volume ($p = 0.19$) between the two groups. The mean % CVS+ was 53.3% in POMS (range: 0-80.7%) and 71.7% (range:45-100%) in AOMS. In the POMS cohort, 3/10 patients did not meet the 40% threshold for the diagnosis of MS while all AOMS patients would have been correctly diagnosed (p=0.041). The mean number of periventricular lesions excluded from the CVS assessment (confluent feature, >1 vein passing throughout the lesions) was higher in POMS than AOMS population [11.6 (13.5) vs 3.1 (3.2); p=0.047)].
Conclusions: The 40% threshold in the context of CVS assessment seemed to show a worse performance for MS diagnosis in POMS population. The higher prevalence of large white matter lesions, especially located in periventricular areas, may represent

a crucial issue in the context of CVS accuracy in POMS patients. Larger samples are needed to confirm our limited findings.

Disclosure
All authors declare nothing to disclose

P223
Alterations in nuclei-specific thalamic resting-state functional connectivity in multiple sclerosis: implications for clinical disability and cognition

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Introduction: Thalamic atrophy occurs early and consistently throughout the course of multiple sclerosis (MS) and is associated with worsening cognition and disability. Recent efforts to study resting-state functional connectivity (FC) of the whole thalamus and sub-regions to the cortex have shown decreased FC to some cortical areas and increased FC to others, with heterogeneous relationships of FC implications and cognitive function.
Aims: In this study, we aimed to (1) assess nuclei-specific thalamic FC to the cortex in people with MS (pwMS) and healthy controls (HC), and (2) examine the correlation between nuclei-specific thalamocortical FC and clinical measures of disability and cognition.
Methods: 39 pwMS and 41 HC underwent imaging on a 3T MRI scanner. Functional imaging included a simultaneous multi-slice resting-state sequence with high spatial and temporal resolution (2mm isotropic, TR=1080ms). Thalamic nuclei were segmented using a FreeSurfer based multimodal imaging tool. FC was calculated between each nuclei and its ipsilateral cortex.
pwMS also underwent clinical and neuropsychological testing using the Expanded Disability Scale Status (EDSS), Paced Auditory Serial Addition Test (PASAT) and Symbol Digit Modalities Test (SDMT).
FC was compared between MS and HC groups and associated with disability and cognition scores using vertex-wise general linear models from the FreeSurfer group analysis pipeline, controlling for age and sex.
Results: Nuclei-specific thalamic FC was increased in occipital and parietal cortices in MS vs HC, based on vertex and cluster-wise significance thresholds of $p < 0.05$. In pwMS, lower thalamic nuclei volumes were associated with increased FC in these same cortical areas. Notably, thalamocortical FC using a whole thalamus seed was not significantly different between MS and HC.
In pwMS, increased EDSS was associated with increased nuclei-specific FC to the occipital cortex and decreased nuclei-specific FC to the frontal cortex. Higher scores on cognitive testing were associated with increased thalamic anteroventral and mediodorsal nuclei FC to frontal and prefrontal cortices.
Conclusions: Increased nuclei-specific thalamic FC in MS vs HC suggests possible presence of maladaptive mechanisms in MS to compensate for ongoing structural damage. Evaluation of nuclei-specific thalamocortical FC may be advantageous over whole thalamus connectivity in improving understanding of the impact of thalamic changes in MS.

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P224
Multiple sclerosis MRI reports vary among neuroradiologists

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Introduction: New and enlarging lesions are key features neurologists use to determine whether a patient with Multiple Sclerosis (MS) is experiencing disease activity that may require medication changes. Studies have shown inter-rater variability among neuroradiologists' (NRs) phrasing and lesion detection can lead to discrepant reports.
Objective: To quantify the level of agreement between NRs' assessment of MS-specific reporting of brain magnetic resonance imaging (MRI).
Methods: 90 de-identified MS subjects with 2 (median 1 year apart) MRI exams from the University of Basel from 2012 to 2019 were retrospectively enrolled. Subjects had varying levels of disease activity. Each exam had 3D pre- and post-gadolinium T1 and T2 FLAIR sequences. Three fellowship-trained NRs visually interpreted the images and reported on image quality (suboptimal, acceptable), degree of preexisting lesion burden and brain atrophy (none, mild, moderate, severe), counts of supratentorial and infratentorial lesions (a number if <10 lesions; otherwise, ">10"), and the presence and count of new, enlarging, and enhancing lesions. One NR was dropped for the analysis of lesion change counts due to a reporting inconsistency. Inter-rater reliability analysis with Fleiss' Kappa statistics was performed. The Kappa value $\leqslant 0$ indicated no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement.
Results: Agreement (% agreement, Kappa, N raters) between the NRs was highest for the enhancing lesion count (100, 1, 2) and the existence of enhancing lesions (96, 0.62, 3) and lowest for atrophy (11, 0.02, 3) and presence of enlarging lesions (70, 0.04, 3). Image quality ratings had a slight level of agreement (59, 0.17, 3), and preexisting lesion burden (37, 0.35, 3), counts of supratentorial (86, 0.32, 3), infratentorial (26, 0.26, 3), counts of enlarging

lesions (94, .15, 2), existence of new (66, 0.3, 3) and new lesion counts (83, 0.4, 2) had fair agreement.
Conclusion: Neurologist decision-making often depends on lesion burden change. Our results show substantial to perfect agreement in the detection of enhancing lesions but only slight-to-fair agreement in the detection of new & enlarging lesions. The varying agreement highlights the need to incorporate quantitative methods to reduce variability in the detection of clinically significant features that impact patient care.

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A DenseNet-based prediction of gadolinium-enhancing lesions presence

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Introduction: Gadolinium-based (Gd) contrast agents provide evidence of blood-brain barrier breakdown and active inflammation in multiple sclerosis (MS). However, the identification of contrast-enhancing lesions (CEL) in clinical practice is challenging, time-consuming, and prone to error, since those lesions are often small and/or located close to vessels.
Objectives: This research aims to use the DenseNet to classify gadolinium-enhanced images with lesions. We fine-tuned the network using the Monai framework to improve its classification and investigate the optimal solution performance.
Methods: We studied 158 patients from the Swiss MS Cohort (158 images). CEL were manually identified on 3D T1 post-contrast images by one experienced neurologist and a neuroradiologist. Patients were classified into groups with (n = 79, CEL scans having 236 CEL in total) and without (n = 79) CEL. The dataset of 158 scans from 158 patients were divided into (i) a validation set of 18%, (n= 28), (ii) a testing set 10%, (n=16), and (iii) a training set 72%, (n= 114). The network modifications include changes in batch size and data augmentation.
Results: The larger batch size (n = 20) achieved an accuracy of 78.6% (sensitivity = 0.875; specificity = 0.667) while the lower batch size (n = 2) obtained an accuracy of 82.1%, 0.615 sensitivity, and a specificity value of 1. After data augmentation with a probability of 0.8, the acquired value was 78.6% for accuracy, 0.875 for sensitivity, and 0.667 for specificity. Data augmentation of a probability of 0.1 achieved 82.1% accuracy, a sensitivity value of 0.765, and a specificity value of 0.818.
Conclusion: The trained DenseNet achieved comparable results in terms of accuracy and specificity compared to previous automated methods for Gd enhancing lesions detection, despite a

relatively lower sample size. Future work will aim at exploring this framework for longitudinal CEL detection.

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Impact of lesion damages along the whole motor pathways on disability in multiple sclerosis

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Introduction: The anatomical substrate of motor disability in MS patients is not fully understood. Studying the distribution of corticospinal tracts (CST) lesions per side, from the brain to the end of the thoracic spinal cord (SC) could provide a better association with patient motor deficits evaluated per limb.
Objectives: i) To describe lesion preferential location along the CST; ii) To investigate the association between CST lesions and motor functional consequences, as measured using the EDSS, and the ASIA motor scores and electrophysiology (Central motor conduction time (CMCT)) per limb.

Methods: 21 relapsing remitting MS (median EDSS=2.5) and 9 progressive MS patients (median EDSS=5.2) with clinical pyramidal symptoms were scanned on a 3T Siemens MRI scanner. White matter lesions were segmented on 3D FLAIR for the brain, on T2* for cervical SC and T2 for thoracic SC. For each patient, registration to an atlas was computed using Anima and SCT toolboxes. Lesion volume fraction along the CST (defined as "lesion volume along the CST"/"overall CST volume") was calculated separately for the both sides on 3 regions: brain including brainstem, C1 to C7 (C1C7) and T1 to T10 (T1T10). Finally, the relationships between lesion volume fraction and the associated lateralized disability scores were assessed using multiple linear models, adjusting for age and disease duration.
Results: In MS patients, lesion volume fraction was higher in the C1C7 portion compared to the brain and T1T10 portion (all p's$<$.001; mean=2%, 10% and 2%, for brain, C1C7 and T1T10, resp). No evidence of correlation was found between lateralized lesion volume fraction in each portion of the CST and EDSS score or ASIA score per limb, except for a mild correlation between EDSS and lesion volume fraction on the right CST (standardized beta=.39, p=.041). We observed strong positive associations between lesion volume fraction in C1C7 and CMCT for superior and inferior limbs on the right side and for superior limbs on the left side (all std-beta$>$.6; all p's$<$.005). Finally, we observed a mild positive association between lesion volume fraction in T1T10 and CMCT for inferior limbs on the left side (std-beta=.53; p=.02).
Conclusions: CST damage is not homogeneous along the tract and predominates in the cervical portion. It has clear consequences on motor conduction velocities measured using electrophysiology. Future work will include an assessment of lesion severity to better explain lesion consequences on motor disability.

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A novel deep learning algorithm for multi-modal multiple sclerosis lesion segmentation

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Introduction: Multiple sclerosis (MS) lesions can be detected as white matter hyperintensities (WMHs) on T2-weighted (T2-w) and FLAIR MRI. Segmentation of such lesions is a pre-requisite for many MRI-based measurements supporting the assessment of MS patients, including total and acute lesion burden.
Objectives: To develop an algorithm to automatically delineate WMHs from any combination of MRI modalities across the set of (pre-contrast) T1-w, T2-w, and FLAIR MRI.
Methods: A multi-modal convolutional neural network for MS lesion segmentation was designed by adapting the self-configuring nnU-Net framework. Our model includes one encoding branch per input MRI modality, each mapping sequence-specific information to a common latent space. A fully learnable fusion operator integrates information across modalities in this latent space, from which a WMH segmentation map could be predicted via a decoding branch.
Brain FLAIR, (pre-contrast) T1-w and T2-w MRIs from the ADVANCE (NCT00906399; n=1512, patients with relapsing-remitting [RR]MS) and ASCEND (NCT01416181; n=886, patients with secondary progressive MS) trials were used for model training. Ground truth WMH masks were obtained via a semi-automatic method designed by NeuroRx. Our model was independently validated on scans from the DECIDE (NCT01064401; n=1841, patients with RRMS) and EXTEND (NCT01797965; n=1501, long-term extension from DECIDE) trials, by comparing predicted WMH masks against ground truth masks via the Dice coefficient.
Results: Our model achieved 0.703 Dice score when combining FLAIR, (pre-contrast) T1-w and T2-w MRI. This score was maintained when T1-w was excluded. When FLAIR was excluded, Dice score was 0.694; when T2-w was excluded, Dice score was 0.683. In the single-modality setting, our model achieved Dice scores of 0.635, 0.652 and 0.686, with (pre-contrast) T1-w, FLAIR and T2-w MRI, respectively. Under all possible conditions of input MRI sequence availability, the predicted total MS lesion volume was strongly correlated with the ground truth volume ($r > 0.92$).
Conclusions: Our deep-learning algorithm can provide automatic delineation of MS lesions from any combination of conventional MRI modalities and can be used for the quantification of MS lesion load across a variety of different clinical sites and scanners. Future work will include benchmarking our approach against other validated MS lesion segmentation algorithms including SLS and LPA.
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On the association between the choroid plexus volume and disease characteristics in multiple sclerosis

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Introduction: The choroid plexus (CP) has been proposed as a modulator of MS-related inflammation. We previously provided evidence that the CP is larger in MS than healthy controls (HCs) and neuromyelitis optica spectrum disease. However, data about the correlations between CP volume (CPV) and MS disease characteristics are scarce.

Objectives/Aims: To investigate the association between CPV and disease characteristics in relapsing-remitting (RR)MS.

Methods: Cross-sectional, retrospective study. We included 109 RRMS patients from the Basel center of the Swiss MS cohort study (mean age 46.9±10.9 years; 69% female; mean disease duration 16±9 years; proportion of patients with a relapse within the antecedent year=11%; median EDSS 2.5 [IQR=2]) and 118 HCs (mean age 44.3±13.4 years; 65% female). The CP of the lateral ventricles was segmented fully automatically using an in-house deep learning algorithm on non-contrast T1-weighted(w) MRI. Serum neurofilament light chain (sNfL) was measured using the latest HDX platform from Quanterix®. We compared the sNfL values of the patients with a large normative database (n>10,000 HC subjects) and calculated z-scores using a generalized additive model for location, scale and shape (Benkert et al. Lancet 2022). Associations between CPV and disease characteristics were investigated using multivariable linear regression models.

Results: CP was larger in RRMS than HCs adjusted for age, gender and TIV (B=221; 95%CI: 111-331; Beta=.25; p<0.001). In HCs, CPV was associated with the lateral ventricle volume (LVV) adjusted for age, gender and TIV (B=.016; 95%CI: .009-.024; Beta=.39; p<.001). In RRMS, there was no association between CPV and disease duration, log(EDSS), relapses in the last 12 months, sNfL z-score or disease-modifying treatment. However, CPV was associated with volume (B=10.6; 95%CI: 5.4-15.9; Beta=.35; p<.001) and number (B=5.8; 95%CI: 2.5-9.1; Beta=.30; p=.001) of the T2w lesions adjusted for age, gender and TIV. Every mL increase of T2w lesion volume was associated with a 11μL larger CP. In a multivariable analysis including age, gender, TIV, disease duration, relapse in the last 12 months (yes/no), log(EDSS), disease-modifying treatment, sNfL z-score, T2w lesion volume and LVV, the LVV was the*only* parameter that was associated with the CPV in RRMS (B=.014; 95%CI: .009-.02; p<.001; Beta=.62).

Conclusion: LVV as a surrogate of brain atrophy is more closely associated to the CPV than the T2w lesion burden in RRMS.

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J. Müller reports no competing interests.
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Comparison of unwrapped phase and quantitative susceptibility mapping for paramagnetic rim lesion detection in patients with multiple sclerosis

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Background and Aim: In patients with multiple sclerosis (MS), chronic active lesions can present as paramagnetic rim lesions (PRLs) on susceptibility-based MRI. Both unwrapped phase and quantitative susceptibility mapping (QSM) enable the identification of PRLs, but their relative sensitivity is not known.
We aimed to compare the visualization of PRLs in unwrapped phase and QSM in patients with MS.
Methods: We randomly selected 100 consecutive MS patients [73% female; mean (SD) age: 52.3 (11.4) years; mean (SD) disease duration: 22.3 (9.4) years; median (IQR) EDSS: 3.0 (2.0-4.5); 83% relapsing-remitting] from the SMSC study (Basel cohort), having 3T-MRI data with susceptibility-based images. MRI scans included: (1) 3D-FLAIR; (2) 3D-EPI (TR/TE: 65/36 ms; FA: 10°; resolution: 0.70x0.65x0.65 mm). From 3D-EPI data, unwrapped-phase and QSM images were obtained. White-matter lesions (WML) were semi-automatically segmented on FLAIR, registered to the EPI space, and used as a reference for PRLs evaluation. The number of PRLs per participant was assessed separately on phase and QSM, independently by two raters. The inter-rater agreement was calculated for both contrasts using the intraclass correlation coefficient (ICC).
The PRLs counts obtained in phase and QSM were compared using: (1) Wilcoxon test for paired samples; (2) ICC for absolute agreement. The associations between PRLs count and clinical variables were explored in negative binomial models.
Results: 3 subjects were excluded due to insufficient image quality. The presence of ⩾1 PRL was detected in 46.4% of patients. PRLs count was associated with WML load (incidence rate ratio (IRR): 1.04; $p<0.001$) but not with age, sex, disease course, and disease duration. When adjusting for disease duration, PRLs count was associated with the EDSS score (IRR: 1.30; p=0.015).
There was no difference in PRLs count obtained with phase and QSM (p=0.59; total number in phase: 118; total number in QSM: 117); the ICC for lesion count in the two contrasts was 0.87 (95% CI: 0.81-0.91). Good inter-rater agreement in PRLs count was obtained in both phase [ICC: 0.83 (95% CI: 0.76-0.89)] and QSM [ICC: 0.81 (95% CI: 0.73-0.87)] contrasts.
Conclusions: Unwrapped phase and QSM were comparable for detecting for PRLs, enabling the identification of chronic active lesions, which are associated with neurological disability.

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Leptomeningeal enhancement in progressive multiple sclerosis is associated with higher risk of future disability progression and persists on Long term follow-up despite high efficacy therapies

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Introduction: Leptomeningeal enhancement (LME) has been described as a potential biomarker of meningeal inflammation in Multiple Sclerosis (MS).
Aim: To assess LME in a cohort of patients with progressive MS (pMS) and its correlation with disease variables over prospective follow-up.
Methods: This study was performed on a cohort of 130 pMS patients (primary or secondary progressive), including also early pMS with active disease. Patients were imaged yearly using a standard 1.5T MRI (according to MAGNIMS recommendations). Post contrast CUBE 3D FLAIR sequences were used for LME detection. Image analysis was performed for brain and upper spinal cord volume and for normalized T2 lesion volume (nT2LV). Presence of LME was correlated with clinical and MRI variables at baseline and during follow-up. Furthermore, neuropathological features and distribution of meningeal inflammation were assessed in a post-mortem cohort of 12 MS and 20 control brains, in order to draw inferences on the pathological substrates of LME.
Results: In this cohort, mean age was 54.2 years, mean EDSS at baseline was 5.8. MRI disease activity at baseline was present in 13.9% of patients. High efficacy treatment (HET) was used in 48.3% of patients. Mean duration of follow-up was 18.4 months (range 12-36). LME at baseline MRI was present in 26.7% of patients, most of which (67.7%) showed multiple LME. No significant differences were observed for LME between patients treated and not treated with HET (27.5% vs 25%). LME was associated with higher baseline EDSS (OR 1.86, p=0.01), higher age (OR 1.06; p=0.01), active disease at baseline MRI (OR 3.70, p=0.03), higher ventricle volume (p=0.004), lower normalized brain volume (p=0.008), while it was not associated with nT2LV or mean upper cervical cord area. LME was unchanged in most patients over follow-up, independently from HET use. Presence of multiple LME at baseline MRI was independently associated with EDSS increase in the past 2 years (OR 5.99, p=0.004) and with higher risk of future EDSS increase during follow-up (Cox regression: OR 4.07, p=0.019). Neuropathological data suggested that LME in MS might be the expression of both leptomeningeal inflammation and post-inflammatory leptomeningeal fibrosis.
Conclusions: LME is frequently detected in pMS patients using standard 1.5 T MRI, is associated with a more aggressive disease, and is independently predictive of past and future progression of disability.

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MRI detected cortical lesions are associated with higher serum neurofilament levels in multiple sclerosis

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Introduction: There is growing interest in serological and imaging markers of multiple sclerosis (MS) disease severity such as paramagnetic rim lesions (PRL), cortical lesions (CL) and serum neurofilaments (sNfL), because they could be used to assess prognosis and treatment response. Recently, sNfL levels, a serological biomarker reflecting neuro-axonal damage, have been correlated to PRL, an MRI marker of chronic white matter inflammation (Maggi et al. Neurology 2021). However, the association between CL and sNfL is mostly unknown.
Objectives: We aim to investigate the association between CL and sNfL levels in MS.
Methods: Fifty-nine MS patients (mean age of 42.6 years, 71% female) were enrolled to undergo 3T brain MRI (GE, SIGNA Premier) and serum sampling: 8 clinically isolated syndrome,

11 radiologically isolated syndrome, 27 relapsing-remitting MS, 5 primary progressive MS, 8 secondary progressive MS. CL and PRL were assessed manually on co-registered 3D-MPRAGE/3D-DIR sequences and susceptibility-based submillimeter 3D-EPI sequence, respectively. Serum samples were collected within 30 days from the MRI sessions and sNfL levels were measured in duplicate using the SIMOA® technology (Quanterix).

Results: The number of CL correlated with the number of PRL per patient (Spearman $r = 0.53$; $p < 0.0001$). Following exclusion of patients with gadolinium-enhancing lesions, sNfL levels positively correlated with the number of CL, and with the cumulative number of CL and PRL per patient (Spearman $r = 0.37$ and $r = 0.39$; $p = 0.008$ and $p = 0.005$, respectively). sNfL levels were significantly higher in patients with CL or with at least one CL or one PRL as compared to patients without ($p = 0.05$ and $p = 0.02$ respectively, Mann-Whitney U-test). Patients with CL and no PRL had higher sNfL when compared to patients without CL and PRL ($p = 0.007$, Mann-Whitney U-test). Patients age did not differ between groups.

Conclusions: The presence and number of CL positively correlated with the levels of sNfL suggesting that CL may contribute to explain MS-related neuro-axonal damage as measured by sNfL. Additional analysis and a larger patient cohort is needed to confirm our findings.

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Thalamic myelin and neurite content is reduced in progressive multiple sclerosis and relates to disability and cognitive impairment

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Background and aims: In multiple sclerosis (MS), the thalamus is characteristically affected by extensive neurodegenerative processes; nevertheless, the microstructural *in vivo* characterization of such changes remains challenging.

We aimed to investigate thalamic microstructure in patients with MS by using quantitative MRI (qMRI) measures.

Methods: 152 MS patients [60% female; mean (SD) age: 45.5 (14.6); 36% with progressive MS] and 103 healthy controls (HCs) [55% female; mean (SD) age: 37.5 (12.9)] underwent 3T MRI study including: (1) 3D-FLAIR; (2) 3D-magnetization prepared 2 rapid acquisition gradient echo (MP2RAGE); (3) fast acquisition with spiral trajectory and adiabatic T2 prep (FAST-T2) for myelin water fraction (MWF); (4) multi-shell diffusion to calculate neurite density index (NDI) maps; (5) 3D-EPI for quantitative susceptibility mapping (QSM); and (6) magnetization transfer saturation for MTsat maps. All patients were examined using the Expanded Disability Status Scale (EDSS) and the Symbol Digit Modalities Test (SDMT). T2-lesion volume (T2LV) was quantified. Normal appearing thalamic volume was manually segmented and used to extract total thalamic intensity of (1) MTsat, (2) MWF, (3) QSM, and (4) neurite density index (NDI). Those measures were used as surrogates of macromolecular integrity, myelin content, iron content, and axon and dendrite density, respectively. qMRI metrics were compared between groups adjusting for age and sex. Associations between qMRI metrics and clinical variables were explored with general linear models.

Results: Compared to HCs, MS patients had lower thalamic MTsat (β=-0.492; $p<0.001$), MWF (β=-0.330; $p<0.001$), and NDI (β=-0.521; $p<0.001$).

In MS patients thalamic MTsat, QSM, and NDI were associated with T2LV (β=-0.470; $p<0.001$; β=-0.251; $p=0.002$; and β=-0.339; $p<0.001$ respectively). Thalamic MTsat and NDI were associated with both EDSS (β=-0.491; $p<0.001$; and β=-0.345; $p<0.001$ respectively) and SDMT (β=0.500; $p<0.001$; and β=0.439; $p<0.001$ respectively), while QSM showed association with the EDSS only (β=-0.301; $p<0.001$).

Compared to relapsing-remitting patients, progressive patients had lower thalamic MTsat (β=-0.482 $p<0.001$), MWF (β=-0.263; $p=0.03$), and NDI (β=-0.460; $p<0.001$).

Conclusions: qMRI measures of thalamic integrity are altered in patients with MS, reflecting myelin and neurite loss. These

alterations are related to lesion burden and disease course, and associate with both disability and cognitive impairment.

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Sensitivity of portable ultra-low-field magnetic resonance imaging for white matter lesions, dissemination in space, and dissemination in time

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Introduction: The recent development of portable, ultra-low-field MRI (ULF-MRI) technology has remarkable potential for impacting the management of and screening for multiple sclerosis (MS) through a "point-of-care" approach.
Objective: To compare sensitivity of ULF-MRI and high-field MRI (HF-MRI) to white matter lesions (WML), dissemination in space (DIS), dissemination in time (DIT), and contrast enhancement in MS.
Aim: To evaluate the performance of ULF-MRI to detect conventional imaging hallmarks of MS compared to HF-MRI.
Methods: We assessed 48 HF-MRI and same-day ULF-MRI (64 mT, Hyperfine, scanned immediately after HF-MRI) from 43 patients (mean±SD age 51±11; 13 male, EDSS median 1.5, range 0–6) at a single center. A neurologist with expertise in MS-MRI evaluated image pairs. WML, DIS, and contrast enhancement were evaluated on pre- and post-contrast (gadobutrol, 0.1 mmol/L; available in 41 patients) T1w and T2-FLAIR at 3T in 45 patients and 7T in 3 patients. Maximum diameters (D_{max}) of the smallest and largest WML detectable at each field strength were measured in 33 scans.
Results: ULF-MRI showed 100% sensitivity for WML when there was at least one lesion with $D_{max}>3.9$ mm (29/31 patients, 94%) but did not detect lesions with smaller D_{max}. Across patients, the D_{max} (mean±SD) for the smallest WML detectable on ULF-MRI and HF-MRI were 6.0±1.4 mm and 2.1±0.6 mm, respectively. DIS was detected in 38/48 ULF-MRI scans (79%). In 1 patient, one gadolinium-enhancing WML (D_{max}=7.3 mm) was detected at HF-MRI but not ULF-MRI. 5 patients had follow-up scans; 1 showed 13 new non-enhancing T2-FLAIR lesions at 3T and at least 2 new lesions at ULF (1 year follow-up), thereby meeting criteria for dissemination in time; the other 4 patients had radiologically stable disease at both HF-MRI and ULF-MRI. There was a single focus of leptomeningeal gadolinium enhancement in 4 patients on ULF-MRI, compared to 26 foci in 13 patients on HF-MRI (15% lesion-level and 31% patient-level sensitivity of ULF-MRI vs. HF-MRI).
Conclusions: ULF-MRI detects WML >3.9 mm in largest diameter and hence can demonstrate DIS. Furthermore, we were able to demonstrate DIT via ULF-MRI at 1-year follow-up. Our results highlight the potential of ULF-MRI for point-of-care diagnosis, and possibly therapeutic monitoring, of MS.

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Medulla oblongata volume measured from clinical routine T2-FLAIR scans is associated with disability progression in a multiple sclerosis real-world dataset

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Background: Spinal cord (SC) atrophy is known to have a role in disability progression (DP) in multiple sclerosis (MS) patients. However, dedicated SC imaging is often not included as part of the clinical routine. Medulla oblongata volume (MOV), measured from 3D-T1 brain images when available, has been shown to serve as a proxy for SC atrophy. Previous work has shown that T2-FLAIR scans are nearly always acquired in the clinical routine.

Objectives: To determine the feasibility of a T2-FLAIR-only measure of MOV as a marker of DP in MS.
Methods: A total of 3,228 MS patients from 9 MSBase centers in 5 countries were enrolled. Of those, 2,875 (218 with clinically isolated syndrome, 2,231 with relapsing-remitting and 426 with progressive disease subtype) fulfilled inclusion and exclusion criteria. Patients were scanned on either 1.5T or 3T MRI scanners without any prior protocol standardization, and 5,750 brain scans were collected at index and on average after 42.3 months at post-index. Demographic and clinical data were collected from the MSBase registry. MOV was measured on clinical routine T2-FLAIR images using an atlas-based warping technique.
Results: Longitudinal MOV analyses were successful in 93% of the scans. 57% of patients had scanner-related changes over the follow-up. After correcting for age, sex, disease duration, disability, disease-modifying therapy and MOV at index, and follow-up time, MS patients with DP (n=629) had significantly greater ($p = 0.005$) annualized percent MOV change (-0.45% $\pm$ 2.69) compared to stable or disability improved (n=1574) (-0.16% $\pm$ 2.97).
Conclusions: FLAIR-based analysis of MOV volume is feasible on clinically acquired T2-FLAIR scans in a multicenter fashion and is associated with DP over mid-term.

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Co-localization of TSPO-PET-detectable chronic active lesions and QSM-MRI-detectable iron rim lesions in multiple sclerosis brain

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Introduction: Chronic active lesions have an increased density of activated microglial cells and macrophages at the lesion rim. Rim-associated microglia contain iron and co-localize with signs of acute axonal injury. 18-kDa translocator protein (TSPO) positron emission tomography (PET) imaging provides a method to quantitate activated microglia/macrophages in patients *in vivo*. Moreover, Quantitative Susceptibility Mapping (QSM)-MRI can be used to detect the iron rims in chronic lesions *in vivo*.
Objectives: We aimed to explore co-localization of TSPO-targeting ^{11}C-PK11195-binding and QSM-MRI-identified iron rims in MS brain to evaluate their comparative performance in measuring smoldering inflammation in MS.
Methods: 11 MS patients (6 RRMS and 5 SPMS), aged 51.2±11.1 years, underwent ^{11}C-PK11195-PET scanning and MRI with QSM. T2 lesions were initially segmented automatically using the nicMSlesions-method. The automated T2 lesion segmentation was quality controlled by hand by two experienced researchers, and T1 lesion masks were drawn. T1-lesions were phenotyped into categories of chronic active, overall active and inactive lesions, based on their ^{11}C-PK11195 uptake. QSM iron rim lesions were first identified in T1 and FLAIR sequences. Lesions having positive susceptibility value (with regard to CSF) were pre-selected, and were further edited to include only those lesions, which had a hyperintense bright rim relative to the lesion core.
Results: A total of 345 lesions were identified in T1 sequence, and the median total volume of the lesions was 15.7 cm^3 (IQR 7.4-29.2). 39 (11.3%) lesions had an iron rim, and 306 (88.7%) lesions did not. The median number of iron rims per patient was 3 (IQR 1-7). Based on the TSPO-PET-identified innate immune cell activation at rim, 66 lesions (19.1%) were phenotyped as chronic active, 188 (54.5%) were overall active and 91 (26.4%) were inactive. Of the 66 PET-identified chronic active lesions, 10 lesions (15.2%) had simultaneous iron rims.
Conclusions: This study provides evidence for presence of iron rims at the edge of a subset of TSPO-PET-detectable chronic active lesions. TSPO-PET may provide a more sensitive method for detecting smoldering inflammation in MS brain, but QSM-MRI may be more widely applicable.

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Evaluation of a supervised approach based on the application of CNN for the recognition of new T2 lesions in patients with multiple sclerosis using different MR magnets

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Introduction: Different automatic tools have been tested in the detection of new T2 lesions in multiple sclerosis (MS), showing more sensitivity than conventional visual analysis. However, these tools generally require that the scans to be compared be obtained from the same MRI equipment.
Objectives: To assess the accuracy of visual and an automated tool that uses a supervised approach based on the application of convolutional neural networks (CNN) for the recognition of new T2 lesions in patients with MS using pair scans acquired with different MR magnets/field strengths in a single institution.
Methods: Two MRI scans were done in different scanners using a standardized protocol on 103 MS patients. 42 patients (group A) underwent MRIs in scanners with different magnetic fields (1.5T and 3T), while 61 patients (group B) underwent both MRIs on

different 3T magnets. The automated technique (AT) and neuroradiological reports (NR) were both tested for recognizing active T2 lesions. After analyzing and comparing the two methodologies, the reference gold standard was established.

Results: Global analysis of the 103 patients showed that AT identified a higher total number of active T2 lesions than NR (98 for AT; and 82 for NR), but also a higher total number of false-positive lesions (18 for AT; and 8 for NR), indicating that the automated technique is more sensitive (86,96%) than the visual analysis (80,43%). But regarding each group, the sensitivity for detecting new lesions in group A was 73,9% for NR and 86,96% for AT, while the sensitivity in group B was the same in both NR and AT (86,96%). The lower sensitivity in the NR results of group A is due to an increased number of false negative lesions. The study also showed that the difference between the NR and AT in true positives, false positives and false negatives is reduced when comparing two 3T scanners.

Conclusion: Even when pair images collected at different scanners are used, the automated technique used in this study provides a potential tool for neuroradiological assessment of disease activity. Visual validation is still essential due to the false positive results received.

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Identify surface-in alterations in normal appearing white matter using multiple quantitative and semi-quantitative MRI metrics

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Introduction: Recent pathological studies in multiple sclerosis (MS) reported a surface-in gradient of demyelination and tissue damage located around the ventricles. The spatial distribution of these abnormalities suggests an association with cerebrospinal fluid (CSF)-derived proinflammatory mediators. Quantitative magnetic resonance imaging (MRI) modalities are sensitive to changes in tissue content and microstructure, thus can be used to assess subtle patterns of tissue alterations in vivo.

Objectives: To identify imaging markers of surface-in gradient of tissue abnormalities in periventricular normal appearing white matter (NAWM) of relapsing-remitting MS (RRMS) patients using multiple quantitative and semi-quantitative MRI metrics.

Methods: 64 RRMS (mean age 36.1±10.4 years, 75% female; disease duration 7.4±6.5 years) patients and 41 healthy controls (HC, mean age 48.6±13.4 years, 68% female) underwent a 3T MRI protocol including magnetization transfer ratio (MTR), magnetization transfer saturation (MTSat), quantitative susceptibility mapping (QSM), transverse relaxation time (T2*) and T1w sequences. The geodesic distance from the ventricles was used to define concentric bands in the NAWM where we computed the mean of all the MRI metrics normalized for the corresponding mean of the HC. Linear mixed effect models were fitted on the periventricular area for each MRI metric including random intercept and slope as well as an interaction term between groups and bands, to investigate possible differences of the RRMS MRI profile compared to the HC profile. Age and sex were also included as potentially confounding factors.

Results: NAWM tissue of RRMS showed significantly lower MTR (estimate=-1.4, $p<0.001$), MTsat (est.=-0.1, $p<0.001$) and QSM (est.=-0.003, $p<0.001$) and higher T2* (est.=0.002, $p<0.001$) with respect to the reference HC values. Moreover, the interaction term between group and band was statistically significant ($p<0.001$) in all the MRI modalities, with the periventricular profile of RRMS showing greater alterations around the ventricles.

Conclusion: A profile of alterations more pronounced closest to the CSF surface was evidenced with multiple MRI techniques

identifying possible imaging markers of surface-in gradient in the periventricular NAWM. The different profile of each MRI modality might help to characterize the underlying tissue damage.

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Association between cerebral blood flow and clinical disability in progressive multiple sclerosis in the MS-OPT Trial baseline data

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Background: Evidence has emerged that changes in cerebral blood flow (CBF) can occur and contribute to the pathophysiology of progression in multiple sclerosis (MS). Indeed, hypoperfusion might indicate neuronal loss and decreased metabolic activity and it has been described in progressive MS (pMS).
Objectives: Simvastatin has been shown to reduce the development of brain atrophy in pMS, but its mechanisms of actions are still unclear. The MS-OPT Trial aimed to test the impact of Simvastatin on CBF in pMS.
Aim: To evaluate the correlation between the CBF in the brain white matter (WM) and grey matter (GM) and clinical outcomes in pMS.
Methods: Data were obtained from the baseline visits of the MS-OPT Trial, a randomised, placebo-controlled study of high dose Simvastatin treatment for pMS (NCT03896217). Forty patients, including 12 primary progressive MS (PP-MS) and 28 secondary progressive MS (SP-MS), aged 18–70 years, and presenting with an Expanded Disability Status Scale (EDSS) score 4.0-6.5 were randomly assigned (1:1) to simvastatin 80 mg or placebo for 16 weeks, stratified by sex, age, EDSS, and type of MS (PP-MS vs SP-MS). At baseline, clinical and radiological data, including pulsed arterial spin labeling (PASL) and pseudo-continuous arterial spin labeling (pCASL) brain imaging were obtained. The Statistical Parameter Mapping-based software package ExploreASL was used to obtain quantitative data on CBF in WM (WM-qCBF) and GM (GM-qCBF). Multiple regression models were applied to evaluate the association between qCBF and clinical outcomes.
Results: The mean WM-qCBF was 20.01±6.31 mL/100g/min and the mean GM-qCBF was 61.25±14.09 mL/100g/min. No differences were observed between PP-MS and SP-MS. We found that both qCBF correlated with the Timed 25-Foot Walk (T25FW) score (*WM-qCBF*: rho=-0.32, p=0.002; *GM-qCBF*: rho=-0.33, p=0.001) and the 9-Hole Peg Test (9HPT) score (*WM-qCBF*: rho=0.23, p=0.031; *GM-qCBF*: rho=0.25, p=0.018). The associations remained significant after adjusting for age, sex, and disease duration (WM: *T25FW*: coeff=-1.26, p=0.001, 95%CI=-2.002 – -0.523; *9HPT*: coeff=0.04, p=0.034, 95%CI=0.004 – 0.085; GM: *T25FW*: coeff=-0.63, p=0.001, 95%CI=-0.980 – -0.284; *9HPT*: coeff=0.02, p=0.048, 95%CI=0.001 – 0.039).
Conclusion: Our results suggest that lower qCBF in WM and GM correlates with increased disability, as assessed by in upper and lower limbs. The next step of the study is to analyse whether perfusion measures are influenced by Simvastatin.

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Imaging and non-imaging biomarkers - OCT

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Asymptomatic optic nerve lesion detected on OCT in CIS predicts CDMS

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Introduction: Symptomatic and asymptomatic optic nerve demyelinating lesions are very frequent at the first clinical stage of multiple sclerosis (MS): clinically isolated syndrome (CIS). Optic nerve is not part of typical location for dissemination in space (DIS) criteria for MS.
Objectives: To assess the prognostic value of optic nerve involvement in CIS in predicting the occurrence of a second clinical relapse (clinically definite MS;CDMS).
Methods: CINOCIS study is a longitudinal cohort study of patients presenting a recent CIS(<4.5months). We enrolled 134 patients between 2013 and 2018 at Lille MS center (France). Each patient had a prospective clinical, OCT and MRI (including 3D-DIR for optic nerve imaging) follow-up. At inclusion, optic nerve involvement was defined as symptomatic when a patient had presented a uni- or bilateral clinical episode of optic neuritis (ON) as a CIS. At inclusion, asymptomatic optic nerve involvement on MRI was defined by the detection of asymptomatic uni or bilateral optic nerve DIR hypersignal. At inclusion, asymptomatic optic nerve involvement on OCT was defined by an inter-eye thickness difference on macular ganglion cells inner plexiform layer complex ⩾1.42µm as we previously demonstrated, among patients without clinical ON. Cox's proportional hazard models were used, adjusted for early initiation of treatment as time-varying.
Results: 125 CIS patients (93%) have been prospectively followed-up. Among them, 39 had presented an ON (31%;37 patients with unilateral ON), 103 (82%) have been diagnosed with MS (2017 criteria) and 26(21%) initiated a first-line treatment before CDMS. All eyes with optic neuritis had an optic nerve DIR hypersignal. By including all patients, optic nerve involvement (clinic + MRI or clinic + OCT) was not associated with a lower or higher risk of CDMS (HR=0.883 [95% confident limits:0.502-1.551] p=0.6641 and HR=1.855 [0.990–3.474] p=0.0536 respectively). Patients with bilateral ON excluded and asymptomatic optic nerve involvement on MRI considered, the presence of an asymptomatic optic nerve lesion was not associated with a lower or higher risk of CDMS (HR=1.025 [0.566-1.858] p=0.9341).ON patients excluded and asymptomatic optic nerve involvement on OCT considered, patients with asymptomatic optic nerve lesions had a higher risk of conversion to CDMS (HR 2.787 [1.386-5.604] p=0.004).
Conclusions: Asymptomatic optic nerve lesions detected by OCT should be considered in the next revision of MS criteria.

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Authors have no disclosures concerning this study

P240
Prognostication of disease activity in multiple sclerosis using retinal layer thickness z-scores

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Introduction: Optical coherence tomography (OCT)-derived peripapillary retinal nerve fiber layer thickness (pRNFL) and ganglion cell-inner plexiform layer thickness (GCIPL) are promising prognostic biomarkers for predicting future disease activity and disability in people with multiple sclerosis (PwMS). But raw OCT measures have multiple dependencies, hindering their interpretation and clinical utility up to an individual level.

Objective: To investigate standardized OCT measures as prognostic biomarkers in PwMS.

Aim: To investigate if age-adjusted z-scores for pRNFL (pRNFL-z) and GCIPL (GCIPL-z) using reference data from a normative cohort allow prognostication of future disability worsening and disease activity in PwMS.

Methods: Age-adjusted reference pRNFL-z and GCIPL-z were derived from 218 healthy controls (mean age 36.5±12.3 years) using generalized additive model for location, scale, and shape. OCT measures in non-optic neuritis eyes were fitted into each model and transformed to z-scores accordingly. We used data from two published studies and Cox proportional-hazards models to assess the association of (1) pRNFL-z with risk of future disability worsening (confirmed Expanded Disability Status Scale increase) in 722 PwMS from an International MS Visual System Consortium study including two OCT devices, and (2) GCIPL-z with subsequent disease activity (not fulfilling the no evidence of disease activity (NEDA-3) criteria) in 78 PwMS from the Berlin CIS cohort. We identified optimal cutoffs using Akaike information criterion and location with log-rank test and likelihood-ratio test.

Results: In the first cohort, 172 (24%) PwMS had disability worsening after a median follow-up of 2.0(interquartile range (IQR):1.0–3.0) years. Optimal cutoffs for defining low/normal pRNFL-z were <-0.97/>0.12. Low pRNFL-z was associated with an increased risk of disability worsening (adjusted hazard ratio (aHR)[95%CI]=1.43[1.05–1.94],p=0.024). In the second cohort, 46 (59%) PwMS did not maintain NEDA-3 status after a median follow-up of 2.0 (IQR:1.9–2.1) years. Optimal cutoffs for determining low/normal GCIPL-z were <-0.46/>0.59. PwMS with low GCIPL-z had a higher risk of showing disease activity (aHR[95%CI]=2.39[1.10–5.19],p=0.028).

Conclusions: pRNFL-z and GCIPL-z have prognostic value for disease activity and disability progression in PwMS. Given the generalizability and interpretability, z-scores are a promising approach for developing OCT-derived markers towards individual prognostication.

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22. A.U. Brandt is cofounder and holds shares of medical technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patents and patent applications describing methods for retinal image analyses, motor function analysis, multiple sclerosis serum biomarkers and myelination therapies utilizing N-glycosylation modification. He is cofounder, member of the board and currently elected Secretary/Treasurer of IMSVISUAL.

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Anterior and posterior visual pathway involvement in myelin oligodendrocyte glycoprotein antibody disorders (MOGAD) patients: an OCT and MRI study

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Background: Despite the frequent involvement of the visual system in MOGAD, studies evaluating the anterior and posterior visual pathway in this disease are scarce. We aimed to investigate the presence of retinal damage independent of optic neuritis (ON) and to explore the existence of anterograde degeneration after ON in MOGAD.
Methods: Cross-sectional, retrospective study of 27 adult MOGAD patients and 23 healthy controls (HC). Clinical, OCT, and MRI data were collected. Peripapillary retinal nerve fibre layer (pRNFL) and ganglion cell inner plexiform layer (GCIPL) were obtained using Heidelberg Spectralis. FreeSurfer7 was used to obtain the lateral geniculate nucleus (LGN), occipital volume fractions (to total estimated intracranial volume), and occipital cortical thickness. For the anterior visual pathway, the analysis was conducted using eyes, classified based on the history of ON (EON+ and EON-) and compared to HC-eyes. The analysis of OCT and brain volumetric measures was conducted comparing MOGAD-ON, MOGAD-NON and HC. The ANCOVA with Bonferroni-adjusted post hoc test was used to test differences between groups and linear regression analysis to evaluate OCT/MRI associations; age, and time from disease onset to OCT were considered as covariates.
Results: 20 (74.1%) patients had a prior ON. Median pRNFL and GCIPL thickness (um) was significantly reduced in EON+ vs EON- and HC (pRNFL:73 (29-98, 92 (56-105), 97.5 (81-117),$p<0.001$; GCIPL:55.88(37.49-71.80), 68.61(49.16-79.22) 73.12(66.49-79.58),$p<0.001$). pRNFL and GCIPL thickness had a negative correlation with the number of ON episodes (β=-0.622, $p<0.001$; β=-0.422, p=0.041). The LGN volume fraction was lower in MOGAD-ON compared to HC (0.33(0.28-0.43) vs 0.38(0.29-0.47), p=0.005). The occipital cortical thickness was lower in MOGAD-ON compared to MOGAD-NON and HC (p=0.002). In MOGAD-ON patients, pRNFL correlated with LGN volume (β=0.583, p=0.02), occipital volume fraction (β=0.506; p=0.012) and occipital thickness (β=0.464, p=0.004). LGN volume fraction showed a significant association with occipital volume fraction (β=0.506; p=0.013).
Conclusion: Compared to HC, MOGAD patients have a decreased retinal thickness mostly driven by ON eyes and the number of ON episodes. Our findings also suggest retinal damage can be present in asymptomatic eyes. MOGAD-ON patients present retinal, subcortical, and cortical atrophy in the visual pathway compared to MOGAD-NON and HC, suggesting an anterograde degeneration.

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Association of iron rim lesions and retinal layer thickness in relapsing multiple sclerosis

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Introduction: Iron rim lesions (IRL) are chronic active lesions surrounded by iron-containing microglia and macrophages that are associated with a more severe disease course in multiple sclerosis (MS). Retinal layer thinning measured by optical coherence tomography (OCT) is a biomarker of neuroaxonal damage associated with disability progression in MS. However, IRLs and OCT have not yet been studied together.
Objectives and aims: We aimed to determine whether there is an association between IRLs and OCT parameters (peripapillary retinal nerve fiber layer [pRNFL] and ganglion cell layer [GCL] thickness) in patients with MS (pwMS).
Methods: In this retrospective study, we included patients with relapsing-remitting MS who underwent a 3T brain MRI between 01.01.2015 and 31.12.2021, and had at least one OCT scan +/– 6 months from MRI. The number of IRLs was univariately analyzed with OCT parameters (pRNFL, GCL) using Pearson or Spearman correlation analyses as appropriate. Linear regression models were calculated with OCT parameters as dependent variables, and the number of IRLs as an independent variable adjusted for age, gender, disease duration and EDSS.
Results: We analyzed 96 pwMS (median age 33.2 years [SD 9.7], 62.5% female, median disease duration 4.5 years [IQR 1–11], median EDSS 1.0 [0–2.5]). Mean pRNFL and GCL thickness were 92.4 µm (14.5) and 35.5 µm (5.3), respectively. Patients with IRLs had lower mean pRNFL (90.2 µm [16.4];p=0.034) and GCL thickness (34.4 µm [5.7];p=0.041) in comparison to patients without them (pRNFL 96.8 µm [13.8]; GCL 37.6 µm [3.9]). In multivariable analyses, pRNFL thickness was associated with disease duration (β= −0.26; 95% CI −1.08, –0.11;p=0.017) and EDSS (β= −0.27; 95% CI −4.77, –0.51;p=0.020), whereas GCL thickness was associated with EDSS (β= −0.40; 95% CI −2.38, –0.34;p=0.007) and the number of IRLs (β= −0.29; 95% CI −0.43, –0.01;p=0.046). A follow-up OCT was available in 29 (30.2%) pwMS (median follow-up interval 2.3 years [1.4–3.5]); however, the sample size did not allow multivariable analyses.
Conclusions: Although patients with IRLs have lower pRNFL thickness, this might be mediated by longer disease duration rather than by the number of IRLs itself. On the contrary, GCL thickness seems to be associated with the number of IRLs regardless of diease duration, making it a more robust biomarker of disease progression. This association should be further elaborated in a larger study cohort with more longitudinal data.

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Optical coherence tomography's quality control in a multicenter study of neuromyelitis optica spectrum disorders

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Introduction: Optical coherence tomography (OCT)-derived measures are emerging biomarkers for quantifying neuroaxonal visual pathway damage in neuroinflammatory disorders. Consistent and high-quality OCT scans are required to produce reliable measurements, but their acquisition can be challenging, e.g. due to severe visual impairment.

Objective: To investigate OCT quality control issues in real world data.

Aim: To perform a systematic analysis of OCT quality in a large international multicenter cohort including blind eyes.

Methods: Macular volumes and peripapillary scans collected in the Collaborative Retrospective study on retinal OCT in Neuromyelitis Optica (CROCTINO) were analyzed. OCT instruments were Heidelberg Engineering Spectralis SD-OCT, Carl Zeiss Meditec Cirrus HD-OCT, or Topcon SD-OCT. Quality control was performed by experienced graders using adjusted OSCAR-IB criteria, including classification of obvious problems (cut-offs, focus, motion artifacts), signal, centration, retinal pathology, illumination, and beam placement. Post-processing correctable errors (i.e. segmentation algorithm failures) were not evaluated. Eyes were stratified by visual acuity into blind/non-blind using a cut-off of 1.0 logMAR and compared using Chi-square test.

Results: A total of 3,080 OCT scans (1,445 macular, 1,635 peripapillary) of 539 patients with neuromyelitis optica spectrum disorders and related conditions from 22 centers were evaluated. A total of 20.1% macular volume scans and 14.5% peripapillary scans were rejected due to data acquisition quality issues. Of these, low OCT signal was the most prevalent quality issue in both macular volume scans (30.8%) and in peripapillary scans (47.3%), followed by illumination problems (23.4% of macular scans, 35.6% of peripapillary scans). Visual acuity was available for a subset of 1,565 scans, of which 295 (18.8%) were from eyes classified as blind. In both macular and peripapillary scans, the frequency of rejected images was higher in blind eyes (macular: 41.6%, peripapillary: 28.9%) than in non-blind eyes (macular: 14.6%, Chi-square=81, $p<0.001$; peripapillary: 10.7%, Chi-square=60, $p<0.001$).

Conclusion: Quality control issues are common in OCT studies, and quality control procedures as well as a uniform protocol need

to be included in studies utilizing OCT biomarkers. A higher frequency of quality-based rejection occurred in blind eyes, which may constitute an intrinsic systematic error.

Disclosure

HS has nothing to disclose.
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PV has received consultancy fees and hold stocks in Accure Therapeutics, Attune Neurosciences, CLight, NeuroPrex, Spiral Therapeutics, and Adhera Health
MRY is founder and shareholder of NovaDigm Therapeutics, Inc. and Metacin, Inc., receives funding from the U.S. National Institutes of Health and U.S. Department of Defense, and was issued patents pertaining to immunotherapy and infectious diseases; he is a member of the Genentech-Roche Scientific Advisory Committee and advisor to The Guthy-Jackson Charitable Foundation.
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FP reports research grants and speaker honoraria from Bayer, Teva, Genzyme, Merck, Novartis, MedImmune and is member of the steering committee of the OCTIMS study (Novartis).
AUB is cofounder and shareholder of Motognosis and Nocturne. He is named as inventor on several patent applications regarding MS serum biomarkers, OCT image analysis and perceptive visual computing.
HGZ reports grants from Novartis and speaking honoraria from Bayer Healthcare.

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OSCAR-MP – a proposal of quality criteria for retinal optical coherence tomography angiography

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Background: Optical coherence tomography angiography (OCT-A) is a novel high-resolution imaging technique able to visualize retinal blood flow. OCT-A has been increasingly used to study retinal vessel alterations in various neurological diseases. Despite its advantages, OCT-A remains technically challenging: For eyes with visual impairment, OCT-A becomes extremely susceptible to imaging artifacts. To date, there are no clearly defined criteria for OCT-A quality control (QC) to rate these artifacts. Furthermore, there is insufficient data on evaluating the effect of OCT-A quality on outcome parameters such as the foveal avascular zone and retinal vessel densities. Therefore, standardized and accepted OCT-A QC criteria to facilitate use in daily clinical and scientific routine are needed.
Objective: To propose and test OCT-A QC criteria for OCT-A quality assessment
Aims and Methods: To propose OCT-A QC criteria for OCT-A quality assessment and to apply these to a set of OCT-A scans from two different centres (Technical University Munich, University College London). By using the Fleiss' kappa-statistics for inter-rater agreement, we aim to identify reasons for rater disagreement and adapt the proposed criteria and teaching material. We also intend to evaluate outcome parameters with QC results by applying revised QC criteria to a set of follow-up OCT-A of different quality.
Results: This is an ongoing study and we present preliminary results. We recognized seven major artifacts affecting OCT-A quality of the superficial vascular complex: (O) Obvious problems, (S) signal strength, (C) centration, (A) algorithm failure, (R) retinal pathology, (M) motion and (P) projection artifacts. Applying the OSCAR-MP criteria to a set of 40 OCT-A scans from patients with multiple sclerosis, Sjogren's syndrome, uveitis and healthy individuals, seven independent raters attained a substantial interrater-kappa (κ) of 0.67. We identified projection artifacts as main criteria of disagreement (κ 0.16) while motion (on average 44% of OCT-A, κ 0.70) and obvious problems (on average 41% of OCT-A, κ 0.65) were the most common causes of artifacts. To enhance artifact recognition and interrater agreement,

we designed a scoring guide and OCT-A training set. Correlation studies of QC and outcome parameters will be finalized in the next few months.
Conclusion: OSCAR-MP, with the aid of multi-centre validation, could serve as OCT-A QC criteria in clinical practice and for research studies.

Disclosure
Conflict of interest:
Rebecca Wicklein, Christina Noll and Charmaine Yam declare no conflict of interest.
Lilian Aly received travel and research support by Novartis.
Bernhard Hemmer has served on scientific advisory boards for Novartis; he has served as DMSC member for AllergyCare, Sandoz, Polpharma and TG therapeutics; he or his institution have received speaker honoraria from Desitin; his institution received research grants from Regeneron for multiple sclerosis research. He holds part of two patents; one for the detection of antibodies against KIR4.1 in a subpopulation of patients with multiple sclerosis and one for genetic determinants of neutralizing antibodies to interferon. All conflicts are not relevant to the topic of the study.
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Rate of retinal layer thinning as a biomarker for conversion to progressive disease in multiple sclerosis

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Background: The diagnosis of secondary progressive multiple sclerosis (SPMS) is often delayed due to the lack of objective clinical tools, which increases the diagnostic uncertainty and hampers the therapeutic development in progressive multiple sclerosis. Optical coherence tomography (OCT) has been proposed as a promising biomarker of progressive neurodegeneration.
Objective: To explore longitudinal changes in the thicknesses of retinal layers on OCT in individuals with relapsing-remitting multiple sclerosis (RRMS) who converted to SPMS versus matched RRMS patients who did not convert to SPMS. Our hypothesis is that the 2 cohorts exhibit different rates of retinal thinning.
Methods: From our prospective observational cohort (AMIR) of MS patients at the American University of Beirut, we selected RRMS patients who converted to SPMS during the observation period and RRMS patients, matched by age, disease duration, and EDSS at first visit. Baseline retinal measurements were obtained using spectral domain OCT, and all patients underwent clinical and OCT evaluation every 6 to 12 months on average throughout the study period (mean = 4 years). Mixed-effect regression models were used to assess the annualized rates of retinal changes and the differences between the 2 groups and between converters to SPMS before and after their conversion.
Results: A total of 61 participants were selected (21 SPMS and 40 RRMS). There were no differences in baseline characteristics and retinal measurements between the two groups. The annualized rates of thinning of all retinal layers, except for macular volume, were greater in converters before conversion compared to non-converters by 112% for pRNFL ($p=0.008$), 344% for tRNFL ($p<0.0001$), and 82% for GCIPL ($p=0.002$). When comparing the annualized rate of thinning for the same SPMS patients before and after conversion, no significant differences were found except for tRNFL and GCIPL with slower thinning rates post-conversion (46% and 68%, respectively).
Conclusions: Patients that converted to SPMS exhibited faster retinal thinning as reflected on OCT. Longitudinal assessment of retinal thinning could confirm the transition to SPMS and help with the therapeutic decision-making for MS patients with clinical suspicion of disease progression.

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The authors have no disclosures relevant to the work

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Usefulness of optical coherence tomography in pediatric patients with an acquired demyelinating syndrome

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Background: Optic neuritis (ON) is a common presentation of childhood acquired central nervous system demyelinating syndrome (ADS). Thinning of the peripapillary retinal nerve fiber layer (pRNFL) thickness measured by optical coherence tomography (OCT) is associated with a poorer visual prognosis.
Objective: This study aimed to evaluate the usefulness of OCT in children with ADS with and without ON.
Methods: Retrospective single-center review of clinical and OCT data of children with ADS with at least two years of follow-up. pRNFL thickness measurements (global and four quadrants) were obtained using the Topcon 3D OCT 2000 device. Values were converted to Z scores using data from an age-matched normal population obtained with the same machine.
Results: Thirty-five children with ADS (18, 51.4% female) with a median age at onset of 10.3 years (IQR 4.5-14.8) were included. Eleven patients have an antibody-mediated ADS (9 MOG, 1 AQP4, 1 anti-GlyR); and 24 were seronegative (19 with multiple sclerosis). Nineteen (54.3%) patients had at least one episode of ON, 8 of them with antibodies and 11 seronegative. Patients with antibody-mediated ADS and ON had worse visual recovery than those seronegative (mean last visual acuity antibody-mediated ADS 1.0 (IQR 0.45-1.0) vs. seronegative 1.0 (IQR 1.0-1.0) p= 0.021. Patients with antibody-mediated ADS had greater global pRNFL thinning than seronegative patients, both in neuritic and non-neuritic eyes (mean Z score neuritic eyes -5.6 vs -1.9, p=0.03; mean Z score non-neuritic eyes: -2.1 vs -0.1, p=0.001).
Conclusions: OCT is a useful and non-invasive tool for evaluating retinal damage in children with ADS and anterior optic pathway dysfunction related to the different serostatus. It also may help to detect patients with worse potential recovery.

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Retinal optical coherence tomography and visual evoked potentials as prognostic markers of future relapses in early multiple sclerosis

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Introduction: Both retinal optical coherence tomography (OCT) and visual evoked potentials (VEP) have been suggested as prognostic markers for future disease activity in MS.
Objectives: To establish prognostic markers derived from subclinical visual pathway neurodegeneration and demyelination early in the disease course.
Aims: To evaluate retinal OCT and VEP in non-optic neuritis eyes to identify prognostic markers for future relapses.
Methods: Three international MS centers retrospectively queried their databases for participants who underwent OCT and VEP within 6 months after their first demyelinating event suggestive of

MS, and were followed up for at least 1 year. Participants were classified as normal/abnormal regarding their VEP and OCT results in non-ON eyes compared to local healthy reference cohorts. OCT-derived peripapillary retinal nerve fiber layer thickness (pRNFL) and combined ganglion cell and inner plexiform layer thickness (GCIP) were classified as abnormal when lower than the 25th percentile, and VEP was classified as abnormal when absent or prolonged as per center discretion. We applied Cox proportional hazard models to determine the risk for future relapses.
Results: We included 175 patients with a demyelinating event (mean age 37.7±8.5 years, 119 female), of which 111 (63%) fulfilled the 2017 MS diagnostic criteria at baseline. Classification into abnormal was established in 30 (17%) cases by pRNFL, 86 cases (49%) by GCIP and 46 cases (26%) by VEP. Subjects were observed over a median period of 4.0 (interquartile range 2.5 – 6.0) years. In total, 57 subjects (32%) presented with a relapse during follow-up. Abnormal pRNFL and GCIP were associated with an increased rate of developing a relapse (pRNFL: Hazard ratio (HR) 2.9 [95% confidence interval 1.6 -5.1], $p<0.001$; GCIP: HR 1.8 [1.0-3.1], p=0.042). Contrary, abnormal VEP was not associated with a future relapse (HR 0.9 [0.5-1.6], p=0.756).
Conclusions: OCT-derived pRNFL and GCIP are superior to VEP for the prognosis of future relapses after an initial demyelinating event in non-ON eyes. These results encourage the evaluation of OCT for the assessment of subclinical optic nerve lesions for diagnosing MS.

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JSG serves as co-Editor for Europe on the editorial board of Multiple Sclerosis Journal and as Editor-in-Chief in Revista de Neurología, receives research support from Fondo de Investigaciones Sanitarias (19/950) and has served as a consultant / speaker for Biogen, Celgene/Bristol Meyers Squibb, Sanofi, Novartis and Merck.
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XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.
FP served on the scientific advisory boards of Novartis and MedImmune; received travel funding and/or speaker honoraria from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is an associate editor ofNeurology: Neuroimmunology & Neuroinflammation; is an academic editor ofPLoS ONE; consulted for Sanofi Genzyme, Biogen, MedImmune, Shire, and Alexion; received research support from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Geynzme, Alexion, and Merck Serono; and received research support from the German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy-Jackson Charitable Foundation, and NMSS.
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AUB is cofounder and holds shares of medical technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patents and patent applications describing methods for retinal image analyses, motor function analysis, multiple sclerosis serum biomarkers and myelination therapies utilizing N-glycosylation modification. He is cofounder, member of the board and currently elected Secretary/Treasurer of IMSVISUAL.

Imaging and non-imaging biomarkers - Fluid Biomarkers

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Coagulation activation in relapsing-remitting multiple sclerosis with relapse-associated lymphopenia

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Introduction: Several recent studies showed coagulation involvement in Multiple sclerosis (MS), an inflammatory-demyelinating and degenerative disease of the central nervous system.
Objectives: To compare the serum/plasma levels of complement/coagulation factors and soluble endothelial markers among healthy controls, relapsing and remitting MS patients; to assess the presence of brain hemodynamic changes in relapsing and remitting MS patients.
Aims: To correlate complement/coagulation factors with both MRI perfusion data and clinical features of MS patients in the hypothesis of the activation of coagulation/complement system associated with pro-inflammatory endothelial alteration and cerebral hypoperfusion in the course of MS relapse.
Methods: 30 relapsing (24F/6M, age41±10.73 years) and 30 remitting (23F/7M,39.3±10.02 years) MS patients, and 30 age/sex-matched controls (23F/7M,40.2±8.38 years) were tested for complement/coagulation and soluble endothelial markers. MS patients had undergone dynamic susceptibility contrast-enhanced 3T MRI.
Results: Relapsing and remitting patients compared to controls hada highereither body-mass-index(p=.006),protein C(p=.001), Complement C9(p=.02) with a trend forfibrinogen(p=.058) and a lowerComplement C4 (p=.001).
Relapsing compared to remitting patients had: a higher EDSS (p<.001); number of relapses either during overall disease (p<.001),previous one (p<.001) or 2 years (p<.001); MCHC (p=.007), a lower count of most lymphocyte subsets: CD3 (p=.01), CD4 (p=.04), CD8 (p=0.02), CD19(p=.04), and when compared to both remitting patients and controls had either a lower Tissue factor (p<.001), Tie-2 (p=.002) or P-selectin (p=.02) and a higher Vitamin A (p<.001).
The dataof Mean Transit Time (MTT), Cerebral Blood Volume (CBV) and Flow (CBF) were evaluated in the normal appearing white matter and in the deep gray matter.Mean (±SD) MTT, CBV, CBF values in relapsing and remitting patients were 5.506 (±1.073), 14.147 (±5.378), 149.378 (±39.794) and 5.432 (±0.836), 14.692 (±3.357),152 (±29.476), respectively.
Conclusions: Our data indicate coagulation activation in relapsing-remitting MS patients compared to controls especially during the relapse in which it is associated with reduction of most lymphocyte subsets.

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A novel signature of lipoxin A_4 and prostaglandin E_2 in plasma associated with disease severity in patients with relapsing-remitting and secondary progressive multiple sclerosis

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Introduction: In multiple sclerosis (MS), chronic neuroinflammation may be due to deregulation of resolution of inflammation. This protective process is normally orchestrated by specialised pro-resolving lipid mediators derived from omega-3/-6 fatty acids. Failed resolution might be caused by a lack of pro-resolving lipid mediators, such as lipoxin A_4 (LXA_4), while pro-inflammatory lipid mediators, such as prostaglandin E_2 (PGE_2), may persist.
Objective: To explore whether LXA_4 and PGE_2 can be used as candidate biomarkers of disease activity in patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS).
Methods: In this post hoc analysis, involving baseline (BL) samples from the Phase 4 study LONGTERMS (N=28 RRMS-SPMS converters) and the Phase 3 study EXPAND (N=55 randomly selected patients with SPMS), LXA_4 and PGE_2 levels were quantified by quantitative liquid chromatography with tandem mass spectrometry. Lipids were categorised as lo (not detectable) or hi (detectable) or as signatures LXA_4(lo)+PGE_2(hi) vs LXA_4(hi)+PGE_2(lo). Mean BL characteristics – such as disease duration (DD), Expanded Disability Status Scale (EDSS) score, normalised brain volume (NBV), T2 lesion volume (LV) & 9-Hole Peg Test (9-HPT) were analysed by lipid category.
Results: In RRMS, 14/28 patients were PGE_2-positive at BL, while LXA_4 was only detectable in 4/28 patients. In SPMS, samples were PGE_2(hi) and LXA_4(hi) in 13/55 and 6/55 of the patients, respectively. SPMS patients with PGE_2(hi) vs PGE_2(lo) showed a trend towards a longer DD (20.6 vs 17.6 years), higher EDSS (5.7 vs 5.5), lower NBV (1384 vs 1425 cm^3), higher LV (20.5 vs 17.1 cm^3), and weaker performance in the 9-HPT (42.5 vs 32.4 seconds). In contrast, SPMS patients with LXA_4(hi) vs LXA_4(lo) trended towards higher NBV (1439 vs 1414 cm^3), lower LV (16.4 vs 18.1 cm^3), and a better performance in the 9-HPT (31.6 vs 35.2 seconds). SPMS patients with the signature LXA_4(lo)+PGE_2(hi) shared a trend of advanced disease severity compared to patients with LXA_4(hi)+PGE_2(lo), based on EDSS (5.8 vs 5.6), NBV (1383 vs 1438 cm^3), LV (21.0 vs 16.7 cm^3), and 9-HPT (43.3 vs 31.3 seconds). In RRMS patients, the signature LXA_4(lo)+PGE_2(hi) showed a similar trend towards association with higher EDSS, advanced brain atrophy, and low performance in the 9-HPT.
Conclusion: Circulating levels of LXA_4 and PGE_2 appear to be a candidate lipid biosignature of disease severity in RRMS and SPMS. Validation in larger studies is underway.

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Using metabolomic and transcriptomic profiles to predict development of anti-drug antibodies in people with relapsing remitting multiple sclerosis

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Background: Neutralising anti-drug antibodies (ADA) can greatly reduce the efficacy of disease modifying treatments in multiple sclerosis (MS) patients. The factors predisposing an individual to develop ADA are poorly characterised, creating an unmet need for biomarkers to predict ADA and subsequent treatment failure. Up to 35% of MS patients treated with beta interferons (IFNβ) develop ADA and are an ideal cohort to investigate potential ADA biomarkers. A multiomic approach was used to predict ADA development in IFNβ treated MS patients.
Methods: Peripheral blood was collected from MS patients as part of a multi-centre study of ADA development (ABIRISK). Samples from before and 3 months after starting IFNβ treatment were analysed by serum metabolomics and whole blood RNA sequencing. ADA status was determined after 12 months on IFNβ, where 30 patients were ADA positive (ADA+). Machine learning models, including lasso logistic regression and sparse partial least squares discriminant analysis, were used to predict ADA status using metabolomic data (n=82), while whole blood transcriptomics were examined in matched patients (n=11) using differential gene expression and pathway enrichment (PE) analysis.
Results: Metabolomic and transcriptomic analysis suggest a disrupted lipid metabolism amongst ADA+ patients prior to starting IFNβ, with "Metabolism of Lipids" amongst the top 15 pathways in the PE analysis (log10[p-value] = -5.375). As such, metabolite concentrations were used to develop models which can classify patients with an accuracy of 85%, while normalised lipid metabolism gene counts were used to cluster patients by ADA status. Strong and significant correlations between these metabolite concentrations and lipid gene counts were observed (p-value < 0.05; absolute correlation coefficient > 0.6). Furthermore, patients who were ADA+ by month 12 had a distinct response to IFNβ in the first 3 months, showing 29 differentially regulated metabolites and a down regulation of 11 IFN signalling genes previously associated with response to IFNβ therapy. These differences in response to treatment, particularly within IFN signalling, can be used to predict development of ADA early in the treatment course.
Conclusion: Metabolite concentration and gene expression signatures are promising tools for prediction of ADA development in MS patients treated with IFNβ and could provide novel insight into mechanisms of immunogenicity, which may apply to other treatments.

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P251

Investigation of serum based proteomic biomarker signatures relative to steroid responsiveness and disease activity status in relapsing multiple sclerosis patients

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Background: An assay that measures the serum concentrations of 18 proteins used to determine 4 disease pathway scores (immune modulation, neuroinflammation, myelin biology and neuroaxonal integrity) and an overall disease activity (DA) score has been analytically and clinically validated. The primary DA endpoint utilized for validation was the count of gadolinium enhancing (Gd+) lesions on an associated MRI. It is hypothesized that the utility of the assay can be expanded beyond DA assessments including identifying serum biomarkers predictive of steroid response.
Objectives: We aimed to assess the association of individual proteins, DA score and disease pathway scores with relapsingremitting multiple sclerosis (RRMS) patients in stable disease phase, with glucocorticosteroid (GC) responsive or GC resistant relapse as well as Gd+ status (0, 1, or 2+ lesions).
Methods: We collected samples from 97 RRMS patients (36 stable, 22 GC responsive and 39 GC resistant). 36 had 0 Gd+ lesions, 28 had 1 lesion, 26 had 2 or more lesions and for 7 Gd+ counts were missing. ANOVA was used to test the association of steroid responsiveness with the DA score, pathway scores, and individual protein concentrations. We evaluated statistical metrics including sensitivity, NPV, accuracy and odds ratio previously used to establish the DA score thresholds for disease activity categories labeled low (L), moderate (M) and high (H).
Results: The DA score, the 4 pathway scores and concentrations of 8 proteins were significantly associated with the GC responsiveness categories ($p < 0.05$). The DA and the 4 pathway scores were significantly associated with Gd+ status ($p < 0.001$). Odds ratios were determined indicating that a patient with a M/H DA score is 12.5 times more likely to have ≥ 1 Gd lesions than a patient with a L DA score and a patient with a H score is 3.77 times more likely to have ≥2 Gd lesions than a patient with a L/M score.
Conclusions: The DA score, pathway scores and several protein biomarkers associated significantly with the GC responsiveness categories. Ongoing analyses include additional multivariate modeling and incorporating transcriptomic data for the 18 biomarkers in the panel. So far, this study underlines the utility of the MSDA test to assess MS patients' radiographic disease activity status. A proteomic test validated to predict a relapsed patient's responsiveness to steroids can be a powerful biomarker tool to help improve outcomes for MS patients.

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P252

The CXCR7 antagonist ACT-1004-1239 increases CXCL12 levels in the CNS and promotes myelination

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Introduction: Targeting remyelination failure remains a challenge for the treatment of multiple sclerosis (MS). Unfortunately, the translation of new MS treatments from animal models to patients is uncertain. Establishing biomarkers to investigate the mechanism of action (MoA) in clinical studies is therefore essential. In several preclinical MS models, ACT-1004-1239, a potent, selective, and orally available first-in-class CXCR7/ACKR3 antagonist, demonstrated a dual MoA: decrease of neuroinflammation and promotion of myelination. The promyelinating effects were associated with an increase of CXCL12 levels in the CNS through the blockade of the CXCR7 scavenging activity, resulting in maturation of oligodendrocyte precursor cells to myelinating oligodendrocytes. In healthy volunteers, ACT-1004-1239 dosedependently increased CXCL12 plasma concentrations. However, biomarkers to investigate the CNS compartment are essential to

translate the promyelinating mechanism of action to patients with MS.

Objective & Methods: Develop translatable CNS biomarkers in preclinical models to support clinical development of ACT-1004-1239 in patients with MS. In the cuprizone-induced demyelination mouse model, the effect of ACT-1004-1239 (100 mg/kg, twice daily) was assessed *in vivo* using diffusion tensor imaging (DTI) after 6 weeks of cuprizone exposure. Furthermore, the ACT-1004-1239 PK/PD relationship was characterized in the plasma and brain of mice and cerebrospinal fluid (CSF) of common marmosets.

Results: Cuprizone exposure significantly reduced fractional anisotropy (FA) in areas of the corpus callosum, suggesting myelin loss and axonal injury. Preventive ACT-1004-1239 treatment significantly improved FA in some areas of the corpus callosum, in line with the observed increase in myelination. This protective effect was observed at a dose leading to sustained plasma CXCL12 increase and CXCL12 increase in the brain, in line with the proposed MoA. In marmosets, at doses (10 and 30 mg/kg, once daily (o.d.)) providing equivalent plasma exposure to the human doses of 30 and 100 mg o.d., respectively, ACT-1004-1239 increased CXCL12 plasma concentrations and CXCL12 levels in the CSF. This suggests that the exposure reached in the CNS causes a pharmacodynamics effect within the CNS compartment.

Conclusion: These results support the use of MRI imaging and CXCL12 CSF measurement as meaningful biomarkers to investigate the promyelinating MoA of ACT-1004-1239 in patients with MS.

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P253

Serum neurofilament light chain and glial fibrillary acidic protein are associated with future brain atrophy and T2 lesion volume in progressive multiple sclerosis patients

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Introduction: Neurodegeneration and astrocytic activation are pathological hallmarks of multiple sclerosis (MS) and can be quantified by serum neurofilament light chain (sNfL) and glial fibrillary acidic protein (sGFAP). The association of sNfL and sGFAP with future brain atrophy and lesion volume in progressive MS has not been explored yet.

Objectives: To investigate the prognostic value of sNfL and sGFAP for MRI measures of brain atrophy and lesion volume in progressive MS patients and differentially in active and non-active patients.

Methods: We included MS patients with a confirmed EDSS⩾3. This was our classifier for progressive MS and corresponded to our baseline visit and sample for sGFAP/sNfL quantification. Progressive patients were classified as "active/non-active" based on the presence or absence of relapses in the two years prior to baseline. Linear regression analysis on log-transformed sGFAP/sNfL assessed the baseline association with brain parenchymal fraction (BPF) and total brain T2 lesion volume (T2LV) measured between 5 and 10 years of follow-up. Analyses were adjusted for the strength of the magnet, time to MRI, and age, sex, EDSS, treatment, presence of relapse at sample.

Results: We identified 131 progressive MS patients with volumetric measurements at 5 to 10 years. The average EDSS at the baseline visit was 4.0 and was 5.1 at the 5 to 10 years follow-up. Baseline biomarker levels were associated with future BPF (sNfL: adjusted-β= -0.019, p=0.005; sGFAP: adjusted-β= -0.022, p=0.01) and future T2LV (sNfL: adjusted-β= 0.561, p=0.004; sGFAP: adjusted-β= 0.575, p=0.025). These associations were present in active patients (BPF, sNfL: adjusted-β= -0.030, p=0.001, sGFAP: adjusted-β= -0.035, p=0.043; T2LV, sNfL: adjusted-β= 0.833, p=0.005; sGFAP: adjusted-β= 1.212, p=0.025) but not in non-active patients (BPF, sNfL: adjusted-β= -0.004, p=0.773, sGFAP: adjusted-β= -0.016, p=0.136; T2LV, sNfL: adjusted-β= 0.237, p=0.469; sGFAP: adjusted-β= 0.39,p=0.173).

Conclusions: Higher levels of sNfL and sGFAP were associated with worse long term MRI volumetric outcomes particularly in active progressive MS patients.

Disclosure

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Prognostic value of neurofilament light and glial fibrillary acidic protein for disability worsening PIRA by age range in multiple sclerosis

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Introduction: Neurodegeneration and astrocytic activation are pathological hallmarks of multiple sclerosis (MS) and can be quantified by serum neurofilament light chain (sNfL) and glial fibrillary acidic protein (sGFAP). The pathology evolves with aging, and it is unclear whether sNfL and sGFAP have a prognostic utility across all age ranges.

Objectives: To evaluate the best approach for the clinical implementation of sNfL and sGFAP as prognostic biomarkers for 6-month confirmed disability worsening (6m-CDW) and for 6-month confirmed progression independent of relapse activity (6m-cPIRA) respective to the age of the patient.

Methods: We investigated the prognostic value of sNfL and sGFAP for 6m-CDW across different age groups (<30, 30-40, 40-50, 50-60, >60 years old). For sNfL we additionally explored the use of annualized change, and we stratified the analyses by sGFAP levels. For sGFAP we additionally performed the analyses in patients stratified by sex and by sNfL levels. Statistical analysis on log-transformed sGFAP/sNfL assessed the associations with future disability.

Results: sNfL and sGFAP levels were available for 1468 samples from 685 MS patients enrolled in our natural history study. The median follow-up was 8.3 years (interquartile range = 4.8, 10.9). Higher sGFAP was prognostic for 6m-CDW (n = 1468; Hazard ratio (HR) = 1.41; 95% confidence interval (CI) = 1.18, 1.68; p<0.001) and particularly in patients between 40 and 50 years of age (n = 451; HR = 1.93; 95% CI = 1.39, 2.69; $p<0.001$). sGFAP was also prognostic when considering only 6m-cPIRA events (HR = 1.36; 95% CI = 1.13, 1.64; $p<0.001$) and the association was stronger in patients that were 40 to 50 years old (HR = 1.86; 95% CI = 1.33, 2.61; $p<0.001$). The results were not statistically different between males and females. sNfL was only prognostic for 6m-CDW in patients older than 60 years of age that had increased sGFAP (n = 96; HR = 2.94; 95% CI = 1.05, 8.23; p=0.04). The annualized change in sNfL was also not prognostic for 6m-CDW or 6m-cPIRA..

Conclusions: sGFAP, but not sNfL, candidates as an easily accessible tool to identify MS patients at higher risk of disability worsening that may require a more intense clinical and MRI follow-up.

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Impact of estimated blood volume and body mass index on glial fibrillary acidic protein and neurofilament light chain measurements in serum and cerebrospinal fluid of multiple sclerosis patients

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Introduction: Serum and cerebrospinal fluid (CSF) biomarkers are powerful tools for the prognosis of disease activity and therapy response in multiple sclerosis (MS).
Objectives: To increase the validity of biomarker measures, potentially confounding factors need to be identified and controlled for.
Aims: Here, we aim to test if the volume of distribution approximated by the patients' estimated blood volume (BV) and body mass index (BMI) affect the serum and CSF concentrations of two of the most intensively studied MS biomarkers - glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL).
Methods: NFL and GFAP concentrations were measured in serum and CSF (sNFL/sGFAP, cNFL/cGFAP) in 98 patients with relapsing-remitting MS, primary progressive MS or clinically isolated syndrome. Additionally, clinical, laboratory and imaging parameters were acquired. Using backward stepwise analyses and multivariate linear regressions for each of the biomarkers, BV and BMI were compared as predictors to age, sex, MS disease phenotype, EDSS, presence of gadolinium-enhancing T1-weighted MRI lesions and acute relapse during sampling. Additionally, overweight/obese MS patients (BMI $\geqslant$ 25) were compared to patients with BMI $<$ 25 regarding their sNFL, sGFAP, cNFL and cGFAP concentrations using general linear model univariate analysis, while controlling for the same covariates.
Results: BV significantly predicted sGFAP (ß = -0.279, 95% CI: -0.464 to -0.092, q = 0.02, correction for multiple comparisons using false-discovery rate). Overweight/obese patients defined by BMI status had lower sGFAP concentrations compared to patients with BMI $<$ 25 after adjusting for covariates (F = 4.765, p = 0.032). Inverse correlations were shown also between BV/body height and sNfL although they did not reach significance.
Conclusions: These findings support the notion that the volume of distribution of sGFAP is a relevant confounding variable and should therefore be controlled for when measuring sGFAP in MS.

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Blood neurofilament light levels predict non-relapsing progression following anti-CD20 therapy in relapsing and primary progressive multiple sclerosis: findings from the ocrelizumab randomised, double-blind phase 3 clinical trials

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Introduction: Neurofilament light chain (NfL), a cytoskeletal protein that is released upon neuroaxonal injury, is associated with multiple sclerosis (MS) relapsing activity and has demonstrated some prognostic ability for future disability progression, yet its value in assessing non-relapsing disability progression remains controversial. Suppression of relapsing biology with high-efficacy immunotherapy, such as the anti-CD20 antibody ocrelizumab (OCR), might allow definition of the relationship between NfL levels and future non-relapsing progression.
Aims: To understand patterns of baseline and on-treatment blood NfL elevations and their prognostic potential for non-relapsing disability progression, assess the impact of OCR on NfL levels and evaluate on-treatment NfL as a treatment-effect surrogate biomarker.
Methods: We examined baseline and longitudinal blood NfL levels in 1421 persons with relapsing MS (RMS) and 596 persons with primary progressive MS (PPMS) from OPERA I/II (NCT01247324, NCT01412333) and ORATORIO (NCT011 94570). NfL treatment response and risk for disease worsening (including confirmed disability progression [CDP] on the Expanded Disability Status Scale into the open-label extension period and slowly evolving lesions [SELs] on brain MRI) at baseline and following treatment with OCR were evaluated using time-to-event analysis and linear regression models.
Results: In persons in the RMS interferon β-1a control arms without acute disease activity and in the entire PPMS placebo control arm, higher baseline NfL predicted greater whole brain and thalamic atrophy, greater volume expansion of SELs and risk for CDP (all $P<.05$). OCR reduced NfL levels vs controls in RMS and PPMS (all $P<.01$) and abrogated the prognostic value of baseline NfL on disability progression. Following effective suppression of acute disease activity by OCR, NfL levels at week 48 were significantly associated with long-term (up to 9 years) risk for CDP, in both RMS and PPMS (all $P<.001$).
Conclusions: Highly elevated NfL from acute MS disease activity may mask a more subtle NfL abnormality that reflects underlying non-relapsing progressive biology. Ocrelizumab significantly reduced NfL levels, consistent with its effects on acute disease activity and disability progression. Persistently elevated NfL levels while under high-efficacy treatment demonstrate potential clinical utility as a predictive biomarker of increased risk for non-relapsing disability progression.

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Increased intrathecal neurofilament light and IgM predict severe disability in relapsing-remitting multiple sclerosis

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Background: Emerging evidence supports intrathecal immunoglobulin M (IgM) synthesis (ITMS) as a disease severity biomarker in relapsing-remitting multiple sclerosis (RRMS), but its clinical utility and relationship with neuronal injury markers remain unknown.

Aims: to investigate whether ITMS at disease onset is a reliable predictor of a more aggressive disease course and to determine whether combining ITMS and cerebrospinal fluid (CSF) neurofilament light (cNfL), a biomarker that previously has been associated with worse prognosis, may exhibit a synergistic predictive effect.

Methods: Monocentric observational longitudinal cohort study in which prospectively collected data were retrospectively retrieved. Included were patients with RRMS (n=457) who had a diagnostic investigation including analysis of ITMS and cNfL. ITMS was calculated with the linear index formula, the intrathecal fraction of IgM according to Reiber (IgM_{IF}), and by qualitative determination of oligoclonal IgM bands (OCMB). Univariate and multivariate models were performed to predict No Evidence of Disease Activity-3 (NEDA-3) status within 24 months from onset, and the risk of Expanded Disability Status Score (EDSS) $\geq$3 and $\geq$6.

Results: All investigated methods to calculate ITMS significantly predicted evidence of disease activity (EDA-3) within 24 months. IgM_{IF}>0% showed the strongest association with EDA-3 status (adjusted hazard ratio [aHR] 3.7, 95%CI 2.7-5, p<0.001). Combining IgM-index>0.1 or OCMB with increased cNfL were strong predictors of EDSS$\geq$3 (for $cNfL^+$/IgM-$index^+$: aHR 4.6, 95%CI 2.6-8.2, p<0.001) and EDSS$\geq$6 (aHR 8.2, 95%CI 2.3-30, p<0.001).

Conclusions: ITMS is a useful biomarker in early RRMS to predict disabling MS and its prognostic value was even stronger in combination with cNfL. Our data suggest that determination of ITMS and cNfL should be included in the diagnostic work-up of RRMS for prognostic purposes and in decisions of disease-modifying therapy.

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KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Roche Diagnostics, and Siemens Healthineers.

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Differential diagnosis of MS patients versus disease state controls and classification of MS subtypes using serum proteomics

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Background: A custom immunoassay panel was developed and analytically validated in serum to measure the concentration of 20 proteins. The proteins represent 4 different biological pathways: immune modulation, neuroinflammation, myelin biology and neuroaxonal integrity. Using the assay panel, multivariate algorithms were successfully developed in prior studies to associate with MS disease activity and disease progression endpoints.. These proteins may also be informative for differential diagnostic applications including classification of various disease states and for distinguishing MS phenotypes.
Objectives: To evaluate the performance of proteomic multivariate models to classify patients from different disease states (MS patients, healthy controls-HC, inflammatory disease controls-IDC, and non-MS neurodegenerative disease controls-OND) and to classify the MS patient samples based on their subtype (CIS, RRMS, SPMS and PPMS).
Methods: We measured the concentrations of the 20 proteins in 334 patient samples from a University Hospital Basel cohort. The cohort consisted of 246 MS patients (120 CIS, 89 RRMS, 23 SPMS, 14 PPMS), 30 HC, 30 IDC, 28 OND. Multivariate classifiers were developed to maximize classification performance for (1) HC vs the 4 MS subtypes and the other disease states, (2) CIS vs RRMS, SPMS, PPMS and, (3) CIS+RRMS vs SPMS+PPMS.
Results: AUROC for classifying HC vs the 4 MS subtypes ranged from 0.731±0.074 (CIS) to 0.955±0.05 (SPMS) and the top 3 performing features in the model for HC vs CIS were NfL, GFAP and VCAN. The AUROC for classifying HC vs IDC and OND was 0.887±0.075 and 0.998±0.005 respectively. AUROC for classifying CIS vs RRMS, SPMS and PPMS was 0.664±0.057, 0.823±0.069 and 0.731±0.044 respectively; the top 3 performing features in the model for CIS vs RRMS were GFAP, OPN and IL-12B. AUROC for classifying CIS+RRMS vs SPMS+PPMS was 0.778±0.069 and the top 3 performing features were CDCP1, IL-12B and GFAP.
Conclusions: Multivariate models classified HC patients from different disease states including the MS subtypes, CIS vs other MS phenotypes, and CIS+RRMS vs progressive MS patients. Ongoing analysis will incorporate demographic and clinical information as covariates. The ability to differentially diagnose MS from other disease states with overlapping pathophysiology and to distinguish MS subtypes from one another has the potential to enhance therapeutic management of patients in clinical practice.

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Clinical implication of serum neurofilament light chain and glial fibrillary acidic protein in idiopathic transverse myelitis

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Introduction: Idiopathic transverse myelitis (ITM) refers to acute transverse myelitis whose etiology remains unknown after diagnostic workup. Due to its close relation with CNS inflammatory disorders, a reliable biomarker for ITM is necessary to monitor its disease activity or severity.
Objectives: (i) To evaluate the clinical usefulness of serum neurofilament light chain (sNfL) and serum glial fibrillary acidic protein (sGFAP) as biomarkers for ITM; (ii) to identify the characteristics of ITM in terms of biomarkers, distinct from other CNS inflammatory disorders.

Methods: We prospectively and consecutively included 56 ITM, 79 aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4+ NMOSD), 102 relapse-remitting multiple sclerosis (RRMS) patients, and 24 myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) patients. sNfL and sGFAP levels were measured by ultrasensitive single-molecular array technique. Associations between serum biomarkers (sNfL, sGFAP, and sGFAP/sNfL ratio) and clinical variables were investigated, and the biomarker levels were compared between disease groups according to disease phases (relapse/remission). Independent clinical factors to determine the levels of sNfL and sGFAP were also investigated.
Results: Both sNfL and sGFAP had significant positive associations with acute attack phase and higher EDSS score in patients with ITM. As compared to AQP4+ NMOSD patients, ITM patients showed lower levels of sGFAP and sGFAP/sNfL ratios regardless of disease phases. This trend was maintained even when compared between the ITM and AQP4+ NMOSD groups, considering the volume of lesion in magnetic resonance imaging. As compared to the other disease (RRMS/MOGAD) groups, ITM patients did not show significant differences in the levels of sNfL and sGFAP in both disease phases. Meanwhile, ITM patients demonstrated significantly lower levels of sGFAP/sNfL ratios than those in RRMS patients during remission phase. For determinants of serum biomarkers, both disease activity (relapse) and severity (higher EDSS score) were independently associated with sNfL levels, but only relapse phase was an independent determinator for sGFAP levels.
Conclusions: In ITM patients, both disease activity and severity were independently associated with sNfL but not with sGFAP levels. ITM patients showed lower GFAP levels and GFAP/NfL ratio compared to patients with other diseases, suggesting that ITM may be distinct from astrocytopathy.

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Small extracellular vesicles derived from b naïve and memory lymphocytes in multiple sclerosis relapse and remission patients as potential plasma biomarkers

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Introduction: No biomarker for relapses in patients with Multiple Sclerosis (PwMS) is available and the diagnosis is still clinical with an important risk of misdiagnosis. Small Extracellular Vesicles (sEV) have gained significant interest in MS as potential biomarkers due to their synthesis by immune cells and their ability to cross the blood-brain barrier. Once thought to be primarily driven by T cells, B cells are emerging as central players in MS immunopathogenesis. the majority of Bmem populating the CSF display an isotype-switched phenotype (71%; CD19+ CD27+ IgD- IgM-)
Objective: To explore the changes in sEV concentrations in PwMS during a relapse (RP) or in remission (rP) and the difference with healthy volunteers (HV).
Methods: sEV from patients in relapse (RP) and remission (rP) and healthy volunteers (HV) were isolated by plasma samples using Dual-Mode Chromatography. Isolated sEV were labelled with CD9+ (specific sEV biomarker) and CD19+CD200+ (B naïve marker) or CD19+CD27+ (B memory marker) and were analysed by flow cytometry using Cytoflex S equipment. Differences in EVs levels between different MS-treatments were also analysed.
Results: Higher CD19+CD27+ sEV were found in relapse vs remission ($p<0,005$). Higher CD19+CD200+ sEV levels were found in HV versus PwMS, independent of disease activity ($p<0,005$). Finally, our study revealed that anti-CD20 treatments alter these patrons.
Conclusions: Our study demonstrates that B-cell phenotypes could be used as potential activity biomarkers in MS, as PwMS in RP presented higher Bmem sEV in comparison with remission. Bmem in peripheral blood may prove useful for monitoring therapeutic effects in MS.

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Serum glial fibrillary acidic protein levels in clinically presumed MRI-negative attacks in neuromyelitis optica spectrum disorder

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Introduction: The blood glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) are biomarker candidates for disease activity in neuromyelitis optica spectrum disorder (NMOSD). However, their clinical significance in NMOSD is not fully understood.
Objectives: To evaluate the attack-discriminating potential of serum GFAP (sGFAP) and NfL (sNfL) in NMOSD.
Methods: We assessed sGFAP and sNfL levels in 15 sera obtained at a presumed relapse using single-molecule array technology. A presumed relapse was defined as the new symptom/sign appearance for*at least*48h, butMRI showed no new/enlarging T2 or T1-enhancing lesion. We also measured sGFAP and sNfL levels in serial samples from 17 patients: at remission (at least 6 months intervals from the prior attack), immediately before relapse, and at MRI-confirmed relapse. Normal-cutoff levels were selected based

on age categories in a 10-year range as ⩾3 standard deviations above the mean levels of 148 healthy controls.
Results: None of the 15 samples obtained at presumed relapses exhibited elevated sGFAP levels, while sNfL levels were elevated in two (13%) samples (19 pg/μL, and 23 pg/μL, respectively). In contrast, sGFAP and sNfL levels were markedly increased in 13 (76%) (median sGFAP level 7809 pg/μL [range, 240~62215]) and six (35%) (median 69 pg/μL, [range, 48~146]) of the 17 relapse samples, respectively. Intriguingly, six (67%) of nine samples obtained within 2 weeks before the attack showed elevated sGFAP levels (median, 643.5 pg/μL [range, 240~2860]), whereas all eight samples obtained 15-30 days before the attack were below the cut-off levels. sNfL levels were not increased in all samples obtained immediately before relapse but were increased in one sample. Remission samples also showed no increase in both sGFAP and sNfL levels, with one exception in sGFAP levels (256 pg/μL).
Conclusions: sGFAP levels were not elevated in clinically presumed MRI-negative attacks, while increased in majority of MRI-confirmed NMOSD attacks. Attack-related increases of sGFAP were seen 14 days before the relapse symptom onset. These results suggest sGFAP may serve as an attack-discriminating biomarker particularly when MRI is unavailable or negative.

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Clinical course of idiopathic acute transverse myelitis in adults with myelin oligodendrocyte glycoprotein antibody, aquaporin-4 antibody, and seronegative

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Introduction: Idiopathic acute transverse myelitis (IATM) comprises between 15 to 30% of cases of non-traumatic acute myelopathies that do not have a causal association. Most studies involve the Caucasian population in the Northern Hemisphere.
Objective and Aims: To investigate the frequency of AQP4-IgG and MOG-IgG and describe their influence on the clinical course and prognosis in a series of patients with IATM from Rio de Janeiro.
Patients and Methods: A longitudinal, translational study with retrospective data collection was performed to assess the clinical course of the IATM subgroups classified by the status of the biomarkers in the period from 2016 to 2021 at the Lagoa Federal Hospital (HFL). The autoantibodies were analyzed by the cell-based assay (CBA).
Results: Of the 588 patients tested for biomarkers, 70 had IATM. Women predominated (81.4%), Afro-descendants (55.7%), with disease onset in the fourth decade (31.4%), seronegative (72.9%) for both autoantibodies; AQP4-IgG + in 21.4% and MOG-IgG + in 5.7%. The first myelitis was partial (52.9%), with sensory (90.0%), motor (78.6%) and sphincter dysfunctions (54.3%); recurrences in 61.4%; median number of relapses was 2 (1-12). Treatment in the acute phase was methylprednisolone IV (68.6%); on prevention, immunosuppression (64.3%). On vertebral MRI, extensive lesions predominated (60.0%) in central axial topography (61.4%). Severe disability occurred in 38.6%, moderate in 25.7%, mild in 15.7%, and complete remission in 20.0%.
Conclusions: We confirmed a lower frequency of positivity for MOG-IgG compared to AQP4-IgG, similarly to what was found in the literature. Only four IATM cases were positive for MOG-IgG, and a comparison of groups was performed between those positive for AQP4-IgG and seronegative ones; Afro-descendants predominated among AQP4 positives and whites among seronegative; in AQP4 positive patients, there was more significant disability in the acute phase of the first TM as well as greater severity of motor and sphincter dysfunctions; the time of immunosuppression was longer in the AQP4 positive group as well as the spinal cord atrophy on MRI. The severity of neurological dysfunctions and long-term disability were not different in the groups. More long-term prospective studies are needed to investigate MOG-IgG-associated IATM and their prognosis.

Disclosure
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Cerebrospinal fluid B cell and neuroaxonal damage biomarkers: correlation with relapses and long-term disability in Multiple Sclerosis

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Introduction: It is of great importance to commence a high-efficacy drug at onset in those Multiple Sclerosis (MS) patients who are at greater risk of a more severe disease course before potentially irreversible damage occurs. Currently, several biomarkers informing on MS pathophysiology, with prognostic properties, can be measured at onset in cerebrospinal fluid (CSF).
Objective: Aim of the study was to assess the long-term prognostic role of multiple CSF biomarkers of B cell activation and of neuroaxonal damage, measured at disease onset, in a longitudinal cohort of MS patients.

Methods: The following biomarkers were measured on CSF, collected for diagnostic purposes and stored at -80°C: neurofilament light chain (NFL), tau protein, chitinase-3-like 1 protein (CHI3L1), CXCL13. Furthermore, IgG and IgM oligoclonal bands (OCB) were sought and kappa index (CSF/serum kappa free light chains divided by CSF/serum albumin) calculated. Biomarkers were correlated with the risk of reaching disability milestones (EDSS of 2,3,4 and 6 and a secondary progressive course), with the time to a relapse, the number of total relapses and with the use of a second-line treatment during follow-up.
Results: Ninety-six patients (61F, 35M, mean age: 34 ± 11 years) were followed up for a median of 135 months (IQR: 100-162). Over this period 34 patients reached an EDSS of 2, 12 of 3, 8 of 4 and only 1 of 6; 4 transitioned to a secondary progressive form and 25 initiated a second-line treatment. EDSS at last follow-up correlated with NFL (rho: 0.3, p=0.004) and CHI3L1 levels (rho=0.3, p=0.004). Baseline CSF NFL and CHI3L1 levels increased the risk of reaching an EDSS of at least 2 (p=0.018 and p=0.038, respectively), but only NFL of reaching an EDSS of at least 3 (p=0.037). CXCL13 and CHI3L1 (rho: 0.3, p<001 and 0.005, respectively) correlated with the number of relapses during follow-up and the time to a first relapse was influenced by high values (> median value) of CXCL13 (>14pg/ml) (p=0.043). NFL levels greater than 1000ng/L influenced the risk of initiating second-line treatment (OR 3.9, 95%CI: 1.5-10.7, p=0.007) and the time to its initiation (p=0.003).
Conclusion: CXCL13 was associated with an early occurrence of relapses and with the total number of relapses, while NFL was associated with long-term disability and predicted the use of second-line treatment during the disease course. This information can be useful during personalized treatment choices at disease onset.

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P264
Plasma cytokine release is differentially reduced in non-active primary Progressive multiple sclerosis with elevated oxidative stress levels in cerebrospinal fluid

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Introduction: Neurodegenerative progression in multiple sclerosis (MS) seems to be related to increased oxidative stress and disruption of pathways involved in mitochondrial homeostasis. A deeper understanding of these altered processes will facilitate distinction between relapsing-remitting (RRMS) and primary progressive (PPMS) phenotypes of the disease. This might, in turn, enhance prediction of the disease course, as well as contribute to improving patient care.
Objectives: Our aim is to identify differential patterns in plasma and cerebrospinal fluid (CSF) biomarkers of inflammation related to mitochondrial status and oxidative stress which could be used to discriminate between different MS phenotypes.
Methods: Plasma and CSF from 29 RRMS patients, 40 PPMS patients (32 non-active, 8 active) and 20 individuals with other neurodegenerative diseases (OND) were collected. Plasma pro-inflammatory cytokines were assessed using a multiplex assay. Oxidative stress in CSF was quantified by H_2O_2 concentration by luminometry. Analysis was performed by non-parametric or parametric tests based on normality.
Results: In plasma, increased levels of IFNα2 and MCP-3 were found in RRMS compared to non-active PPMS and OND ($p < 0.01$). IL-8 concentration was significantly higher in RRMS compared to non-active PPMS ($p < 0.05$), while IL-6 levels were higher in active PPMS compared to non-active PPMS ($p < 0.05$). In CSF, H_2O_2 concentration was significantly increased in non-active PPMS compared to all other groups ($p < 0.05$), but the most important difference was with RRMS ($p < 0.001$).
Conclusions: These results point to a differential release of several inflammatory and oxidative stress biomarkers, potentially related to mitochondrial status. Therefore, it could be helpful tools to differentiate RRMS and PPMS, as well as between active and non-active PPMS. However, further research must be performed to determine the mechanisms that are involved in altered mitochondrial activity during neurodegeneration.

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P265

Serum glial fibrillary acidic protein is associated with afferent visual system damage in neuromyelitis optica spectrum disorder only in eyes without prior optic neuritis

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Introduction: Aquaporin-4 immunoglobulin G associated neuromyelitis optica spectrum disorder (AQP4-NMOSD) is a relapsing autoinflammatory astrocytopathy frequently presenting with optic neuritis (ON). Astrocyte derived serum glial fibrillary acidic protein (sGFAP) is associated with disability and disease severity in AQP4-NMOSD and correlates with structural and functional measures of afferent visual system damage in non-ON eyes.

Objectives: To investigate sGFAP as a marker for attack-dependent and -independent afferent visual system damage in AQP4-NMOSD.

Aims: We assessed the association of sGFAP with retinal structural and visual functional changes in eyes with and without a history of ON in AQP4-NMOSD.

Methods: sGFAP was quantified by single molecule array assay in 33 clinically stable patients (time since last attack $>$ 2 months) with AQP4-NMOSD (22 eyes with (ON^+) and 34 eyes without (ON^-) a history of ON). Optical coherence tomography was conducted as a structural outcome, visually evoked potentials were assessed as a functional measure. Linear mixed models were applied and adjusted for age. To assess the inter-group difference between ON^+ and ON^-, interaction effects were calculated (interaction effect size measure: partial eta squared h_p^2).

Results: In patients with AQP4-NMOSD (median age = 50 years, female / male = 30 / 3, median time since last attack = 26 months), higher sGFAP is associated with thinner macular ganglion cell-inner plexiform layer (GCIPL), and thinner peri-papillary retinal nerve fiber layer (pRNFL), as well as with longer P100 latency in ON^- but not in ON^+ eyes (GCIPL, ON^-: standardized effect size (SES) = -1.11 [95% confidence interval: -2.02 – -0.20], ON^+: SES = -0.13 [-1.07 – 0.82], interaction: h_p^2 = 0.11, p = 0.03; pRNFL, ON^-: SES =-0.67 [-1.32 – -0.02], ON^+: SES = -0.02 [-0.71 – 0.67], interaction: h_p^2 = 0.06, p = 0.07; P100, ON^-: SES = 0.68 [0.00 – 1.36], ON^+: SES = 0.22 [-0.54 – 0.98], interaction: h_p^2 = 0.02,p = 0.27).

Conclusions: In AQP4-NMOSD, sGFAP is associated with afferent visual system neurodegeneration and demyelination in ON^- but not in ON^+ eyes. This suggests that sGFAP concentrations may reflect subclinical ongoing disease activity in clinically stable patients with AQP4-NMOSD.

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Csf and serum biomarkers in human neural stem cell-treated secondary progressive multiple sclerosis patients

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In the study of multiple sclerosis (MS) one of the most important challenges is finding specific biomarkers, as they are essential for predicting the progression of disability, monitoring the course of the disease and assessing the response to treatment. The aim of this study is the evaluation of potential biomarkers in the cerebrospinal fluid (CSF) and serum of patients with Secondary Progressive MS (SPMS), enrolled in the clinical trial EudraCT 2015-004855-37 (NCT03282760). The intent is to visualize any biomarker alterations following the implantation of human Neural Stem Cells (hNSCs) in the cerebral-ventricle to evaluate the response to treatment. The study was performed on fifteen patients treated with four different hNSC dosages, CSF and Serum samples were collected before treatment, at follow up (FU) 1, 3, 6, 9 and 12 months following implantation and were analyzed by microfluidic ultrasensitive ELISA (Biotechne, USA). The results shown that in the CSF at every time point, IL-2, IL-17a and TNF-a were below the detection limit: these molecules are indices of acute inflammation and for this reason are probably not significantly detectable due to the chronicity of the disease on the contrary, TNF-a was detected in serum therefore indicating a systemic inflammatory condition. OPN, CHI3L, Fractalkine and CCL2 were found in high levels both in serum and CSF. CCL3 and VEGF instead were more present in serum than in CSF and interestingly the healthy patients had the lowest concentration of CCL3. Fractalkine a powerful neuroprotector, instead has an unclear trend in serum but in the CSF has a drastic decrease in FU1 and following a sudden rise to FU6 and this could be an index of plaque ignition, data that would also justify the simultaneous raising of IL-8. OPN has an opposite trend: it presents peaks in correspondence of FU1 in the CSF and FU6 in serum. Although this is classically recognized as inflammatory molecule, many paper demonstrates that has an anti-inflammatory activity making us suppose an increase in relation to the treatment. Even though these are preliminary analysis, these could lead to think that the treatment with hNSCs may contribute to the decrease of biomarkers related to demyelination and chronic inflammation. The data obtained, although interesting, require further analysis, and to completely understand their significance, we will perform a statistical analysis and comparisons with clinical data after their full collection.

Disclosure

D'Aloisio Giada: nothing to disclose

P267

Diagnostic biomarker in cerebrospinal fluid in late-onset and progressive multiple sclerosis including the intrathecal fraction of free light chains kappa

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Introduction: An intrathecal humoral response is the characteristic diagnostic finding in cerebrospinal fluid (CSF) analysis of adult patients with multiple sclerosis (MS). As the average age of MS patients increases, the diagnosis and treatment of older MS patients becomes of great importance. Nevertheless, little is known about the sensitivity of diagnostic markers in the elderly and the changes in the humoral immune profile in older MS patients.

Methods: Retrospective observational study at two centers. As a newer diagnostic biomarker for MS diagnosis, intrathecal free light chains kappa fraction (FLCk IF) was studied in a large cohort of patients with early- and late-onset MS. A detailed humoral immune profile consisting of intrathecal immunoglobulin G, A, M and FLCk concentrations, oligoclonal band (OCB) pattern, and MRZ response was analyzed in this cohort with particular reference to different MS courses.

Results: While the frequency of positive OCB findings did not differ between early and late onset MS (99% vs. 97%) and relapsing (RMS) and progressive MS (PMS) (98% vs. 97%), the sensitivity of a positive FLCk IF was lower in PMS patients compared to RMS patients (98% vs. 91%, p=0.02). Late onset MS patients and PMS patients have lower absolute FLCk IF values than early onset and RMS patients ($p<0.001$), and thus are at higher risk for false negative FLCk IF findings. Type 3 OCB patterns are more common in older MS patients ($p<0.001$). PMS patients have higher local IgA concentrations than RMS patients (<0.001), while local IgM concentrations are higher in MS patients with early disease onset ($p<0.001$). MRZ reaction was positive with equal frequency in MS patients with early and late disease onset (61% vs. 59%, p=0.75) and in RMS and PMS patients (64.8% vs. n=94, 59.1%, p=0.521).

Conclusion: OCB are slightly superior to FLCk IF in late onset and progressive MS in terms of sensitivity for detecting intrathecal immunoglobulin synthesis. MRZ reaction as the most specific parameter for MS is also applicable in patients with late onset and progressive MS.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The diagnostic utility of kappa free light chains in people with multiple sclerosis and other neuroinflammatory disorders

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Introduction: Multiple sclerosis (MS) is diagnostically characterized by an intrathecal immunoglobulin (Ig) G synthesis as detected by cerebrospinal fluid (CSF)-restricted oligoclonal bands (OCB). Kappa free light chains (KFLC), a byproduct of Ig synthesis by plasma cells, have been proposed as an additional biomarker for the detection of an intrathecal Ig synthesis. However, KFLC analysis has not yet been included in routine diagnostics, since many unanswered issues remain.
Objectives/aims: The aim of the present study was to investigate the influence of various pre-analytic factors, to compare different interpretation methods for KFLC in CSF/serum sample pairs, and to clarify the role of KFLC concentrations in neuroinflammatory diseases.
Methods: Concentrations of KFLC were determined using a nephelometric assay (N-Latex, Siemens) and CSF-specific OCB by isoelectric focusing on polyacrylamide gels with consecutive silver staining in CSF/serum sample pairs from patients with various neurological diseases including MS (n=971). KFLC were interpreted according to the approaches of different authors (Reiber's non-linear diagram, linear KFLC index, Presslauer's exponential function, Senel's linear function). In addition, different pre-analytic influencing factors (immunomodulatory therapies, storage conditions, blood contamination in CSF, renal function impairment) were investigated (n=505).
Results: In MS patients, the prevalence of CSF-restricted OCB was very high at 99% (n=119/120). The diagnostic sensitivity of intrathecally produced KFLC interpreted according to the Reiber diagram was also high at 98% (n=118/120). Applying the KFLC index cut-off of 5.9 and the formulas according to Presslauer and Senel to determine an intrathecal KFLC synthesis, high values with 96% (115/120) were also yielded. Similarly, intrathecal KFLC synthesis could be detected in other neuroinflammatory diseases using the Reiber diagram, and a comparable high sensitivity as intrathecal IgG detection by CSF-restricted OCB could be shown. Except for renal function impairment and steroid therapy, the other pre-analytical factors did not influence KFLC results.
Conclusions: OCB determination in MS showed the highest diagnostic sensitivity with respect to the detection of an intrathecal IgG synthesis. Using Reiber's diagram for KFLC, similarly high values were found. Thus, KFLC represent an additional diagnostic biomarker to measure intrathecal Ig synthesis in neuroinflammatory diseases.

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Using serum metabolomic signatures to classify multiple sclerosis progression using machine learning models

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Introduction: Currently, there are no blood-based biomarkers for multiple sclerosis (MS) diagnosis or to differentiate between relapsing-remitting (RRMS) and progressive (PMS) disease phenotypes (patients with primary or secondary MS combined). Serum metabolites have been associated with MS disease activity, therefore a comprehensive metabolomic and machine learning (ML) analysis was used to define serum biomarkers associated with MS disease, MS disease progression and to investigate potential underlying mechanisms of progression.
Methods: Serum metabolites (n=250) were quantified by Nightingale Health using NMR-spectroscopy from 128 MS patients and 80 matched healthy controls. Data was analysed using supervised ML models including logistic regression (LR), LR with interactions, sparse partial least squares discriminant analysis, and ensemble methods bagging and boosting LR for classification of patient groups. Metabolites were ranked by variable importance and top metabolites were used for metabolite set enrichment analysis (MSE).
Results: Boosted LR stratified RRMS from PMS patients with the highest accuracy (96.8%). Furthermore, metabolomic signatures specific to RRMS and PMS when compared with healthy donors were also defined, revealing significant elevations in ketones and apolipoprotein(Apo)B/ApoA1 and reductions in glucose, fatty acid ratios and amino acid (aa) metabolism in PMS compared to RRMS. MSE analysis identified valine, leucine, and isoleucine biosynthesis (p-adj: 3.54E-03) to be specific to RRMS. In PMS, identified metabolites were over-represented in phenylalanine, tyrosine and tryptophan biosynthesis (p-adj: 3.87E-02), pyruvate metabolism (FDR: 2.39E-02) and glycolysis/gluconeogenesis (FDR: 2.39E-02).
Conclusions: These results suggest a potential energy shift from glycolysis towards increased gluconeogenesis and ketogenesis, supported by increased fatty acid β-oxidation and conversion of ketogenic and gluconeogenic aa, phenylalanine and tyrosine in PMS. This may be linked to progression, whereby as MS progresses, the brain becomes reliant on ketones as alternative energy sources. Lastly, phenylalanine and tyrosine (known dopamine precursors) reductions may link to lowered dopamine levels and dopaminergic abnormalities in T cells, previously observed in MS patients. Taken together, if validated these metabolites could be potential MS and progression biomarkers and support a role for dopaminergic therapeutics in MS.

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P270

Neurofilament light chain and platelet-derived growth factor receptor β for monitoring disease activity in relapsing-remitting multiple sclerosis: a prospective single center study

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Introduction: Neurofilament light chain (NfL) is a biomarker of axonal damage which mainly reflects disease activity in relapsing-remitting multiple sclerosis (RRMS). Platelet-derived growth factor receptor β (PDGFRβ) is a neurotrophic factor that may promote repair during the post-acute phases of CNS damage and could be involved in clinical recovery. When measured in CSF, it has also been suggested a marker of blood-brain barrier function. Our aim was to determine the levels of NfL and PDGFRβ in serum and CSF in RRMS patients with recent disease activity.
Method: This prospective cohort study included 44 patients with suspected or known RRMS with recent relapse or contrast-enhancing lesion (CEL) on brain MRI and 89 healthy controls (HC). Serum and CSF samples were obtained at baseline and patients were prospectively followed during a period of 55 weeks. Serum NfL (sNfL) concentration and NfL in CSF were measured with an ultrasensitive Single molecule array (Simoa) assay; PDGFRβ in serum and CSF were measured with ELISA.
Results: In the study population of 44 RRMS the median concentration of sNfL at baseline was 12.1 ng/L (IQR 8.4-23.5), peaked week two at 14.4 ng/L (9.4-25.7, p=0.004) and reached the lowest value 9.3 ng/L at week 28 (IQR 6.3-19.3, p=0.005). In patients included due to ongoing clinical relapse without CEL on MRI (n=17), median sNfL showed an increase from baseline (8.8 ng/L, IQR 8.0-12.7) peaked at week eight (13.3 ng/L, IQR 10.2-16.1) and decreased at week 55 at the end of the study (6.9 ng/L, IQR 4.8-9.4). In patients with CELs but without relapse (n=5) and in patients with clinical relapse and CELs (n=22), sNfL showed similar change over time from baseline (14.2 ng/L, IQR 11.5-31.6)

peaked at week four (20.1 ng/L, IQR 8.3-40.6) and declined at the end of the study (10.6 ng/L, IQR 6.9-20.5). There was a weak but significant correlation between sPDGFRβ and sNfL (r=0.176, p = 0.008), and a stronger correlation between sPDGFRβ and the number of CELs on MRI (r=0.483, p= 0.001). However, disease activity had no significant influence on the concentration of sPDGFRβ. The median concentration of sPDGFRβ at baseline was 7.1, IQR 5.7-8.1 ng/mL in HC and 7.0, IQR 6.1-8.3 ng/mL in MS (p=0.302)

Conclusion: Repeated sNfL samples showed an initial increase followed by a gradual decrease. PDGFRβ concentrations in serum did not show the same pattern as sNfL. The results of this study support using sNfL as a biomarker of ongoing disease activity in MS.

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Imaging and non-imaging biomarkers - Other Biomarkers

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Visual magnetic evoked responses as a biomarker of functional changes after an acute optic neuritis

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Introduction: Optic neuritis (ON) is frequently studied in remyelination trials as optic nerve pathology, can be easily accessible through visual evoked potentials (VEP) and MRI. However, they do not fully reflect ON-induced changes. Magnetoencephalography (MEG) is a non-invasive technique to investigate whole cortex activity with a very high temporal resolution, thus appropriate to track functional changes.

Aim: To investigate magnetic evoked response as a biomarker of functional changes in visual pathway after ON.

Method: Twenty patients with ON (<3 months) and 10 controls underwent: i) standard visual testing including VEP; ii) brain 3T MRI for coregistration with MEG data and sequences for optic nerve assessment; iii) MEG protocol including visual stimulation with alternating checkerboards to generate a magnetic evoked response in monocular condition. Each trial was repeated twice for reproducibility. Magnetic response was recorded using 306 sensors to accurately reconstruct brain activity in different regions.

Results: Magnetic evoked responses were obtained through the visual cortex in all controls and all patients except for 2 patients with a very severe visual impairment. Magnetic P100 wave latencies (mP100L) were retrieved from the primary visual cortex (V1).

Mean mP100L in V1 was 87 ms (SD 32) in controls, 100 ms (SD 25) for the fellow eye (FE) and 115 ms (SD 34) for the affected eye (AE) in patients.

In addition to mP100L lengthening, the N75 wave disappeared in 5 patients for the AE.

The evoked responses for AE were transmitted from V1 to extrastriate visual areas including the lateral occipital cortex (role in shape recognition) and the mediotemporal area (role in motion processing) similarly to healthy eyes without additional delay or distortion.

mP100L in V1 were reproducible across 2 trials with excellent intraclass correlation coefficient (ICC) for both FE and AE (ICC=0.95, 95%CI [0.88-0.98] for FE and ICC=0.99, 95%CI [0.99-1.00]).

Moreover, mP100L correlated with VEP (ICC=0.72 for AE, 95%CI [0.43-0.93]; ICC=0.86 for FE, 95%CI [0.74-0.90]) and with lesion length of the optic nerve measured on MRI (r=0.74, 95%CI [0.51-0.87]).

Conclusion: MEG is a promising technique to follow cortical functional changes occurring after ON, allowing to localize and quantify precisely cortical response to standard visual stimulation with very good interrater reliability. MEG could be an interesting surrogate of demyelination and remyelination in clinical trials.

Disclosure

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Role of circulating extracellular vesicles as specific biomarkers of multiple sclerosis

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Background: Blood-derived extracellular vesicles (EVs) are heterogenous groups of membrane-bound particles secreted by almost all cell types that contain information on the pathological processes of Multiple Sclerosis (MS).
Aims: The goal of the present study is address blood EVs originating from the nervous and immune system cells to obtain in-depth information about the processes taking place in MS and about their disease-associated specificity as biomarkers.
Methods: We isolated total EVs from the blood of 86 MS patients, 46 controls suffering non-neurological autoimmune disease [rheumatoid arthritis (RA)], 23 controls with non-immune-triggered white matter lesions [subcortical stroke (SS)] and 29 healthy controls (HCs). We pulled-out neuron-derived EVs (NEVs), T and B lymphocytes-derived EVs (TLEVs and BLEVs) by immunoprecipitation. EV levels were analyzed by Nanosight. Mass spectrometry-based proteomics was used to analyze the EV protein content.
Results: Lower levels of NEVs (p=0,017) were found in MS compared to RA patients. These NEVs from patients with MS showed lower levels of C-reactive protein and complement components compared to AR. Higher levels of BLEVs (p=0,001) and lower levels of TLEVs (p=0,001) were found in MS when comparing to SS patients, carrying higher levels of C4BP, complement factors and mannose-binding protein. Lastly, lower levels of BLEVs (P=0.004), TLEVs (P=0.004), and higher levels of NEVs (P=0.010) were found in MS compared to HCs, bringing higher levels of Properdin, CD5 antigen like and Gelsolin proteins.
Conclusions: Levels of nervous system-derived EV subpopulation was able to reflect the white matter involvement of MS when compared to no-neurological autoimmune disease and HCs, while those B and T-lymphocytes EVs highlight the implication of immune system in MS in contrast to non-immune-triggered white matter lesions and HCs. Protein analysis reflects that these circulating EVs may play important roles in host innate immunity, complement system activation and inflammation processes in MS.

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Immune and nervous system-derived Extracellular Vesicles could act as diagnostic biomarkers and may provide information on disease activity and neurological dysfunction in multiple sclerosis

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Background: Biomarkers have become to be important tools to support diagnosis and clinical decision-making process in Multiple Sclerosis (MS). In this regards, blood-derived Extracellular Vesicles (EVs) largely reflect processes that take place in their parent cells during MS and could provide information on clinical settings, emerging as potential biomarker in this demyelinating disease.
Methods: Blood-derived EVs from 86 Multiple Sclerosis patients (MS) and 29 healthy controls (HC) were isolated from neurons, oligodendrocytes, B and T lymphocytes by immunoprecipitation. The levels and size of EVs have been studied by Nanosight. EVs antibodies content was measured by ELISA. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic efficacy of circulating EVs-derived antibodies content in Multiple Sclerosis. Correlations between the circulating EVs characteristics and clinical settings (disease activity, lesion volume and neurological dysfunction) were also evaluated. EV protein content was analyzed by mass spectrometry-based proteomics.
Results: Patients with relapse showed higher size of B Lymphocyte-derived EVs compared to patients with no active disease. Patients with new MRI lesions showed higher size of Neuron-derived EVs (p=0.05). EV size from oligodendrocyte correlated with lesion volume and neurological dysfunction (using

EDSS and symbol digit test) (p=0.002, p=0.001, p=0.001, respectively). Analyzing their content, we found the anti-MBP antibodies levels significantly higher in MS patients than in HC. ROC curve analysis of these anti-MBP antibodies (AUC=0.96) indicated a cut-off value of 2.94 ug/ml (sensitivity: 96,3%, specificity: 88%). Moreover, higher levels of C1q, AMBP, Attractin and LRG1 were found in EVs from patients with active disease compared to those with stable disease. These proteins are involved in the complement system, macrophage activation, remyelination and angiogenesis, respectively.

Conclusions: Anti-MBP antibodies expression in B lymphocyte-derived EVs could be a potential auxiliary diagnostic biomarker for Multiple Sclerosis. Levels and size characteristics of immune system-derived EVs may reflect disease activity, while neuron and oligodendrocyte-derived EVs inform about brain damage, cognitive and motor dysfunction in MS patients. EVs from MS patients with active disease may be implicated in immune system activity and brain repair mechanisms.

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P274

Bedside digital videooculography could be a biomarker of neurodegenerescence in early multiple sclerosis patients

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Introduction: We previously reported that video oculography (VOG) could highlight subclinical eye movement abnormalities (EMA) in patients with multiple sclerosis (MS) or radiologically isolated syndrome (RIS) without correlation to brain MRI T2 lesion load (LL).

We also demonstrated that eVOG, a home-developed iPad application, could be a reliable and mobile tool to detect eye movement abnormalities (EMA) compared to VOG.

Objectives: To evaluate whether eVOG could be relevant as a bedside tool to assess patients with MS or RIS.

Aims: To assess correlations between EMA and MRI parameters, particularly global and regional brain atrophy.

Methods: We conducted a monocentric, prospective, transversal study including patients with MS or RIS. Each patient was assessed with eVOG to detect abnormalities regarding horizontal or vertical saccades, smooth pursuit or antisaccades. The presence of fixation abnormalities such as square wave jerks were also detected.

Each patient had a brain MRI including a 3D FLAIR sequence which was analyzed using volBrain software to obtain regional volumetric measures of 135 brain structures and T2 lesion load (LL) volume.

Results: 44 patients were included (24 MS/20 RIS, mean age 46.4 yrs (26-70); F/M 1.6, mean EDSS 1.9 (0-6)

Patients had an average of 2.5 EMA, and 35 patients had at least 2 EMA.

28 patients had smooth pursuit impairment (SPI). In comparison with patients without SPI, we found significant difference regarding global brain volume (1153 vs 1226cm3, $p = 0.04$), and particularly cerebellar vermis (p=0.005), thalamus (p=0.03), and supplementary motor cortex (p=0.007).

No other correlation was found regarding other brain structures, other EMA and global or regional T2-LL.

Conclusions: Detection of SPI using eVOG was associated with increased regional brain atrophy in specific areas involved in the control of eye movements.

eVOG could be an easy to deploy bedside tool to detect RIS or MS patients with significant neurodegenerescence.

Disclosure

Authors have nothing to disclose in relationship with this study

P275

Digital biomarkers are associated with regional brain atrophy in radiologically isolated syndrome

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Introduction: We previously reported that a fast digital neurological assessment using a home developed mobile application called MS Screen Test (MSST) could highlight subclinical differences between subjects with a radiologically isolated syndrome (RIS) compared to matched healthy controls (HC)

Objectives: To evaluate whether MSST could be a relevant tool to assess RIS subjects.

Aims: To assess correlations between digital biomarkers and MRI parameters, particularly global and regional brain atrophy.

Methods: This is a post hoc analysis of a previously reported cross sectional, mono centric study involving RIS subjects that were evaluated with MSST application including a fast evaluation of finger tapping, hand synchronization, low contrast visual acuity (LCVA) and reaction time during a vision-based cognitive task.

Each subject had a brain MRI including a 3D T1 sequence which was analyzed using volBrain software to obtain regional volumetric measures of 135 brain structures.

Results: 21 RIS subjects were included (mean age 44 yrs (25-56); F/M 2)

Cerebellar gray matter volume was positively associated with finger tapping speed for dominant hand ($r = 0.57$; $p = 0.007$), and negatively associated with inter hand interval at the hand synchronization test ($r = -0.59$, $p = 0.03$)

Occipital lobe volume was positively associated with LCVA score ($r = 0.48$, $p = 0.02$) and negatively associated with reaction time ($r = -0.5$, $p = 0.02$) at the vision-based cognitive task
Left thalamus volume was positively associated with LCVA score ($r = 0.49$, $p = 0.02$)
We found no other statistical correlations regarding other brain structures and observed effect was independent of age.
Conclusions: Digital biomarkers may reflect neurodegenerative process in RIS subjects.
A prospective study is ongoing to confirm those findings on a larger cohort and evaluate the prognostic value regarding the risk on conversion to multiple sclerosis.

Disclosure
Authors have nothing to disclose in relationship with this study

P276
Molecular imaging of microglia activation in patients with multiple sclerosis before and after high efficacy treatment with ocrelizumab

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Background: Magnetic resonance imaging (MRI) visualise unspecific structural changes in the central nervous system (CNS) of patients with multiple sclerosis (MS), but is not a specific biomarker for CNS neuroinflammation. The 18-kDa translocator protein (TSPO) is a mitochondrial membrane protein upregulated in brain-resident activated microglia in MS pathology. The single photon emission computed tomography (SPECT) tracer [123I]-CLINDE binds to the TSPO-receptor and can be used to directly visualise and quantify microglia activation.
Aim: To test microglia activation as a clinical biomarker for disease activity and treatment efficacy.
Method: Nine MS patients (67 % women) with aggressive relapsing-remitting MS (RRMS) were included in this study. [123I]-CLINDE-SPECT, MRI and expanded disability status scale (EDSS) were performed before and six months after start of treatment with Ocrelizumab. The patients were genotyped for the TSPO polymorphism rs697. SPECT images were co-registered with corresponding T1 3D-MRI using manual interactive overlay and regions of interest (ROIs) were delineated automatically for anatomical ROIs and MS lesion ROIs were delineated manually. ROIs were defined as whole brain, cortical grey matter, deep grey matter, white matter, brain stem and cerebellum. MS lesions were all inspected and ROI's manually corrected if necessary. The volume of distribution (VT) for every ROI were used to quantify [123I]-CLINDE-binding to TSPO.
Results: Median age was 34 years (IQR 14.5), median disease duration 22 months (IQR 93) and median EDSS score was 3 (IQR 1.5). VT of [123I]-CLINDE-SPECT were statistically unchanged both globally as well as in predefined ROIs and in MS lesions after treatment with Ocrelizumab. We found relative VT increase in three patients, three had unchanged levels, and three had decreased levels, the latter three being the only decreases in EDSS score within a year after start of treatment. We found no statistical relationship between VT and EDSS changes.
Conclusion: Our study showed unsignificant changes and a heterogenic pattern of TSPO binding in MS patients after treatment with ocrelizumab with no evident clinical correlate on a group level. Due to methodological challenges and a small cohort, data might not be sufficient to exclude [123I]-CLINDE-SPECT as a possible clinical biomarker for disease activity and treatment efficacy in patients with MS.

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P277
Ageing and multiple sclerosis, a prospective study

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Introduction: Life expectancy of persons with multiple sclerosis (PwMS) has been rising, making it essential to gather information on elderly patients.
Objective: To compare baseline clinical, hormonal, and radiological parameters of a prospectively followed-up cohort of older versus young PwMS.
Methods: Prospective two-year study including PwMS. Patients were divided into younger (18-35 years) and older (>50 years) age groups. Demographic data and presence of comorbidities were assessed. Disease-modifying therapies (DMTs) were classified as low efficacy (LE; interferons, glatiramer acetate, teriflunomide, and dimethyl fumarate) or high efficacy (HE; fingolimod, cladribine, monoclonal antibodies). Each visit included physical and cognitive evaluations, 3T brain MRIs post-processed with Deep Learning Software, retinal nerve fiber layer (RNFL) measurement, TSH and vitamin D levels. Stata program version 15 (Statacorp) was used for statistical analysis. Independent t-tests and Pearson's correlation coefficient were used for assessment of continuous variables; chi-squared test for categorical data and Mann Whitney for non-parametric variables.

Results: As of May 2022, 92 patients had been included, 56 younger and 36 older patients (58% female). Mean disease duration was 5 vs 4 years, respectively. Comorbidities were more common in older adults (61.1% vs 19.6%). Aging patients received LE DMT (63.8%) more often, whereas younger patients received HE DMT in 58.9% of cases (p=0.05). At study entry, EDSS, T25F, 9HPT, mean RNFL thickness, vitamin D and TSH levels were similar in both groups. Significant differences were found in whole brain volume (WBV), gray matter volume (GMV), and CSF volume (CSFv) between younger and older pwMS (WBV 1190 vs 1114 cm3 p=0.03; GMV 670 vs 604 cm3 p=0.009; CSFv 326 vs 349 cm3 p=0.04, respectively). Thalamic atrophy was significant in both groups (44.6 vs 33.3%). However, global atrophy was only observed in younger patients (10.7 vs 0%) ($p<0.05$), and poorer performance in all cognitive domains except for verbal fluency was seen in older pwMS, ($p<0.05$). Interestingly, we found correlation between disability scales (EDSS, T25F and 9HPT) and executive functions only in young patients (rho= 0.37).
Conclusion: Our study characterizes two cohorts of adult PwMS of different ages but similar disease duration. Comparison between them should allow better understanding of the course of the disease and of the real impact of aging on MS.

Disclosure
Dr Marcela Fiol has received fees for educational presentations and/or conference attendance from Merck-Serono Argentina, Biogen-Idec Argentina, Genzyme Argentina, Bayer Inc, Novartis Argentina, Roche Argentina and TEVA.
Dr Jorge Correale In recent years has received financial compensation for academic presentations, and attended advisory boards from: Biogen, Merck, Novartis, Roche, Bayer, Sanofi-Genzyme, Gador, Raffo, Bristol Myers Squibb, and Janssen.
Dr Celica Ysrraelit has received reimbursement for developing educational presentations, attendance to advisory boards and travel/accommodations stipends from Merck-Serono Argentina, Biogen, Genzyme Argentina, Bayer Inc, Novartis Argentina, TEVA and Roche Argentina.
Dr Mariano Marrodan has received fees for educational presentations and/or conference attendance from Merck-Serono Argentina, Biogen-Idec Argentina, Novartis Argentina, Gador and Roche Argentina.
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P278
The eye as a digital biomarker for multiple sclerosis: oculomotor behaviours yield a novel digital biomarker for detecting and monitoring high-level motor and cognitive alterations

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Introduction: The eyes hold a key to unveil motor and cognitive manifestations of Multiple Sclerosis (MS) pathology. Eye movement analysis provide considerable insight beyond the integrity of control circuits and descending motor pathways in MS. They could also provide valuable information concerning the relationship of cognition on movement control and motor function.
Objectives: There is a need for more robust and automatic methods that can provide affordable solutions for monitoring the progression of MS.
Aims: To provide affordable solutions for monitoring the progression of MS from Relapsing Remitting to Secondary Progressive. .
Methods: A sample of 40 MS patients from Bahia Blanca, Argentina, entered the study. From the 40 patients 35 were Relapsing Remitting (RR) and 5 were Secondary Progressive (SP). The EDSS mean score in RR was 2.0 (SD=1.4); and in SP the mean score was 4.9 (SD= 1). MS patients were assessed with the N-Back task (NBKT) coupled with an Eye Tracking (ET) device. The NBKT assesses the ability to visualize and store three circles that were presented sequentially in three different places through the screen device (encoding time). In a second stage, subjects had to remember where the circles had been presented and in what order (recognition time). Oculomotor behaviours recorded using ET were subjected to ViewMind's modelling.
Results: Relative to SP, RR patients displayed shorter fixation durations ($p<0.0001$) and larger saccades ($p<0.0001$). Further, RR patients displayed significant differences between them when considering fixation duration and saccades ($p<0.0001$ and $p<0.0001$, respectively). Finally, when analysing within RR patients we find a strong correlation between fixation duration, saccade amplitude and the time from when the pathology was clinically diagnosed (in years) ($p<0.0001$ and $p<0.001$, respectively).
Conclusion: Taken together, the results above suggest that ViewMind's eye-tracking analysis combined with NBKT can (1) enrich the identification of clinical features in MS, (2) unveil novel features of MS unknown to date, and (3) provide more sensitive tools which can monitor and trace motor and cognitive aspects of patients at risk of progression from RR to SP.

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P279
Early prediction of multiple sclerosis using scanning laser ophthalmoscopy (SLO) video sequence data with a Deep Learning (DL) based approach

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Introduction: Multiple Sclerosis (MS) is a chronic immune-mediated inflammatory disease (IMID) of the central nervous system (CNS). Early identification of MS, especially as a screening method for at-risk individuals, is crucial to delay disease progression and improve patient outcomes by preventing future irreversible neurologic damage. In this work, we utilize well-validated tracking scanning laser ophthalmoscope (TSLO) image to predict MS compared to the unaffected controls. While traditional Machine Learning (ML) methods, such as Logistic Regression (LR), have demonstrated a strong predictive power [Mauro F. Pinto et al., 2020] in disease identification, we propose the use of a novel DL based model. Though the use of Deep Neural Network (DNN), this model can have a much higher learning capacity to capture latent features embedded in the retinal images. We hypothesize that such latent information, often hidden in ML feature engineering processes, plays an important role for the prediction of disease and can be well represented by DL models.
Objectives: To establish a DL based model capable of learning latent image features to provide predictive power for the presence of MS.
Aims: Utilize a deep convolutional neural network to extract the retinal coding and implement a recurrent neural network to learn the temporal correlations in video sequences.
Methods: Our approaches were tested using a 250-subject MS/control database collected at the UCSF. Patients with Expanded Disability Status Scale (EDSS)< 4 are compared to healthy subjects. Both raw retinal images and the frequency and spatial patterns of the eye motion are combined to construct a hybrid image, denoted as "retinal coding", and directly fed to the DL model for training and testing.
Results: Preliminary results on predictive power were measured using Area-under-Curve (AUC) of the Receiver Operating Characteristics (ROC) curve, sensitivity, and specificity, as well as an F-1 score. We observe an AUC of 0.920, sensitivity of 0.90, specificity of 0.89 and F-1 score of 0.89 using the DL model to distinguish MS from controls, which outperforms the baseline LR model by 24%.
Conclusions: This work can be considered as a proof-of-concept concerning the possibility of identifying MS disease using a DL based approach. The results demonstrate the possibility of predicting early-stage MS and understanding disease's dynamics. Such end-to-end model could be generalizable and trained on other disease states.

Disclosure
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P280
Visual and motor evoked potentials in experimental autoimmune encephalomyelitis

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Introduction: Experimental autoimmune encephalomyelitis (EAE) is associated with abnormalities in motor (MEP) and visual (VEP) evoked potentials and neuroretinal thinning at optical coherence tomography (OCT), consistently with clinical symptoms observed in multiple sclerosis.
Objectives and aims: To understand the time course of visual and motor abnormalities in EAE for translational monitoring of novel therapeutic strategies.
Methods: We performed VEP, MEP and OCT in 30 C57BL/6 mice immunized with MOG 35-55 (vs 10 controls), at 7, 14 and 31 days post-immunization-dpi (10 mice sacrificed at each timepoint-dpi). We report electrophysiological and OCT data. Histological analyses are intended to validate functional outcomes.
Results: Compared with controls, EAE mice had delayed VEPs at all consecutive time points (p=.00009, p=.014, p<.001, respectively; Student's t-test) and reduced neuroretinal thickness at 7 (p=.003) and 31 dpi (p=.013). Whilst MEPs in EAE did not significantly differ from controls at 7 and 14 dpi, at 31 dpi, MEPs were delayed in 5 hindlimbs of 4 mice (1 bilateral, 3 unilateral) and absent in 10 hindlimbs of 6 mice (4 bilateral, 2 unilateral). Regarding the appearance of functional visual and motor abnormalities, abnormal VEPs were more frequent compared with MEPs at 7 dpi (56.7% eyes vs 6.7% hindlimbs, p<.001, McNemar's test), at 14 dpi (35% vs 10%; p =.031), and at clinical onset (13, 15 ±0.95 dpi, 42.5 % vs 10.5%, p=.004). There were no longer significant differences between the percentage of abnormal VEPs and MEPs at 31 dpi (55.6% vs 83.3% respectively; p=.227). The early discrepancy between visual and motor involvement was accompanied by significant demyelination in EAE optic nerves at 7 dpi, whilst no damage was found in spinal cords.
Conclusions: VEPs abnormalities appear before electrophysiological or clinical motor involvement, pointing to the relevance of electrophysiological measures to detect early, subclinical demyelination as a potential target of novel therapeutic approaches targeting inflammation, demyelination, and neuroaxonal loss.

Disclosure
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P281
Pain and the Brain: pain shifts the balance of Brain excitability in multiple sclerosis

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Introduction: Central neuropathic pain is a common and debilitating feature of multiple sclerosis (MS) that may be related to defective neuronal conduction. A greater understanding of central neuropathic pain in MS is critical to improving current therapies. The literature reports aberrant corticospinal tract excitability in

chronic neuropathic pain; however, this has not been well characterized in MS. Transcranial magnetic stimulation (TMS) is a non-invasive tool that is well suited for exploring corticospinal function.

Objectives/aims: We aimed to investigate relationships between TMS-derived markers of corticospinal excitability and pain in a sample of MS patients.

Methods: In this cross-sectional study, 64 persons with MS self-reported pain on a visual analog scale. Usage of neuropathic pain medication was retrieved from the participants' medical charts. TMS was used to characterize participants' corticospinal excitability. Specifically, motor evoked potential (MEP) amplitude and cortical silent period were plotted to index overall excitability and inhibition, respectively. Other extracted measures included MEP latency and active motor threshold.

Results: Fifty-five percent of participants reported pain and 30% were taking at least one pain medication (age: 47.69 ± 10.3 years; disease duration: 14.7 ± 8.0 years; EDSS: 2.0 ±1.0; female/male: 46/18; relapse-remitting/progressive: 57/7). Participants who reported pain had lower corticospinal excitability ($p = .019$) and greater inhibition ($p = .021$) than those without pain. Moreover, corticospinal excitability significantly predicted pain levels, after controlling for MS disability (EDSS) and medication use ($R^2 = 0.16$, $p = .021$).

Conclusions: More than half of MS patients reported pain that impacts their daily life. Reduced corticospinal excitability in these individuals was a significant predictor of pain. Reduced corticospinal excitability, indexed using TMS, may thus be a marker for the neuropathophysiology of central neuropathic pain in MS.

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Therapy - Immunomodulation/ Immunosuppression

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Immunadsorption versus double-dose methyl prednisolone in steroid-refractory multiple sclerosis relapses: results from the INCIDENT-MS study

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Introduction and Objectives: Intravenous methyl prednisolone (IVMPS) is treatment-of-choice for acute multiple sclerosis (MS) relapses. However, up to 25 percent of patients remain with significant disability following treatment and thus, these relapses are deemed "steroid-refractory". Immunoadsorption (IA) has entered clinical routine as rescue therapy yet controlled trials comparing safety, effectiveness or even mechanism-of-action are missing.

Aims: To compare safety and effectiveness of IA versus IVMPS in acute MS relapses.

Methods: We enrolled patients with significant persisting disability following a first course of IVMPS defined as a post-treatment increase of respective function system score of at least 1 point into this prospective observational study. These patients either received six courses of tryptophan-immunoadsorption or a second course of IVMPS (double-dose, 5x2000mg). Patients were intensively monitored for safety and effectiveness outcomes and we included evoked potentials and neurofilament light-chain (NFL) serum level quantification. Furthermore, we performed extensive peripheral blood immunophenotyping using multi-panel flow cytometry and Olink® proteomic analysis(NCT04450030).

Results: Of 86 patients initially screened, 42 patients were enrolled from August 2018 to August 2020. 26 patients underwent double-dose IVMPS and 16 patients received IA. Upon discharge, adjusted odds ratio for any treatment response towards escalation treatment was 10.7 favouring IA ($p=0.005$). Upon 3-months follow-up, odds ratio for best clinical response was 50.7 favouring IA ($p<0.001$). Similar findings were made regarding evoked potentials and NFL levels. Immunophenotyping showed a prominent reduction of several B cell subsets following IA treatment which was closely correlated to treatment response whereas such effect was absent following IVMPS treatment. Accordingly, IA reduced serum levels of various pro-inflammatory cytokines involved in B cell-maturation or activation.

Conclusion: The use of tryptophan-immunoadsorption showed favourable outcomes compared to a second course of IVMPS in patients with steroid-refractory MS relapses. We observed no new security signals for IA treatment which was generally well-tolerated whereas our study underlines serious risks of double-dose IVMPS including infections or even psychosis. Findings from immunologic analyses underline a potential role for B cells in relapse pathology and warrant further evaluation.

Disclosure

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Conflicts of interest:

Steffen Pfeuffer: received travel grants from Sanofi Genzyme and Merck Serono, lecturing honoraria from Sanofi Genzyme, Mylan Healthcare, and Biogen, and research support from Diamed, Merck Serono, and the German Multiple Sclerosis Society Northrhine-Westphalia.
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Heinz Wiendl: received compensation for serving on Scientific Advisory Boards/Steering Committees for Bayer Healthcare, Biogen Idec, Sanofi Genzyme, Merck Serono, and Novartis. He received speaker honoraria and travel support from Bayer Vital GmbH, Bayer Schering AG, Biogen, CSL Behring, EMD Serono, Fresenius Medical Care, Genzyme, Merck Serono, Omniamed, Novartis, and Sanofi Aventis. He received compensation as a consultant from Biogen Idec, Merck Serono, Novartis, Roche, and Sanofi-Genzyme. Heinz Wiendl also received research support from Bayer Healthcare, Bayer Vital, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, Sanofi US, and Teva.

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Ocrelizumab and hypogammaglobulinemia: a real-world retrospective MS cohort study

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Introduction: Ocrelizumab is an effective anti-CD20 therapy approved for Relapsing Remitting (RRMS) and Primary Progressive Multiple Sclerosis (PPMS). In the OPERA and ORATORIO clinical trials, infections were among the most frequent side effect. Extension studies revealed a proportion of patients with hypogammaglobulinemia which could contribute to infection risk.
Objective: We aimed to find an association and identify risk factors for hypogammaglobulinemia and potential associated serious infection risk in a large real-world cohort of patients outside of the clinical trial setting.
Methods: All PPMS and RRMS patients treated with ocrelizumab in a Quebec City MS clinic, Canada until July 2021 were included. Detailed demographic data, MS disease characteristics and serious infection rate were collected by chart review. A serious infection was defined as an infection requiring hospitalization or emergency room treatment. Levels of specific immunoglobulins (IgA, IgG and IgM) were assessed prior to each treatment. Association between hypogammaglobulinemia and potential risk factors was analyzed.
Results: A total of 266 patients (average follow-up 2.05 years) were included (87% RRMS, 13% PPMS) and the majority (72.5%) had at least one previous disease-modifying therapy. After 6 perfusions, 3.5%, 4.2% and 32.8% of patients had at least one IgA, IgG and IgM hypogammaglobulinemia event respectively. A significant annual decrease over time was seen for IgA (-0.06 g/L/yr, $p < 0.0001$), IgG (-0.17, $p<0.0009$) and IgM (-0.18, $p<0.0001$). Aside from pre-treatment hypogammaglobulinemia, there were no consistent variables associated with on-treatment hypogammaglobulinemia. There was a total of 21 serious infections (3.36 and 12.33 per 100 person-years in RRMS and PPMS). Having at least one hypogammaglobulinemia event during treatment was not associated with serious infection. A Cox Regression analysis did not show any significant associations between serious infection and patient and key disease characteristics.
Conclusion: Similar to ocrelizumab extension studies, our cohort demonstrated a significant rate of hypogammaglobulinemia over time, mostly with IgM. No association was found between hypogammaglobulinemia and serious infection. Patient demographics and key disease characteristics were also not associated with serious infection risk. Association could arise from longer patient follow-up studies due to cumulative risk and exposure associated with anti-CD20 therapies.

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Intravenous immunoglobulin treatment in pregnancy and the post-partum period reduces relapse rates in women with multiple sclerosis

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Introduction: Relapsing remitting multiple sclerosis (RRMS) affects predominantly young women within reproductive years. The majority of these patients are interested to conceive and have children. As increased risk of relapses is known to occur during the post-partum period it is important to consider treatment options. Currently, only scarce data exists on the effects of disease-modifying treatments during the post-partum period.

Aims: Evaluate the effects of intravenous IgG immunoglobulins (IVIg) to prevent post-partum relapses.
Methods: We prospectively followed 198 pregnant female RRMS patients, 67 patients treated with IVIg before conception, during pregnancy and up to 3 months following delivery, mean±SD age 32.6±5.5 years, disease duration 7.2± 4.4 years, and 131 patients similarly followed without immunomodulatory treatment that served as controls, age 32.9±4.9 years, disease duration 7.8±4.5 years.
Results: Pre-gestational relapse rates did not differ between the groups (0.5 and 0.4, respectively). Low relapse rates were observed during pregnancy. There were 35 relapses during the post-partum period, 6 relapses (17.1%) occurred in the IVIg treated group, and 29 relapses (82.9%) in the untreated group. IVIg treatment significantly reduced the relapse rate during the 3-months post-partum as compared to the untreated group (0.1 and 0.6, respectively, p=0.014).
In the IVIG group there was 1(1.5%) mild relapse, 5(7.5%) moderate and no severe relapses. In the untreated group 5(3.8%) were mild, 14(10.7%) were moderate, and 10(7.6%) were severe. EDSS during the post-partum relapse was 2.5±1.3 in the IVIg-treated group as compared to 3.4±1.5 in the untreated group.
Conclusions: IVIg treatment proved efficient to reduce the rate and severity of relapses during the 3-months post-partum.

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Treatment-naive patients with early-stage relapsing-remitting multiple sclerosis showed low disease activity after 2-year ocrelizumab therapy, with no new safety signals; the Phase IIIb ENSEMBLE study

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Background: Early high-efficacy treatment of multiple sclerosis (MS) may provide long-term clinical benefits, improving disease outcomes and patient quality of life. ENSEMBLE is a multicentre, open-label, single-arm Phase IIIb study, evaluating the effectiveness and safety of ocrelizumab (OCR) in patients with early-stage relapsing-remitting MS (RRMS).
Aims: To report 2-year interim efficacy and safety data of the full cohort of patients with early-stage RRMS from the ENSEMBLE trial (NCT03085810), using no evidence of disease activity (NEDA)-3 as the primary endpoint.
Methods: Treatment-naive patients with early-stage RRMS (age 18–55 years; disease duration ⩽3 years; Expanded Disability Status Scale [EDSS] ⩽3.5; with one or more clinically reported relapse(s) or one or more signs of MRI activity in the prior 12 months) received OCR 600 mg every 24 weeks for 192 weeks (planned study duration). Key endpoints were NEDA-3 (defined as no relapses, 24-week [W] confirmed disability progression [CDP] and MRI activity [T1-weighted contract enhanced images or new/enlarging T2-weighted lesions, with MRI measurements rebaselined at W8]), annualised relapse rate (ARR), mean change in EDSS score from baseline (BL) and a safety overview.
Results: BL demographics and disease characteristics of the ENSEMBLE population (N=1,225) were consistent with early-stage RRMS disease (patients ⩽40 years, 78.9%; female, 64.0%; median: Age, 32.0 years; duration since MS symptom onset, 0.74 years; duration since RRMS diagnosis, 0.22 years; BL EDSS score, 1.75; mean BL EDSS score [SD], 1.80 [0.93]). At W96, the majority of patients (n=857, 77.3%) had NEDA, 88.9% had no MRI activity, 93.4% had no relapses and 90.7% had no 24W-CDP. The adjusted ARR at W96 was low, 0.033 (95% CI, 0.026–0.042), and the mean (SD) EDSS score showed a statistically significant improvement between BL and W96, decreasing by 0.13 (0.89; p<0.0001), from 1.80 (0.93) to 1.67 (1.12). Safety results were consistent with prior OCR studies. Infections were reported by 760 (62.0%) patients; rates of serious infections were low (n=33 [2.7%] patients); 32 (2.6%) of patients contracted a COVID-19 infection.
Conclusions: In the ENSEMBLE study of treatment-naive patients with early-stage RRMS, disease activity based on clinical and MRI measures was minimal in most patients treated with ocrelizumab over 2 years; safety was consistent with prior ocrelizumab experience, with no new safety signals.

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T Kuenzel is an employee of F. Hoffmann-La Roche Ltd.
K Kadner is an employee of F. Hoffmann-La Roche Ltd.
I Kulyk is an employee of F. Hoffmann-La Roche Ltd.
J Killestein has carried out contracted research for F. Hoffmann-La Roche Ltd, Biogen, Teva, Merck, Novartis and Sanofi/Genzyme.

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Autologous hematopoietic stem cell transplantation in relapsing remitting multiple sclerosis patients: A single centre experience

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Introduction: Autologous hematopoetic stem cell transplantation has been used as an experimental treatment for patients with aggressive Multiple Sclerosis (MS) in Sweden for more than 15 years.
Objective: To investigate clinical outcome and adverse events of AHSCT in relapsing remitting MS (RRMS) in a single centre cohort.
Methods: Retrospective observational single-centre study. Patients with a diagnosis of RRMS that underwent AHSCT at the Karolinska University Hospital, Stockholm, Sweden during 2007 to 2019 were included. All data was retrieved from medical reports and from the Swedish MS registry.
Results: A total of 39 RRMS patients (19 females), with a median age of 36 years (range 21-52) were included. All patients had prior failed disease modifying therapy (DMT) and had been treated with DMT for a mean time of 5 years (range 14-1).The patients had a median follow-up period of 6,4 years (range 2-14). The mean hospitalisation time for the AHSCT procedure was 25 days during which the great majority experienced neutropenic fever successfully treated with antibiotics and 26% of the patients exhibited transient Herpes virus reactivation (Epstein-Barr virus, Cytomegalovirus or both). A total of 50% of the patients had an improved Expanded Disability Status Scale (EDSS) score on the first visit 1 year after AHSCT while 45% were stable. Mortality rate was 0%, four patients developed secondary autoimmune disease and none experienced malignancy during follow up after AHSCT. A total of 67% of the patients had NEDA (no evidence of disease activity) defined as absence of new relapses or new MRI lesions and stable/improved EDSS at last clinical evaluation.
Conclusions: Our study provides evidence that AHSCT is an effective treatment to halt disease progression in RRMS. Interestingly, male predominance was observed within the cohort in contrast to the general MS population which suggest possible gender bias in treatment approaches for MS patients.

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Cladribine and pregnancy in women with multiple sclerosis – a case series from Germany

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Introduction: Information on pregnancy outcomes after cladribine exposure in women with multiple sclerosis (MS) is scarce and data on disease activity during pregnancy and postpartum is also lacking.
Objectives: To asses pregnancy outcomes and disease activity after cladribine treatment in women with MS.
Aims: To add to the body of evidence regarding cladribine intake before and after conception in women with MS, as well as that of data to disease activity during pregnancy and postpartum.

Methods: Pregnancies after cladribine treatment documented in the German Multiple Sclerosis and Pregnancy Registry (DMSKW) are presented. Information on pregnancy outcomes and disease course was collected with a standardized questionnaire during pregnancy and postpartum. For descriptive analysis, this cohort was stratified to last cladribine intake i) after last menstrual period (LMP), ii) between LMP and 6 months prior to LMP and iii) more than 6 months prior to LMP.
Results: 42 pregnancies in women with MS occurred after cladribine treatment, two with pregnancy exposure after LMP (median exposure duration 24 days; range 19 – 29), 16 with pregnancy exposure during the last 6 months prior to LMP (median days between CLAD and LMP 114,5 days; range 2 – 180) and 24 without pregnancy exposure (median days between CLAD and LMP 218 days; range 189 – 576). So far, 27 healthy babies and one elective abortion were reported. 11 pregnancies are ongoing and one woman is lost to follow up. One (2.6%) major and one minor (2.6%) congenital malformation were reported. Only one relapse occurred in 30 women with completed pregnancy follow-up (3.3%) and one postpartum relapse in 23 women with at least 3-months postpartum follow up (4.3%). Updated information will be presented at the time of the meeting.
Conclusions: Our data adds useful information on pregnancies with generally healthy newborns after cladribine treatment and excellent disease control during pregnancy and postpartum, but is limited by the small sample size.

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Sustained low relapse rate with highly variable B cell re-population dynamics with extended rituximab dosing intervals in multiple sclerosis

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Background and Objectives: B cell depleting therapies are highly effective in relapsing-remitting multiple sclerosis (RRMS), but are associated with increased infection risk and blunted humoral vaccination responses. Extension of dosing intervals may mitigate such negative effects, but its consequences on MS disease activity is unknown. The objective of this study was to determine clinical and neuroradiological disease activity, as well as B cell re-population dynamics, after implementation of extended rituximab dosing in RRMS.
Methods: We conducted a prospective observational study in a specialized-care, single-center setting, including RRMS patients participating in the COMBAT-MS and MultipleMS observational drug trials, who had received at least two courses of rituximab (median follow up time 4.8 years, range 0.5 – 9.8). Using Cox regression, hazard ratios (HR) of clinical relapse and/or occurrence of contrast-enhancing lesions on MRI were calculated in relation to time since last administered dose of rituximab.
Results: A total of 3,904 dose intervals were accumulated in 718 patients and stratified into four intervals: $<$8 months, $\geqslant$8 to 12, $\geqslant$12 to 18 and $\geqslant$18 months. We identified 24 relapses of which 20 occurred within 8 months since previous infusion and four with intervals over 8 months. HRs for relapse when comparing $\geqslant$8 to 12, $\geqslant$12 to 18, and $\geqslant$18 months to $<$8 months since last dose were 0.28 (95% confidence interval (CI) 0.04-2.10), 0.38 (95%CI 0.05-2.94) and 0.89 (95%CI 0.20-4.04), respectively, and thus non-significant. Neuroradiological outcomes were in agreement with relapse rates. Dynamics of total B cell reconstitution varied considerably, but median total B cell counts reached lower level of normal (LLN) after 11 months. In contrast, median memory B cell counts remained below LLN.
Conclusions: In this prospective cohort of rituximab-treated RRMS patients exposed to extended dosing intervals we could not detect a relation between clinical or neuroradiological disease activity and time since last infusion. While memory B cell counts remained low in most patients, total B cell re-population kinetics varied considerably. These findings, relevant for assessing risk mitigation strategies with anti-CD20 therapies in RRMS, suggest that relapse risk remains low with extended infusion intervals. Further studies are needed to investigate the relation between B cell repopulation dynamics and adverse event risks associated with B cell depletion.

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Efficacy and safety of ocrelizumab is maintained in patients with RRMS with suboptimal response to prior disease-modifying therapies: 4-year NEDA data from CASTING-LIBERTO

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Background: Despite treatment with disease-modifying therapies (DMTs), patients with relapsing-remitting multiple sclerosis (RRMS) frequently experience disease activity. The Phase IIIb CASTING study (NCT02861014) examined the efficacy and safety of ocrelizumab (OCR) in patients with RRMS with previous suboptimal response to ⩾6 months DMTs. Eligible CASTING patients enrolled into LIBERTO (NCT03599245), an open-label extension study assessing the efficacy and safety of OCR in patients previously registered in OCR Phase IIIb/IV trials.
Aims: To assess the efficacy and safety of OCR over 4 years in patients with RRMS with a suboptimal response to prior DMTs from CASTING-LIBERTO.
Methods: Patients who completed the 2-year CASTING study were offered to rollover to LIBERTO and continue intravenous OCR 600 mg every 24 weeks for 2 years. Efficacy endpoint was no evidence of disease activity (NEDA; defined as no protocol-defined relapses, 24-week confirmed disability progression [24W-CDP], contrast-enhancing T1-weighted and new/enlarging T2-weighted lesions [T1w-CEL and N/E T2w-L], with MRI rebaselining at Week 8). Safety objectives included the rate and nature of adverse events (AEs).
Results: Overall, 12 out of 17 countries that participated in CASTING entered LIBERTO, resulting in a rollover of 439/680 patients from CASTING to LIBERTO. Patient baseline demographics were consistent between trials (CASTING/LIBERTO: Age [years], 34.2/36.0; % female, 64.1/62.9; mean Expanded Disability Status Scale, 2.1/2.0). During 4 years in CASTING-LIBERTO, 56.8% of patients had NEDA, 64.6% had no clinical activity (84.1% no relapses and 73.9% no 24W-CDP), 87.2% had no MRI activity (96.8% no T1w-CEL and 87.2% no N/E T2w-L). Of the 71 CASTING-LIBERTO patients who had EDA during CASTING, 45 (63.4%) achieved NEDA during LIBERTO. Of the 246 CASTING-LIBERTO patients who had NEDA during CASTING, 189 (76.8%) maintained NEDA during LIBERTO. AEs were reported in 92.7% of patients and serious AEs in 8.7%. Infections were observed in 72.2% patients. In total, 3 patients withdrew from LIBERTO due to AEs (0.7%); no deaths occurred in LIBERTO.
Conclusions: The majority of patients with RRMS with a suboptimal response to prior DMTs who switched to OCR showed NEDA during the 4-year follow-up of CASTING-LIBERTO, based on clinical and MRI measures. A high proportion of patients with EDA during the first 2 years of treatment achieved NEDA over 2 years in LIBERTO. No new safety signals were observed.

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Functional systems scores and expanded disability status scale score evaluations in the ultimate I and II studies of ublituximab versus teriflunomide in participants with relapsing multiple sclerosis

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Introduction: Ublituximab is a novel monoclonal antibody targeting a unique epitope of CD20. Ublituximab is glycoengineered for enhanced antibody-dependent cellular cytotoxicity and is administered in 1-hour maintenance infusions after the first infusion. In ULTIMATE I and II, ublituximab significantly improved annualised relapse rate as well as number of gadolinium-enhancing T1 lesions and new/enlarging T2 lesions, and a higher proportion of participants achieved no evidence of disease activity versus teriflunomide in participants with relapsing multiple sclerosis (RMS).
Objectives/Aims: To evaluate Functional Systems Scores (FSS) and Expanded Disability Status Scale (EDSS) score with ublituximab versus teriflunomide in pooled post hoc analyses of ULTIMATE I and II.
Methods: The Phase 3 ULTIMATE I (N=549) and II (N=545) studies evaluated ublituximab 450 mg intravenous infusion every 24 weeks or teriflunomide 14 mg oral once daily for 96 weeks in participants with RMS. Clinical evaluations were performed at baseline and every 12 weeks. Pooled post hoc analyses evaluated the change from baseline in EDSS score and FSS at each visit. A repeated measures proportional odds model was used to estimate the odds ratio (OR) between the two arms for the change from baseline across all visits during the studies.
Results: Across all visits, significant improvements (OR [95% confidence interval]) with ublituximab versus teriflunomide were seen in: EDSS score, 1.7 (1.2-2.4), P=0.0010; bowel/bladder functions, 1.4 (1.0-1.8), P=0.0222; and sensory functions, 1.4 (1.1-1.9), P=0.0052. By individual visits, significant improvements were seen with ublituximab versus teriflunomide in EDSS score (Weeks 48-96), bowel/bladder (Weeks 24-96), sensory (Weeks 48-96), cerebellar (Weeks 48, 84, 96), cerebral/mental (Weeks 48, 72, 84), and ambulation and pyramidal (Week 96) functions ($P<0.05$).
Conclusions: Pooled post hoc analyses of ULTIMATE I and II demonstrated significant improvements with ublituximab versus teriflunomide in EDSS score and multiple FSS. These results further support prior data on improved disability outcomes with ublituximab versus teriflunomide in participants with RMS.

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Autologous hematopoietic stem cell transplantation does not affect paramagnetic rim lesion number in aggressive multiple sclerosis: a pilot study

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Introduction: In people with multiple sclerosis (pwMS), iron paramagnetic rim(PRL) lesions detected by MRi seem a valid biomarker of chronic active lesions - compartmentalized inflammation, but longitudinal data on the effect of disease-modifying treatments (DMT) on PRL are lacking. Besides efficacy, DMT bioavailability within the central nervous system (CNS) is a prerequisite for acting on such inflammation, and highly CNS bioavailable and effective drugs are used as conditioning protocol during BEAM - autologous haematopoietic stem cell transplantation (aHSCT).
Aim: To investigate the effect of aHSCT on PRL in pwMS, longitudinally assessing the variation of PRL number.
Methods: Patients with aggressive MS treated with aHSCT underwent serial brain MRis with a standardized protocol including susceptibility-weighted imaging (3T device), either before and after aHSCT or following aHSCT only. PwMS receiving alternative DMT were scanned with the same protocol at two timepoints at least 6 months apart (control group). The presence and number of PRL and T2 lesion loads were analysed. Values are reported as median (range).
Results: AHSCT group:10pwMS,including3 relapsing-remitting (RR) MS scanned before and 6 to 14 months after transplant; and 7 (3 RR; 4 secondary-progressive - SP) MS who underwent the first MRi 23 (5 - 50) months following aHSCT and the subsequent scan after 14 (10 – 21) months. Control group: 11 pwMS (6 RR, 5 SP); median interscan period: 7 (6 - 12) months. Age and disease duration at inclusion were 43.5 (28 – 51) years and 15 (5 – 26) years in the AHSCT group, and 43 (18 - 59) years and 12 (1 – 29) years in the control group, respectively. Before aHSCT, PRL were detected in 2 of 3 patients and their number was unchanged over follow-up; disability was stable or improved in all the cases. PRL were observed in 7/7 pwMS with post-aHSCT only scans (median PRL number: 4; 1 - 11) and in 9/11 control patients (median PRL number: 2; 1 - 4), without any changes in the subsequent MRi. Baseline T2 lesion load was stable over follow-up.
Conclusions: According to these preliminary results, aHSCT seems not to affect PRL number in aggressive MS patients over a one-year follow-up, despite disability stabilization. As the iron rim may persist at lesion edges even if a DMT would remove CNS-resident inflammation, long-term prospective observation in larger patient populations is needed to properly explore the impact of aHSCT on compartmentalized inflammation.

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MRI, efficacy, and safety of tolebrutinib in patients with highly active disease (HAD): 2-year data from the phase 2b Long-term safety (LTS) Study

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Intoduction: In the phase 2b trial (NCT03889639), brain-penetrant Bruton's tyrosine kinase inhibitor tolebrutinib was well tolerated with dose-dependent reductions in new/enlarging MRI lesions.
Objective/Aim: Report MRI, efficacy, and safety outcomes at Week (W)96 (2 years) of the phase 2b trial long-term safety (LTS) extension (NCT03996291) in relapsing MS patients with highly active disease (HAD).
Methods: In the double-blind portion of LTS (Part A), patients continued their core study tolebrutinib dose (5, 15, 30, or 60 mg/day). In the open-label Part B, all participants received 60 mg/day. HAD was defined as one relapse in the year prior to screening and one of the following: >1 gadolinium (Gd)-enhancing lesion within the prior 6 months, or ⩾9 T2 lesions at baseline (BL) or ⩾2 relapses in the prior year. Outcomes included Gd-enhancing and new/enlarging T2 lesions, annualized relapse rate (ARR), and Expanded Disability Status Scale (EDSS) score.
Results: 61 patients met the HAD criteria at BL; 60 continued in LTS Part A and 59 transitioned to Part B. As of 7 March 2022, 55 (92%) patients remained on study. New Gd-enhancing lesion counts remained low in the 60/60-mg arm through W96 and were reduced in other arms by W48 through W96, except for 5/60 at W96 (mean±SD at W96: 2.00±3.83, 0.56±1.04, 0.47±1.13, 0.23±0.44 in 5/60-, 15/60-, 30/60-, 60/60-mg arms, respectively). New/enlarging T2 lesion counts remained low for 15/60, 30/60, and 60/60 mg. T2 lesion volume remained unchanged for 60/60 mg. The most common treatment-emergent adverse events (TEAE) were COVID-19 (20%), nasopharyngitis (16.7%), headache (13.3%), and upper respiratory tract infection (8.3%). There was no dose-relationship for TEAE/serious AE in Part A and no new safety findings for patients switching to 60 mg in Part B. Of the patients who received tolebrutinib 60 mg/day for a minimum of 8 weeks, ARR was 0.10 (95% CI: 0.02, 0.66) and 92.9% remained relapse-free at W96. Mean EDSS scores were stable through W96.
Conclusion: Through LTS Week 96, in the HAD cohort, tolebrutinib 60 mg demonstrated favourable safety (similar to the overall population), tolerability, and low ARR. New Gd-enhancing lesion counts remained low for the 60/60-mg arm.

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IL-6 receptor antagonism prevents neurological disease in mice with AQP4 peptide immunization

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Background: Neuromyelitis optica spectrum disorder (NMOSD) is a severe inflammatory demyelinating disease of the central nervous system (CNS) mainly associated with pathogenic autoantibodies against the astrocytic water channel protein aquaporin-4 (AQP4). We previously reported creation of an AQP4-immunized mouse model with clinical and histologic manifestations of CNS autoimmunity in ECTRIMS 2021 (Poster No. P321). In the present study, we evaluated inhibition of IL-6 signal activity, which is one of the approved therapeutic targets in NMOSD, in novel established AQP4 peptide-immunized mice.
Materials and Methods: In female C57BL/6J mice, we performed intradermal immunization with AQP4 p201-220 peptide emulsified in complete Freund's adjuvant supplemented with*Mycobacterium tuberculosis* extract H37Ra in multiple places (Day 0). Pertussis toxin was administered at Days 0 and 2. Control mice were treated with complete Freund's adjuvant and saline alone. Anti-IL-6 receptor antibody (MR16-1) was intraperitoneally administered just after immunization (Day 0). Mice were sequentially scored for clinical signs and assessed pain sensitivity by the von Frey test.
Results: Intradermal immunization of AQP4 peptide induced paralytic clinical signs. In the spinal cord of AQP4 peptide-immunized mice, pathological features of NMOSD were observed, including glial fibrillary acidic protein (GFAP)/AQP4 protein loss and complement deposition. In addition, CD138+TACI+ antibody secreting B cells and AQP4-IgG autoantibody levels were increased in AQP4 peptide-immunized mice. Administration of MR16-1 inhibited the induction of clinical sign accompanied with preventing loss of GFAP and AQP4 and complement deposition in AQP4 peptide-immunized mice. MR16-1 did not reduce CD138+ TACI+ antibody-secreting B cells in lymph node, whereas

MR16-1 reduced infiltration of albumin, T cells and monocytes into the spinal cord of AQP4 peptide-immunized mice. MR16-1 tended to prevent the migration of neutrophils into the spinal cord of AQP4-immunized mice. Furthermore, MR16-1 decreased pain sensitivity in AQP4 peptide-immunized mice.
Conclusion: IL-6 receptor antagonism exerted beneficial effects in AQP4 peptide-immunized mice through prevention of infiltrating pathogenic factors into the spinal cord.

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Immunological consequences of cladribine treatment in multiple sclerosis: a real-world study

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Background: Cladribine is considered to be a semi-selective immune-reconstitution therapy (IRT) for relapsing multiple sclerosis (RMS).
Aims: To evaluate the effect of cladribine on immune cell reduction and reconstitution during the first two years of treatment.
Methods: In our prospective, real-world cohort of 80 RMS patients, laboratory testing was conducted monthly. Laboratory outcomes were correlated with infectious adverse events and disease activity.
Results: Alterations in immune cell populations were most marked in year two of treatment. Specifically, a rapid reduction in $CD56^+CD16^+$natural killer cells (nadir: month 1 (year 1) and 14 (year 2); -37 and -41% from baseline) was followed by a greater reduction in $CD19^+$B cells (nadir: month 2 and 14; -81 and -82%); a moderate effect on $CD4^+$(nadir: month 3 and 15; -48 and -61%) and $CD8^+$T cells (nadir: month 5 and 18; -40 and -48%). Immunoglobulin levels were unaffected. There was no or minimal effect on thrombocytes and innate immune cells. Clinical and paraclinical disease activity was unrelated to the observed immune alterations. Lymphopenia was the most commonly observed AE (86.3% of patients; grade III-IV lymphopenia: 38.8%). The cumulative incidence of infections was 55% with cladribine treatment, with 97% of infections rated mild or moderate. In total, 19 herpes infections developed in 8 (10%) cladribine-treated patients; all cases were dermatomal and 94.7% of the herpetic infections occurred during a period of lymphopenia.
Conclusions: The immunophenotyping data are comparable to those from clinical trials, providing further evidence that cladribine represents a form of IRT. However, regarding the side-effect profile of cladribine, severe lymphopenia was more frequent, which may have prompted the development of herpes infections. Although likely underlying the clinical effect, the pronounced reduction and recovery dynamics of lymphocytes did not correlate with clinical and paraclinical measures of disease activity.

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Disability changes in the absence of relapse in the phase 3 ULTIMATE I and II studies of ublituximab versus teriflunomide in participants with relapsing multiple sclerosis

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Introduction: Ublituximab is a novel monoclonal antibody targeting a unique epitope of CD20. Ublituximab is glycoengineered for enhanced antibody-dependent cellular cytotoxicity and is administered in 1-hour maintenance infusions after the first infusion. In ULTIMATE I and II, ublituximab significantly improved annualised relapse rate, number of gadolinium-enhancing T1 lesions and new/enlarging T2 lesions, and proportion of participants achieving no evidence of disease activity versus teriflunomide in participants with relapsing multiple sclerosis (RMS).

Objectives/Aims: To evaluate disability changes in the absence of relapse with ublituximab in ULTIMATE I and II.

Methods: The Phase 3 ULTIMATE I (N=549) and II (N=545) studies evaluated ublituximab 450 mg intravenous infusion every 24 weeks or teriflunomide 14 mg oral once daily for 96 weeks in participants with RMS. Pooled post hoc analyses evaluated measures of disease progression in the subset of participants with no Independent Relapse Adjudication Panel–confirmed relapses during the study (ublituximab, n=473; teriflunomide, n=406).

Results: In confirmed relapse-free participants, the mean change in Expanded Disability Status Scale score from baseline was significantly improved with ublituximab versus teriflunomide at Weeks 48 (-0.13 versus -0.06), 84 (-0.19 versus -0.08), and 96 (-0.19 versus -0.07) ($P<0.05$ for all). The least squares means change from baseline at all postbaseline timepoints up to Week 96 in Multiple Sclerosis Functional Composite (MSFC), 9-Hole Peg Test (9-HPT), and Timed 25-Foot Walk (T25FW) scores was significantly improved for ublituximab versus teriflunomide: MSFC, 0.56 versus 0.36, P=0.0095; 9-HPT, 0.15 versus 0.03, P=0.0005; T25FW, 0.07 versus -0.02, P=0.0375.

Conclusions: In pooled post hoc analyses of ULTIMATE I and II, ublituximab was associated with significant improvement versus teriflunomide across multiple disability measures in the subset of participants without confirmed relapses during the study. These results further support improved disability outcomes with ublituximab versus teriflunomide in participants with RMS, independent of a reduced risk of relapse.

Disclosure

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Lack of rebound disease activity in patients with relapsing multiple sclerosis following placebo run-out in the tolebrutinib phase 2b trial

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Background: Rebound disease activity, characterised by recrudescence of neurological symptoms and brain lesions, has been reported after stopping some multiple sclerosis (MS) disease-modifying treatments. The 16-week Phase 2b trial (NCT03889639) of tolebrutinib, the brain-penetrant Bruton's tyrosine kinase (BTK) inhibitor, in patients with relapsing MS (RMS) showed dose-dependent reductions in new gadolinium-enhancing (Gd+) T1 and new/enlarging T2 lesions. The unique cross-over trial design, which included 4-week placebo run-in and run-out periods to minimise placebo exposure, enabled assessment of potential rebound disease after tolebrutinib discontinuation.
Objective/Aim: To assess potential rebound disease recrudescence in patients with RMS after the tolebrutinib Phase 2b trial placebo run-out period.
Methods: The 16-week, double-blind, crossover trial randomized 130 patients with RMS (1:1:1:1) to tolebrutinib 5, 15, 30, or 60 mg/day. Magnetic resonance imaging (MRI) scans were obtained at screening and every 4 weeks for 16 weeks. Cohort 1 (n=64) received tolebrutinib for 12 weeks followed by a 4-week placebo run-out; Cohort 2 (n=66) received a 4-week placebo run-in followed by 12 weeks of tolebrutinib.
Results: There was 1 relapse during the Cohort 1 placebo run-out (98.4% of patients were relapse-free) vs 4 relapses in the Cohort 2 placebo run-in (93.9% relapse free). After 12 weeks of tolebrutinib treatment (Cohort 1), 83.3% of patients had no new Gd+ lesions; 4 weeks after discontinuing tolebrutinib (placebo run-out), 85.2% of patients had no new Gd+ lesions. In Cohort 1, the mean (SD) Gd+ lesion count after 12 weeks of tolebrutinib was 0.37 (0.99) and 0.44 (1.70) after 4 weeks of placebo run-out. For those in Cohort 1 receiving tolebrutinib 60 mg/day – the dose used in the phase 3 study – the mean (SD) Gd+ lesion count was 0.20 (0.56) after 12 weeks of tolebrutinib and 0.31 (0.70) after 4 weeks of placebo run-out. The mean (SD) Gd+ lesion count after the 4-week placebo run-in (Cohort 2) was 1.03 (2.50). At Week 12 in Cohort 1, the mean (SD) number of new/enlarging T2 lesions was 0.58 (1.27) vs 0.95 (2.72) after 4 weeks of placebo run-out, while it was 2.12 (5.16) after the 4-week placebo run-in (Cohort 2).
Conclusions: These preliminary findings suggest that discontinuation of tolebrutinib in patients with RMS does not induce rebound disease activity. Longer observation periods will be needed to validate this finding.

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MRI outcomes from the long-term extension study of tolebrutinib in patients with relapsing multiple sclerosis: 2-year results

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Introduction: Tolebrutinib is a brain-penetrant inhibitor of Bruton's tyrosine kinase currently under evaluation for multiple sclerosis treatment. In the double-blind phase (DBP) of the phase 2b trial (NCT03889639), tolebrutinib was well tolerated over 12 weeks with dose-dependent reduction in new gadolinium (Gd)-enhancing T1 and new/enlarging T2 lesions. LTS16004 (NCT03996291) is an ongoing LTS extension study of tolebrutinib in patients who completed the phase 2b study.

Objective/Aim: Report MRI outcomes at Week (W)96 (Year 2) in the long-term safety (LTS) extension of the phase 2b tolebrutinib trial in patients with relapsing multiple sclerosis.
Methods: After the last DBP tolebrutinib dose, followed by a variable treatment gap (0–21 weeks), patients began the LTS extension Part A, where they continued receiving their DBP dose (5, 15, 30, or 60 mg/day) in a double-blinded manner until the phase 3 dose was selected. In the current open-label extension Part B, all patients receive 60 mg/day. MRI outcomes include numbers of new Gd-enhancing and new/enlarging T2 lesions, T2 lesion volume change from baseline, slowly evolving lesions (SEL), and paramagnetic rim lesions (PRL).
Results: 124 of 125 patients treated in the LTS extension completed Part A and transitioned to Part B; 114 (90.5%) remain on study as of 18 February 2022 (W96 cut-off). At DBP baseline, the mean age±SD of enrolled patients was 37.7±9.6 years (range 19–56); 69% were women. Numbers of new Gd-enhancing lesions remained low in the 60/60-mg arm through W96 and were reduced in other arms at W48 through W96 (W96 mean±SD: 0.85±2.5, 0.41±0.91, 0.90±2.16, 0.31±0.66 in 5/60-, 15/60-, 30/60-, 60/60-mg arms, respectively). New/enlarging T2 lesion counts remained low for 60/60 mg. T2 lesion volume change remained low for 60/60 mg (W96 vs baseline [mean±SD]: +0.38±2.11 cm^3). Median (IQR) W96 SEL volume was 247.5 (84–420), 258 (66–906), 570 (133.5–1011), and 244.5 (87–939) mm3 for 5/60-, 15/60-, 30/60-, and 60/60-mg, respectively. PRL count remained unchanged in 18 patients; 2 patients had 1 PRL at baseline but none at W96, and 3 patients had 1–3 additional PRL at W96 vs baseline (none in the 60/60 mg arm).
Conclusions: New Gd-enhancing lesion counts remained low for tolebrutinib 60/60 mg and were reduced in the lower dose arms by LTS W48 through W96, when all patients had switched to 60 mg.

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Comparative pharmacology of ofatumumab versus ocrelizumab in humanised-CD20 transgenic mice

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Introduction: Therapeutic strategies aiming at depleting $CD20^+$ B cells are effective in treating MS. Pilot work suggested improved lymph node (LN)-targeting for subcutaneous ofatumumab (OMB-sc)*vs* intravenous ocrelizumab (OCR-iv) and further differentiation is expected from a head-to-head comparison.
Objective: To benchmark the potency of OMB-sc and OCR-iv at depleting B cells expressing the human-CD20 molecule (*hu*CD20) in transgenic mice.
Design/Methods: *Hu*CD20 mice (C57BL/6-Ms4a1tm2(hCD20) Smoc) treated once with OMB-sc or OCR-iv at various doses were monitored for drug levels (IgG-binding ELISA assays) and B-cell counts (flow cytometry) in blood and lymphoid organs (spleen, inguinal LN, bone marrow).
Results: Both OMB-sc and OCR-iv achieved dose-proportional drug levels with B-cell depletion in all compartments. In blood, at 3 days post-treatment, serum levels needed for 50%/90% efficacy (EC50/EC90) were ~0.01/0.3 mg/mL for OMB-sc *vs* 0.2/5.0 mg/mL for OCR-iv, indicating a 20-fold higher potency for OMB-sc at depleting circulating B cells. At human-equivalent dose (*hu*D), OMB-sc (6 mg/mouse) reached its EC50 whereas OCR-iv (200 mg/mouse) was supramaximal (~40-fold above its EC90). In spleen and LN, drug level ratios *vs* serum were 5-20 and ⩽1 for OMB-sc and OCR-iv, respectively, confirming improved lymphoid organ targeting for OMB-sc. With similar EC50s around 0.2 mg/mL, both OMB-sc and OCR-iv treatments appeared equipotent at depleting non-circulating B cells. Further analysis revealed that marginal zone (MZ) and follicular (FO) B cells in secondary lymphoid organs were markedly depleted by OCR-iv but spared by OMB-sc, both at *hu*D. In BM, at*hu*D, OMB-sc achieved drug levels 10-fold below EC50 whereas OCR-iv reached its EC90, suggesting a lower impact for OMB-sc on BM-resident CD20 expressing cells.
Conclusions: OMB-sc demonstrated better efficiency vs OCR-iv at targeting lymphoid organs and showed a 20-fold higher depleting potency on circulating B cells and equipotency on non-circulating B cells. Furthermore, a sparing effect on MZ and FO B cells, key for the development of germinal center reactions and for immune surveillance, as well as on bone marrow, important for B-cell repletion and preservation of immune responses, was observed with OMB-sc. If translating to humans, OMB-sc offers a convenient s.c. pharmacological-dose medication combining high efficacy and potential lower risks for long term safety *vs* supra-maximal in vivo dosing for OCR-iv.

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Relationship of SARS-CoV-2 spike antibody response to lymphocyte subsets and timepoint of ocrelizumab dosing in multiple sclerosis patients

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Introduction: B-cell depletion agents such as ocrelizumab (OCR) are highly effective treatment options for active multiple sclerosis (MS). However, it is known, that B-cell depletion can be associated with a lower antibody response after SARS-CoV-2 immunisation. The individual factors that contribute to the immune response are less understood.
Objective, aims and method: Here, we retrospectively analysed single centre, structured clinical routine SARS-CoV-2 spike antibody response data after completion of basic immunization in 42 consecutive included MS patients under OCR therapy who are standardised investigated in our outpatient clinic. In particular, we examined treatment duration, previous immunotherapies, immunoglobulin levels, and lymphocyte subsets includingB-cell and lymphocyte countsas well as time interval between last OCR treatment and SARS-CoV-2 vaccination as influencing factors in patients with and without SARS-CoV-2 spike antibody response. All patients gave written ethical consent.
Results: 42 MS patients were identified and included (38 RRMS, 4 PPMS patients, 28 females, median age: 42.0 years, median disease duration: 11.2 years), which are treated with OCR (median treatment duration: 2.0 years. 29 patients (69.1 %) and showed no SARS-CoV-2 spike antibody response. Median IgG and IgM levels and B-cell counts were marginally lower in patients without SARS-CoV-2 spike antibody response.The time interval between last OCR administration and first vaccination, however, was significantly longer (median = 2.8 [0.3; 5.1] months vs median = 4.0 [2.9; 5.7] months [min; max]) in patients with positive SARS-CoV-2 spike antibody response. Antibody response was not associated with age, sex, number of previous immunotherapies and duration of OCR therapy. Further data regarding lymphocyte subsets will be presented during the ECTRIMS congress.
Conclusion: As an influencing factor the time interval between last OCR dosing and vaccination affects SARS-CoV-2 spike antibody response to vaccination. Our results support previous findings and help to advise patients for the best timepoint of vaccination under B-cell depleting therapies. We identified the time interval between OCR dosing and vaccination date as the main influencing factor after SARS-CoV-2 vaccination. Against expectation, the duration of ocrelizumab therapy and the number of previous therapies do not seem to be an influencing factor.

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B-lymphocyte-guided retreatment contributes to establish a good effectiveness/safety profile in MS patients treated with rituximab

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Background: Rituximab is extensively used for multiple sclerosis treatment (MS). However the best dosage remains to be established. It has been proposed that retreatment could be guided by B lymphocyte (BL) percentages.
Objective: To establish the best BL value for retreatment with Rituximab in MS and confirm safety and efficacy of this approach.
Methods: Prospective study with two cohorts (exploratory and confirmatory) of MS patients treated with Rituximab between 2017 and 2021. The first one comprised 10 MS patients with BL assessed every 3 months after Rituximab infusion and retreatment made at BL values ⩾0.5%. The confirmatory cohort included 41 MS patients (41.5% women, 87.8% with a secondary progressive MS, age=46.3(41.3-52.1) years (Median, interquartile range), disease duration=14.1(9-19.6), EDSS score=5.5(4.0-6.5)) treated with rituximab following the pattern established in the exploratory cohort.

Results: Exploratory cohort: We established ⩾0.2% of BL as the best value for retreatment because in most cases a substantial increase of BL counts was preceded by initial 0.2-0.3% values.
Confirmatory cohort: Rituximab reduced the annualized relapse rate (ARR 0.56 vs 0.125, $p<0.001$), proportion of patients with appearance of new/enlarged T2 lesion (63.4% vs 12.2%, $p<0.001$), gadolinium-enhancing lesions (39% vs 0%, $p<0.001$) and confirmed disabiltity progression (55% vs 27.5%, $p=0.037$). Twenty-two patients (53.7%) achieved NEDA-3. No patients had severe infections and there were 10.7% cases of reduced IgG levels.
Conclusion: Rituximab guided by BL showed high effectiveness and a good safety profile in MS patients after one year of treatment.

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High dose vitamin D_3 supplementation does not reduce disease activity in relapsing remitting multiple sclerosis in a large randomized controlled trial

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Introduction: Vitamin D insufficiency is a risk factor for multiple sclerosis (MS), but it is uncertain if it influences prognosis after MS onset. The Vitamin D to Ameliorate MS (VIDAMS) trial is a multi-center, randomized controlled, double blind trial assessing if high dose vitamin D supplementation as an add-on to first-line therapy reduces disease activity in people with relapsing-remitting (RR) MS.
Objectives/Aims: To determine if high dose compared to low dose vitamin D_3, as add-on to glatiramer acetate (GA), is associated with a decreased risk of clinical relapse (primary outcome) or other clinical or imaging measures of MS activity in people with RRMS.
Methods: People aged 18 to 50 years with RRMS (2010 criteria) and recent disease activity were enrolled at sixteen neurology clinics in the United States. Key additional eligibility criteria included Expanded Disability Status Scale (EDSS) score$<$ 4.0; minimum serum 25-hydroxyvitamin D level of 15 ng/ml within 30 days of screening, and no more than an average of 1000 IU supplemental vitamin D_3daily (in addition to multivitamin) within 90 days of screening. After screening and a 30-day run-in of daily 20 mg subcutaneous GA injections, those with adequate adherence ($<$ 3 missed injections) were randomized 1:1 to low dose vitamin D_3(LDVD; 600 International Units (IU)/day) or high dose Vitamin D_3(HDVD; 5000 IU/day) and were followed every 12 weeks for up to 96 weeks. Treating clinicians and participants were blinded to study drug assignment; outcomes assessors were also blinded to participants' clinical course. The primary outcome was analyzed using Kaplan Meier and Cox proportional hazards models.
Results: 172 participants (83 LDVD vs. 89 HDVD) were randomized, 165 returned for$>$ 1 study visit and were included in the analysis according to their assigned treatment and 140 completed a week 96 visit. The proportion that experienced a confirmed relapse did not differ between LDVD and HDVD arms [at 96 weeks: 32% vs. 34%, $p=0.60$; hazard ratio (HR): 1.17 (0.67, 2.05), $p=0.57$]. Annualized relapse rate did not differ between LDVD and HDVD arms [0.20 (0.11, 0.35) vs. 0.34 (0.20, 0.56), $p=0.07$; HR: 1.70 (0.97, 2.97), $p=0.06$]. Other secondary clinical and MRI outcomes were also not meaningfully different between groups.
Conclusions: Findings from the VIDAMS trial provide Class I evidence that high dose vitamin D_3supplementation, as add-on to GA therapy, does not reduce disease activity in established RRMS.

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P302

Discontinuation of first-line disease-modifying therapy in multiple sclerosis

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Background: It is still not fully known if and when first-line disease modifying therapy (DMT) can safely be discontinued in relapse onset multiple sclerosis (MS) patients. Previous studies suggest higher age and longer duration of disease stability are associated with a lower risk of recurrent disease activity, but most studies are focused on clinical relapses, and less is known of radiological outcome measures after discontinuation.
Aim: To investigate the characteristics of patients who discontinued first-line DMT in our cohort, and the occurrence of clinical and radiological inflammatory disease activity after discontinuation.
Methods: Data were collected of patients at the MS Center Amsterdam and the Rijnstate Hospital Arnhem. Patients with relapse onset MS who discontinued first-line DMT with no intention of restarting or switching treatment, and with a minimum radiological follow-up of 3 months after discontinuation, were included. Clinical and MRI parameters were collected. MRI activity was defined as any new T2-lesions or contrast-enhancing lesions on MRI during follow-up.
Results: 130 patients were included in the analyses. Mean age at DMT discontinuation was 45.3 years (SD 9.46). Median follow-up duration after discontinuation was 59.5 months (IQR 26.5-99.9). 62 patients (47.7%) showed MRI activity after DMT discontinuation, of whom 33 did not have a clinical relapse. 40 patients (30.8%) experienced relapse(s) after discontinuation, of whom 25 also showed MRI activity. 29 patients (22.3%) restarted DMT after initial discontinuation, with a median time until restart of 17.0 months (IQR 5.5-41.5). Higher age at DMT discontinuation was associated with a lower risk of MRI activity after discontinuation (45 -55 vs. <45 years: OR 0.287, p=0.002, >55 vs. <45 years, OR: 0.248, p=0.018, and with a lower total number of new T2-lesions after discontinuation (45-55 vs. <45 years: rate ratio(RR)=0.621, p=0.097, >55 vs. 45-55 years: RR=0.249, p=0.012). Higher age at DMT discontinuation was also associated with a lower risk of relapse(s) after discontinuation (45-55 vs. <45 years: OR=0.439, p=0.057, >55 vs. 45-55 years: OR=0.064, p=0.012). No other statistically significant predictors of disease activity were found.
Conclusion: Higher age at first-line DMT discontinuation is associated with lower a risk and severity of radiological disease activity in MS, and a lower risk of relapse(s) after discontinuation. MRI activity was not always accompanied by clinical relapse(s) in our cohort.

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Microparticle-delivered stimulator of interferon genes (STING) agonist suppresses experimental autoimmune encephalomyelitis (EAE) via expansion of FoxP3$^+$CD4$^+$Tregs

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Introduction: We reported that STING agonist cGAMP, encapsulated in acetylated dextran (Ace-DEX) Microparticles (MPs) suppressed EAE via type I IFN-dependent and independent mechanisms.
Objectives: To determine to what extent cGAMP MPs-induced IL-27 and IL-10-producing tolerogenic dendritic cells (DCs) induce expansion of T-regulatory (Treg) cells.

Aims: To determine that cGAMP MP treatment of EAE induces tolerogenic DCs and expands CD4+CD25+FOXP3 in CNS inflammatory infiltrate and to demonstrate that cGAMP MP treated monocytes isolated from spleen EAE induces anti-inflammatory cytokines and expand of Treg *invitro*cultures.
Methods: The treatment with cGAMP MP or control blank MPs started at the onset (day 9 p.i.) or at the peak of the of EAE disease (day 15 p.i.), I.M. every other day, 5 doses. Flow cytometry studies were performed on CNS infiltrates and ELISA cytokine measurements in plasma.*In vitro*experiments were performed on spleen monocytes, treated with cGAMP MP or blank MPs and co-cultured with $CD4^+$splenocytes to detect the induction of $FoxP3^+CD4^+$Tregs, and the SN cytokine secretion.
Results: cGAMP MP treatment reduced clinical disease scores after 3 doses. cGAMP MPs decreased absolute number of mononuclear cells in the CNS infiltrates, and the percentages of $CD3^+CD45^{hi}CD11b^+Ly6C^+$monocytes, $CD11c^+$and $CD11c^+CD11b^+$DCs, as well as their expression of CD80 and CD86, suggestive of tolerogenic phenotype.We detected an increased percentage of $FOXP3^+CD4^+$Tregs in CNS infiltrates, with increased expression of IL-10, IL-27R, and Granzyme B, and decreased percentage of $IL\text{-}17^+CD4^+$cells in cGAMP MP-treated mice.We found an increased IL-27 and IL-10 plasma levels. The *in vitro*studies of cGAMP MP-treated monocytes confirmed suppression of CD80 and CD86 and increased secretion of IL-27 and IL-10, and co-cultures detected increased percentage of $FOXP3^+CD4^+$Tregs with increased expression of CTLA-4, and GITR and increased IL-10 and IL-27 levels in the supernatants.
Conclusion: cGAMP MPs suppress RREAE when given at the onset or at the peak of disease. cGAMP MPs induce decreased CD80/CD86 tolerogenic phenotype in monocytes and DCs and increased secretion of IL-10 and IL-27, which induce T reg expansion indicating its potential use as a tolerogenic therapy in patients with RRMS.

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P304
Decision-making factors in patient choice to initiate treatment with cladribine: a preliminary baseline analysis from the STATURE study

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Introduction: Multiple sclerosis (MS) disease modifying therapy (DMT) decision making is a collaborative process between the person with MS and their MS healthcare team, with consideration to the person's priorities and life circumstances. Given that there are now 16 available DMT options, it is important to understand patient's treatment decision-making influences.
Objective: STATURE is a multi-site prospective longitudinal trial to assess the relationship between treatment burden, medication adherence and quality of life in people newly prescribed oral DMTs: cladribine, dimethyl fumarate, fingolimod, teriflunomide and ozanimod, within routine care.
Aim: The current analysis utilised preliminary baseline data from the STATURE study to identify DMT decision-making influences in people with MS who commenced the oral DMT, cladribine.
Methods: Here we present data from 63 participants with MS newly prescribed cladribine (79.4% female; age M=45.2 (SD=14.3) years). Participants were asked to rank order their 5 most influential decision-making factors from 9 pre-set options and an 'other' text option when choosing their*current* DMT.
Results: Participants ranked their MS healthcare specialist's recommendation as the highest decision making factor, with 41.3% (n=26) of participants ranking it as their top decision making factor and 36.5% (n=23) ranking it as a factor (ranked 2-5). Following this, the two most important factors were lifestyle fit (rank 1: n=10, 15.9%; rank 2-5: n=29, 46.0%) and efficacy (rank 1: n=7, 11.1%; rank 2-5: n=34, 54.0%). Minimal side-effects (rank 1: n=5, 7.9%; rank 2-5: n=29, 46.0%) and ease of use (rank 1: n=4, 6.5%; rank 2-5: n=30, 47.6%) were both ranked highly as secondary considerations, followed by perceived safety (rank 1: n=0, 00.0%; rank 2-5: n=23, 36.5%). In contrast, oral administration route, monitoring test frequency and family planning were the least ranked decision influences (unranked: n=49, 77.8%; n=52, 82.5%; n=61, 96.8%, respectively).
Conclusions: An understanding of the influential factors in DMT decision making is important to person-centred healthcare that respects patient choice and maximises quality of life. Research is required to assess different decision-making influences in DMT choice so that healthcare professionals working with people with MS are better informed when considering DMT options within the context of the person and their lifestyle.

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P305
The Antwerp experience with patient requests for AHSCT in multiple sclerosis

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Introduction: Autologous hematopoietic stem cell transplantation (AHSCT) has gained a lot of patient attention as a highly efficacious treatment for MS and is perceived as a potential curative treatment by MS patients. Many patients consult with a request for this treatment, however most of them are not good candidates as per Belgian and international guidelines for AHSCT in MS.
Objectives: First, to assess the proportion of patients fulfilling the indication for AHSCT versus request for AHSCT in patients with MS, consulting the outpatient clinic of the Antwerp University Hospital. Second, to describe the reasons why the indication for AHSCT was lacking.
Methods: Retrospective chart review.
Results: Between 2018 and 2022, 49 patients (19 male, 30 female) were seen at the outpatient MS clinic of the Antwerp University Hospital with the specific request for AHSCT. Mean age was 41 years +/- 10 years. Mean EDSS was 5 +/-1.5. 22 were diagnosed with RRMS, 17 SPMS and 10 PPMS. Only 6 of them (12%) had an indication for AHSCT (active MS with relapse and MRI activity, while under high efficacy disease modifying treatment (DMT) for at least 6 months; 4 RRMS, 1 SPMS and 1 PPMS). 5 of them underwent AHSCT in our hospital. Out of the 43 patients without an indication, 30 patients had no relapse and no MRI activity in the previous year, despite EDSS progression in 16 of them. 5 patients who had relapses did not fullfill the criteria of the second line treatment and/or duration of this treatment. In 3 patients there were signs of functional aggravation on clinical examination. 16 of the 43 patients were not using a high efficacy DMT.
Conclusion: Most patients requesting AHSCT do not fulfill an indication and most frequently this is due to lack of clinical and MRI activity. Patient education on current indications of AHSCT is needed.

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MS patients not treated in french expert centers: explanatory factors and evolution between 2016 and 2019

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Introduction: We showed in a first study, covering the year 2016, that 31.3% of all MS patients seen in French expert centers were not receiving any disease modifying treatment (DMT) during the study period. In addition, 14.7% had never received any DMT.
Objectives: See the evolution of these parameters (patients without any current DMT and patients never treated) three years later (year 2019), following the publication of the new diagnostic criteria and the marketing of new DMTs.
Aims: Identify factors that explain the lack of DMT.
Methods: We conducted a retrospective cohort study. Data were extracted from the 38 centers participating in the European Database for Multiple Sclerosis (EDMUS) on June 15, 2021, and

patients with MS seen at least once during the study period (from December 15, 2018 to December 14, 2019) were included.
Results: 24822 patients with MS were seen at least once during the period of interest. 29.2% of them were untreated, vs 31.3% previously ($p<0.001$). 12.5% of patients had never received any DMT (vs 14.7%, $p<0.001$). Older age, longer duration of MS, progressive disease course, relapsing remitting disease course with single relapse, and male gender were associated with a higher probability of non-treatment. In 2016, 37.0% of patients with RR-MS were not receiving DMT 1 year after the first signs or symptoms. This proportion decreased to 29.1% in 2019 ($p<0.001$).
Conclusions: This study shows a significant decrease in the proportion of untreated patients in just 3 years. However, there is still a significant proportion of patients not receiving DMT, showing the existence of unmet needs, particularly in terms of very early management and management of progressive forms.

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Evobrutinib exerts a therapeutic action on EAE by increasing the peripheral and central classical dendritic cell number and maturation

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Introduction: Multiple sclerosis (MS) is a chronic, inflammatory and neurodegenerative disease of the central nervous system. Currently, the search for new therapeutic strategies to control the immune attack is an active topic in the field. Evobrutinib is an oral, highly selective covalent Bruton's tyrosine kinase (BTK) inhibitor with promising results in recent clinical studies. Although absent in T cells, BTK is present in B cells and myeloid cells, important cell subsets with a prominent role on the pathogenesis of MS through the control of T cell activity.
Objectives: In the present study, we assess the effect of evobrutinib on myeloid cells in the MOG_{35-55}-induced chronic-progressive experimental autoimmune encephalomyelitis (EAE) MS model, in which the contribution of B cells is very limited.
Methods: Female EAE mice received an individualized daily oral treatment of vehicle (EAE-Veh) or evobrutinib (EAE-Evo) for 4 consecutive days from the day of disease onset. EAE was scored clinically on a daily basis and flow cytometry analyses of the spleens and spinal cords, together with the histopathological examination, were performed at the end of each individualized treatment. EAE-Evo mice with a clinical course indistinguishable from that of EAE-Veh were classified as non-responders (Evo-NR), whereas those with a less severe disease were considered responders (Evo-R).
Results: EAE-Evo mice presented significantly milder clinical courses than EAE-Veh mice, together with lower demyelination and axonal damage in the spinal cord. In Evo-R mice, evobrutinib treatment induced an increase in the presence and maturation of splenic $CD11b^+CD11c^+Ly\text{-}6C^-$classical dendritic cells (cDCs), which was strongly associated with milder clinical signs. Moreover, the immunological ratio and balance between activated $CD69^+$ T-cells/cDCs was dramatically reduced in EAE-Evo mice, which significantly correlated with milder EAE clinical courses. On the contrary, Evo-NR animals showed a myeloid content similar to the EAE-Veh mice. Remarkably, Evo-R mice exhibited a lower myeloid cell infiltrate in the spinal cord, albeit enriched in mature cDCs.
Conclusion: Our data suggest that evobrutinib exerts a therapeutic action in EAE by increasing the abundance and maturation of cDCs, which were associated with milder EAE clinical courses. The interpretation of the immunological alteration of cDCs by evobrutinib will be further investigated using functional *in vivo* and *ex vivo* assays.

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Safety and clinical efficacy outcomes from the Long-term extension study of tolebrutinib in patients with relapsing multiple sclerosis: 2-year results

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Introduction: Phase 2b trial (NCT03889639) findings in patients with relapsing multiple sclerosis showed central nervous system-penetrant Bruton's tyrosine kinase inhibitor tolebrutinib was well tolerated over 12 weeks and elicited dose-dependent reductions in new gadolinium-enhancing T1 and new/enlarging T2 lesions.

Objective/Aim: To characterise tolebrutinib's safety and efficacy at Week 96 (2 years) in the phase 2b trial's long-term safety (LTS) extension (NCT03996291).
Methods: In LTS extension Part A, patients continued their core study tolebrutinib dose (5, 15, 30, or 60 mg/day) double-blind until the phase 3 study dose selection (60 mg/day). In Part B, patients received open-label tolebrutinib 60 mg/day. Safety was assessed via adverse event (AE) reporting. Efficacy outcomes included annualised relapse rate (ARR) and change from baseline Expanded Disability Status Scale (EDSS) score.
Results: 124 of 125 patients completed Part A and transitioned to Part B; 114 (90.5%) remained on study as of 7 March 2022. One patient receiving tolebrutinib 5 mg/day discontinued Part A because of progressive disease and 10 discontinued Part B because of AEs (n=3), perceived lack of efficacy (n=4), emigration (n=2), and patient decision (n=1). At Week 96, no new safety signals have been observed. The most common treatment-emergent AEs (TEAEs) were COVID-19 (20.8% [26/125]), headache (13.6% [17/125]), nasopharyngitis and upper respiratory tract infection (both 11.2% [14/125]), bacterial cystitis (7.2% [9/125]), and pharyngitis and arthralgia (both 5.6% [7/125]). No tolebrutinib dose effects for TEAEs or serious AEs were observed in Part A and no safety signals emerged for patients switching to tolebrutinib 60 mg/day in Part B. Of those who received tolebrutinib 60 mg/day for a minimum of 8 weeks, ARR was 0.17 (95% CI: 0.12, 0.25) and 80.6% remained relapse-free. Mean EDSS remained stable to Week 96.
Conclusions: Through LTS Week 96, tolebrutinib 60 mg/day continues to show favourable safety, and is associated with a low ARR and stable disability status.

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P309
MOG-loaded liposomes as an antigen-specific therapy for multiple sclerosis: preclinical studies

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Background: Multiple sclerosis (MS) is a chronic demyelinating disorder of the central nervous system that causes disability in patients. Since it is an immune-mediated disorder, MS is considered an autoimmune disease. For this reason, many strategies based on the restauration of immune tolerance towards myelin antigens have been explored. In previous studies, liposomes mimicking apoptotic bodies and loaded with autoantigens have been proved to be effective to induce antigen-specific tolerance in an animal model of diabetes and MS.
Aim: We aimed to (i) confirm the efficacy of an antigen-specific therapy based on the use of liposomes mimicking apoptotic bodies and loaded with 35-55 myelin oligodendrocyte glycoprotein (MOG 35-55) peptide in experimental autoimmune encephalomyelitis (EAE), and adjust the dose and the concentration of MOG 35-55 peptide charged on liposomes, (ii) elucidate the mechanisms of action of the therapy and (iii) explore different routes of administration to make the therapy feasible for clinical translation.
Methods: EAE was induced with MOG 35-55 peptide. Intraperitoneal administration of MOG-liposomes was tested in preventive, early therapeutic and therapeutic approaches. The frequency of T cell subsets after treatment was studied by flow cytometry. Abrogation of regulatory T (Treg) cells, IL10 or TGF-beta in MOG-liposome treated EAE-mice was performed through the administration of specific blocking antibodies. Intradermal, intranasal and intravenous routes of administration were tested as candidates for clinical translation.
Results: The early therapeutic administration of MOG-liposomes led to a significant improvement of EAE clinical outcome affecting the development and the severity of the disease. Therapeutic administration of MOG-liposomes in symptomatic EAE mice significantly ameliorated the severity of the disease. The therapy with MOG-liposomes expanded Treg cells and promoted the expression of inhibitory molecules in effector/effector memory T cells. Specific elimination of Treg cells enhanced the severity of EAE in MOG-liposome treated mice. Intradermal and intravenous routes of administration also elicited a tolerogenic effect.
Conclusion: Our results indicate that treatment of EAE mice with MOG-loaded liposomes leads to an antigen-specific immune tolerance that is mediated by the expansion of Treg cells.
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M Vives-Pi, M Dalmases, S Rodríguez-Vidal, M Salvado and B Barneda-Zahonero are employees of Ahead Therapeutics SL.

P310
The pepducin P2pal-18S attenuates neuroinflammation in experimental autoimmune encephalomyelitis

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Introduction: Proteinase-activated receptor 2 (PAR2) is a proteinase-activated G-protein-coupled receptor that is activated by proteinases and modulates inflammatory responses. PAR2 expression is elevated in the central nervous system (CNS) in multiple sclerosis (MS) and its murine experimental autoimmune encephalomyelitis (EAE) model. EAE disease severity is markedly reduced in PAR2-null mice. We therefore hypothesized that a receptor-selective PAR2 antagonist, the pepducin P2pal-18S, would attenuate the progression of EAE, in part by affecting immune cell function.
Objective: To assess the therapeutic potential of PAR2 inhibitors for the treatment of MS.
Aims: To determine the treatment effect and mechanism of action of P2pal-18S in EAE.
Methods: To evaluate the impact of PAR2 blockade on EAE progression, P2pal-18S (10mg/kg) was administered on day 0 and day 10 post immunization and motor disability was monitored. Spinal cords were isolated at the peak of disease expression (day 15) and assessed by immunohistochemistry for axon myelination, T cell- and macrophage- specific markers. Serum was isolated from EAE-affected mice to survey the circulating inflammatory and anti-inflammatory cytokines by Luminex assay. To analyze the effect of P2pal-18S on T cell and bone marrow-derived macrophage function, primary cells were treated with P2pal-18S *in vitro* and proliferation and cytokine-mediated differentiation was assessed, respectively. In addition, cytokine production by treated splenocytes and bone marrow-derived macrophages were analyzed.
Results: P2pal-18S treatment resulted in significantly reduced clinical severity of EAE and reduced infiltration of T cells and macrophages, serum levels of several cytokines, including GM-CSF, as well as demyelination. Further, P2pal-18S decreased anti CD3/CD28-triggered lymphocyte proliferation, and prevented cytokine-induced macrophage M1/M2 differentiation. The decrease of serum GM-CSF in P2pal-18S–treated EAE mice paralleled the decreased production of GM-CSF by pepducin-treated CD3/CD28-activated splenocytes.
Conclusions: We conclude that PAR2 plays a key role in neuroinflammation in EAE and that this GPCR may represent a novel therapeutic target for treating MS and other neuroinflammatory diseases.

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P311
Real-world experience with cladribine tablets in an aged ⩾50 years cohort

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Background: Cladribine tablets are indicated for the treatment of adults with relapsing forms of multiple sclerosis (MS) based on data from pivotal clinical trials, including the phase 3 study, CLARITY, and its extension.
Objectives: Our study aims to present real-world experience in aged ⩾50 years in MS patients treated with cladribine. Understanding the benefit/risk profile of using a non-continuous immunosuppressive DMD in this population is of utmost importance given immunosenescence and the increased risk of comorbidities with age.
Methods: Prospective and retrospective chart review.
Results: We report on a subgroup of 48 aged>50 years patients out of 84 total patients who have initiated therapy with cladribine tablets. The median age at cladribine initiation was 60.8 years in the aged ⩾50 subgroup and 52.5 years (range 29-72 years) in the all patients group. The median disease duration was 14.7 years in the ⩾50 subgroup and 11.6 years in the all patients group. Mean follow-up was 568 days in the ⩾50 subgroup and 555 in the all patients group.
43 patients of 84 completed both treatment courses by the data cutoff. 89.6% of patients experienced any grade of lymphopenia. In the all patients group, one patient (1.4%) who was also in the⩾50 subgroup experienced grade 4 lymphopenia at 8 weeks post treatment. No patients experienced grade 4 lymphopenia at 24, 52 & 60 weeks post treatment. Fatigue, upper respiratory and urinary tract infection occurred in > 10% of patients.
The mean number of relapses in the 12 months prior to cladribine initiation was 0.5 in the ⩾50 subgroup and 0.7 in the all patients group. The mean number of relapses since cladribine initiation was 0.09 in the>50 subgroup, and 0.16 in the all patients group. In the ⩾50 subgroup 87.5% of patients were relapse free, 81% in the all patients group. 12.5% of patients had one relapse in the ⩾50 subgroup, and 14.5% in the all patients group.
Conclusions: In this cohort of patients initiating therapy with cladribine tablets in a real-world setting, the treatment was well-tolerated. There were no new safety signals. The side effect profile was consistent with that seen in the clinical trial program, even in an aging patient population where co-morbid conditions and immunosenescence may increase. Owing to short follow-up time, it was not possible to assess long-term outcomes. Ongoing follow-up will further expand on these results as more patients complete their full treatment course.

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P312
In the absence of inflammation, BTK inhibition interferes with maturation of B cells, but does not affect myeloid phagocytes

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Background: Bruton's tyrosine kinase (BTK) is an essential signaling molecule in the development of Bcells and its inhibition provides an efficient therapeutic target for multiple sclerosis. However, its expression is not restricted to Bcells. It is also expressed in different myeloid cells like monocytes/macrophages, dendritic cells and neutrophils and plays a role in Fc receptor, toll-like receptor, cytokine and chemokine receptor signaling. Inhibition of BTK has been shown to reduce Fcγ receptor-mediated phagocytosis of macrophages, rendering it a promising target in the treatment of demyelinating disorders triggered by pathogenic antibodies.
Objectives: We investigated the impact of the BTK inhibitor evobrutinib on the differentiation and activation of Bcells and Tcells in naïve 2D2 mice. Furthermore, we analyzed whether evobrutinib changes the composition and activation of myeloid cells with an emphasis on professional antigen-presenting cells.
Methods: We treated naïve 2D2 mice orally with the BTK inhibitor evobrutinib at a daily dose of 3 mg/kg or control substance for three weeks and investigated the impact of the BTK inhibition on different cell types in spleen, cervical and inguinal lymph nodes using flow cytometry.
Results: Upon treatment with evobrutinib, the maturation of Blymphocytes was altered towards an accumulation of the less mature follicularII Bcells, while the phenotype and differentiation of macrophages and dendritic cells was unchanged. The expression of Fc receptors as well as molecules involved in antigen presentation were neither altered on phagocytic cells nor on myeloid antigen-presenting cells upon BTK inhibition. However, the frequency of Tcells was increased upon treatment with evobrutinib, although those cells do not express BTK themselves.
Conclusion: In the absence of an inflammatory environment, evobrutinib leads to an inhibition of Bcell maturation, while it does not alter the phenotype nor the differentiation of myeloid phagocytes.

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P313
Omicron breakthrough disease activity in the Swiss multiple sclerosis cohort study

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Introduction: In patients with Multiple Sclerosis (pwMS), specific disease modifying treatments (DMTs) may compromise immune response following SARS-CoV-2 vaccination. Limited information is available, whether levels of anti-SARS-CoV-2 antibodies are linked to the risk of breakthrough infections in pwMS.
Objectives: To determine the rate of Omicron breakthrough infection and severity of COVID-19 in a cohort of MS patients treated with different DMTs and to estimate the impact of SARS-CoV-2-specific antibody level on breakthrough infection risk.
Methods: This study is nested within the Swiss MS Cohort, a nationwide multicenter study that has recruited 1585 pwMS. Patients who received two doses of SARS-CoV-2 vaccines before Omicron became the dominant variant in Switzerland on Dec-15, 2021 and had a follow-up thereafter were included. Data on SARS-CoV-2 infections, severity of COVID-19 according to the WHO scale and SARS-CoV-2 vaccines were collected by questionnaires. Anti-SARS-CoV-2-S antibody levels were measured after the second vaccine dose. Incidence of infections grouped by antibody level after second vaccination was visualized using Kaplan-Meier curves. Cox regression models were used to estimate the impact of antibody levels on the hazard of breakthrough infection during follow-up.
Results: 242 pwMS (median age 49y [39,58], 162 (67%) female, 36 (15%) with progressive disease, median EDSS 2.5 [1.5,4.0])

were included. 22 (9%) had SARS-CoV-2 infection and 137 (57%) at least one additional vaccine dose prior to Omicron start. Since then, 57 breakthrough infections were reported. Severity of breakthrough disease on WHO scale ranged from 1-10: 7 were asymptomatic, 46 were symptomatic as outpatients, 3 were hospitalized and 1 died. Patients with antibody levels >150U/ml (n = 95, 39%) after second vaccination had a 64% reduced risk for Omicron breakthrough-infection compared to patients with antibody levels <0.7U/ml (n = 81, 33%) (HR 0.36, 95%CI=0.18-0.71, p<0.01). This effect was maintained after adjustment for DMT at vaccination and time since second vaccination

Conclusions: Humoral immune response after second SARS-CoV-2 vaccination is associated with Omicron breakthrough infection rate, a finding contrasting general populations, where antibody levels seem to have little impact on protecting from Omicron infection. Most breakthrough infections in our cohort were mild. Analyses on the effect of booster vaccinations on serology and infection rates will follow.

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GD

SM reports nothing to disclose.

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CP is an employee and a shareholder of F. Hoffmann-La Roche Ltd

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CG

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P314

Autologous hematopoietic stem cell transplantation in multiple sclerosis: updating outcomes in the Valencian cohort

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Introduction: Autologous hematopoietic stem cell transplantation (aHSCT) has been recognized as a therapeutic option for very aggressive multiple sclerosis (MS) patients, although it is not a commonly used technique. The current aHSCT indications are highly active MS (clinical relapses and activity on brain MRI), with a short duration of disease (⩽ 5 years), and a suboptimal response to high-efficacy available treatments.
Objectives and aims: The main objective of this study is to update the characteristics of patients and outcomes in the Valencian cohort.
Methods: A prospective cohort of 46 consecutive MS patients undergoing aHSCT between 1999 and 2022 was included in the analysis. The main indication for transplantation was clinical relapse despite active targeted treatment for at least one year; in a minority of patients the procedure was indicated due to criteria of high inflammatory activity with catastrophic relapse or disease progression. Clinical and demographic characteristics were registered. Efficacy was assessed in patients followed for, at least, 2 years and toxicity was assessed during the entire follow-up.
Results: The baseline characteristics of the patients prior to treatment with aHSCT were, mean age 36.53 years (SD 9.2), 31 women and 15 men, 33 recurrent MS - 11 secondary progressive MS - 2 primary progressive MS and disability measured with EDSS of 5 (SD 4 – 6). 24 patients had gadolinium enhancing lesions gel at baseline prior to aHSCT. All the patients studied received targeted treatment previously to aHSCT and from them, 7 (15.5 %) were treated with anti-CD20 therapies and 4 (8,8%) with alemtuzumab. The median time to follow-up was 8 years (2,5 - 13). 28 patients had lost NEDA-3 status at last visit, 8 patients progressed*de novo* and 20 required re-initiation of specific treatment. Median EDSS post-aHSCT was 4 (SD 3 – 6.5), we found a median overall EDSS improvement of 0.5 (SD -1.5 – 1). Higher baseline EDSS was predictive of worse outcomes. Malignancies and autoimmune events were infrequent (3 for each group).
Conclusions: aHSCT as an alternative therapy to manage aggressive MS patients is a relatively safe and effective procedure. It is necessary to propose comparative studies with adverse effects and effectiveness between immunomodulatory treatments and aHSCT.

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P315

Cyclophosphamide in acute treatment of severe neuroinflammatory disorders

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Introduction: Central nervous system (CNS) neuroinflammatory disorders including CNS vasculitis, neuromyelitis optica, autoimmune encephalitis, tumefactive and aggressive multiple sclerosis (MS) can be difficult to treat. Cyclophosphamide is a chemotherapy and immunosuppressive agent which may be a good option for patients who fail first line therapy.
Objectives: To review outcomes of patients who received cyclophosphamide for severe CNS neuroinflammatory conditions at Rush University Medical Center.
Methods: Retrospective chart review was performed to identify patients who failed first line immunosuppressive therapy and were subsequently treated with cyclophosphamide. Primary outcomes included targeted neurologic deficits (TNDs) and radiologic activity. TNDs were graded numerically as follows 1) no improvement, 2) mild improvement not impacting functioning, 3) marked improvement impacting functioning, and 4) return or near return to baseline. Patients were divided into two categories: non and atypical MS patients or typical MS patients.
Results: We identified 46 patients who received cyclophosphamide for treatment of neuroinflammatory CNS conditions who had all failed intravenous (IV) steroids, IV immunoglobulin therapy, plasma exchange, or a combination of these therapies. Median age was 35. The majority of patients (82.2%) had improvement in TNDs with 62.2% having scores 2 or above. Overall improvement was similar among the two groups; however, the non and atypical MS group had a more robust clinical response with 76.9% having a TND score of 3 or 4. Similar rates of improvement persisted at second follow up (median of 6 months). At a median of 3 months, 85.4% of patients had stable or improving imaging. One-third of patients developed side effects with most common being nausea, vomiting, alopecia, and headache. One patient was diagnosed with uterine cancer 5 years after exposure to cyclophosphamide. There were no other malignancies reported in a median follow up time of 7 years.
Conclusion: Treatment with Cyclophosphamide can result in disease stabilization of severe CNS neuroinflammatory disorders.

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P316

Different type and timing of S1P receptor modulator therapy impacts T and B cell response after SARS-CoV2 vaccination

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Introduction: The generation of humoral and cellular responses by SARS-CoV2 vaccination in patients with multiple sclerosis (pwMS) especially onsphingosin-1-phosphat receptor (S1PR) modulator treatment is not yet understood. In this study we aim to differentiate the immunological response profiles after 2 mRNA SARS-CoV2 vaccinations depending on timing and unselective vs. selective S1PR modulators in pwMS.
Methods: We conducted a cross-sectional study among pwMS on ozanimod (OZA), fingolimod (FTY) or without disease-modifying treatment. Two courses of mRNA SARS-CoV-2 vaccinations were performed on treatment resp. before treatment start. Demographic data on age, sex and disease progression did no significantly differ in selected groups. Blood was analyzed for SARS-CoV-2 spike protein-specific antibodies and for CD4 and CD8 T cell response by interferon-gamma release assay upon stimulation.
Results: All untreated pwMS (n=31) developed positive antibodies (930.9 +/-803.7 BAU/mL), but only in 50% positive T cell responses were seen (S1 0.39 +/-0.68; S2 0.43 +/-0.67 IU/mL). PwMS on longterm FTY treatment (n=86) showed B cell responses (45.0 +/-117.9 BAU/mL) only in 27,9% and T cell responses (S1 0.11 +/-0.86; S2 0.01 +/-0.05 IU/mL) only in 5,9% both with significant lower titers compared to untreated pwMS. In contrast, pwMS on OZA (n= 22) developed B cell responses in 84.2% of patients (703.8 +/-837.5 BAU/mL) with lower titers than untreated pwMS. T cell responses were present in only 4,5% of patients on OZA (S1 0.02 +/-0.05; S2 0.03 +/-0.09 IU/mL). When patients were vaccinated before OZA start (n=25) and tested later on OZA treatment, all patients presented with positive antibody titers comparable to untreated patients (1466.2 +/-838.8 BAU/mL). However, T cell responses could be detected only in 19,0% of these OZA patients (S1 0.05 +/-0.11; S2 0.06 +/-0.14 IU/mL). In summary, only 15.8% OZA, but 69,8% FTY patients did neither develop B nor T cell response. In contrast untreated patients as well as vaccinated patients before OZA treatment start present with at least one B or T cell response.
Conclusion: In this study, we present that B and T cell responses to SARS-CoV2 mRNA vaccines are selectively affected by different S1PR modulators. Vaccination before start of S1PR modulation induced a stable B cell response which could be demonstrated on treatment. These findings should be considered for vaccination strategies during S1PR modulatory therapy.

Disclosure
Katja Akgün reports consulting or serving on speaker bureaus for Roche, Sanofi, Alexion, Teva, BMS, Merckand Celgene as well as research support from Roche. Tjalf Ziemssen reports consulting or serving on speaker bureaus for Biogen, Roche, Novartis, Celgene, Merck and Sanofi as well as research support from Biogen, Novartis, Merck and Sanofi. Georges Katoul Al Rahbani, Christina Woopen and Marie Dunsche have nothing to disclose.

Therapy - Neuroprotection and Repair

P317
Siponimod ameliorates metabolic oligodendrocyte injury via the sphingosine-1 phosphate receptor 5

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Introduction: Multiple sclerosis (MS), an autoimmune-driven, inflammatory demyelinating disease of the central nervous system, causes irreversible accumulation of neurological deficits to a variable extent. Although there are potent disease-modifying agents for its initial relapsing-remitting phase, immunosuppressive therapies show limited efficacy in secondary progressive MS (SPMS). Although modulation of sphingosine-1 phosphate receptors has proven beneficial during SPM, the underlying mechanisms are poorly understood.
Objectives: In this project, we followed the hypothesis that Siponimod, a sphingosine-1 phosphate receptor modulator, exerts protective effects by a direct modulation of glia cell function (id est either astrocytes, microglia or oligodendrocytes).
Aims: We aimed to demonstrate direct protective effects of Siponimod in the central nervous systems which are independent of a modulation of adaptive immune cells.
Methods: We used the toxin-mediated, non-autoimmune MS animal model of cuprizone intoxication and investigated potential protective effects of Siponimod as well as underlying mechanisms.
Results: On the histological level, Siponimod ameliorated cuprizone-induced oligodendrocyte degeneration, demyelination and axonal injury. Protective effects were as well evident using GE180 TSPO-PET/CT imaging or next generation sequencing. Siponimod as well ameliorated the cuprizone-induced pathologies in *Rag1*-deficient mice, demonstrating that the protection is independent of T- and B-cell modulation. Pro-inflammatory responses in primary mixed astrocytes/microglia cell cultures were not modulated by Siponimod, suggesting that other cell types than microglia and astrocytes are targeted. Of note, Siponimod completely lost its protective effects in*S1pr5*-deficient mice suggesting a direct protection of degenerating oligodendrocytes.
Conclusions: Our study demonstrates that Siponimod exerts protective effects in the brain in a S1PR5-dependent manner. This finding is not just relevant in the context of MS but as well other neuropathologies characterized by a degeneration of the axon-myelin unit.

Disclosure
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P318
Siponimod inhibits IFN-gamma-induced microglial activation through a dual central and peripheral mechanism of action

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Introduction: A hallmark feature of secondary progressive multiple sclerosis (SPMS) is microglial activation. The presence of central nervous system (CNS) T cell infiltrates in SPMS supports the hypothesis of a T cell-driven microglial inflammation as motor of progressive disease. Siponimod, an approved treatment for active SPMS, is a CNS-penetrating modulator of sphingosine-1-phosphate receptor subtypes 1 (S1P1R) and 5 (S1P5R) with the ability to modulate microglial S1P1R.
Objectives: In this study, our objective was to assess the effect of siponimod treatment on the phenotype of microglia and T cells in chronic experimental autoimmune encephalomyelitis (EAE) and to analyse direct effects of siponimod on microglia in vitro.
Aims: The aim of this study was to investigate the effect of siponimod on T cell-mediated microglial activation in chronic neuroinflammation.
Methods: EAE was induced in wild type C57BL/6 mice aged 8-12 weeks with MOG_{35-55} peptide emulsified in CFA and with pertussis toxin. Mice were fed with vehicle food or food containing 3 mg, 10 mg or 30 mg siponimod/kg. Siponimod treatment was started after the peak of disease, 20 days post immunization. After 2 months of treatment, mice were sacrificed either for histology or ex vivo FACS analysis of microglia and leukocytes isolated from blood, inguinal lymph nodes and spleen. Mixed glial cultures were prepared from neonatal wild type C57BL/6 mice. Microglial cells were cultured with siponimod or its solvent and subsequently stimulated with TNF-alpha, LPS or IFN-gamma. The microglial phenotype and S1P1R expression was assessed by flow cytometry, ELISA and/or qRT-PCR.
Results: Siponimod treatment of chronic EAE induced an amelioration of disease severity associated with a significant downregulation of microglial MHC class II expression and a reduction of CNS T cell infiltration. In the periphery, the proportion of T cells was reduced with effector memory T cells as predominant phenotype. In vitro, the treatment of primary microglial cultures with siponimod could inhibit IFN-gamma-induced activation.
Conclusions: Therapeutic siponimod treatment of chronic EAE led to an improved clinical outcome associated with a reduced microglial expression of MHC class II. We assume that the altered microglial phenotype is due to a direct, central siponimod effect with inhibition of IFN-gamma-induced microglial activation as well as to an indirect, peripheral effect based on a reduction of circulating T cells.

Disclosure
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NVG-291 phase 1 results and phase 2 study design in individuals with relapsing-remitting multiple sclerosis

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Introduction: Chondroitin sulphate proteoglycans (CSPGs) are increased at sites of CNS damage, including MS lesions, and inhibit neural repair mechanisms, in part through interaction with receptor protein tyrosine phosphatase sigma (PTPσ). NVG-291 is a subcutaneously (SC) administered peptide that modulates PTPσ. In various animal models of CNS damage, including demyelination, NVG-291 treatment resulted in functional improvements such as locomotion due to augmented oligodendrocyte progenitor cell survival, migration, and differentiation, remyelination, axonal regeneration and plasticity.
Objectives and Aims: Present Phase 1 results and Phase 2 RRMS study design.
Methods: In the single ascending dose (SAD) portion of a Phase 1 trial in healthy subjects, 37 subjects were enrolled in 6 dose cohorts of NVG-291 or placebo. The multiple ascending dose (MAD) portion of the study is dosing up to 18 subjects randomly assigned into 3 dose cohorts to receive NVG-291 or placebo SC once-daily for 14 days. NVG-291 doses exceed levels that showed efficacy in animal models. CSF is being collected from additional NVG-291-treated subjects. The multicentre Phase 2 trial will randomise ~84 subjects with RRMS and ambulatory impairment (timed 25-foot walk [T25FW] 8-30 sec) to NVG-291 or placebo administered by daily SC injection x 12 weeks; the objectives are to assess whether subjects with mild-moderate disability and ambulatory impairment show improvement following NVG-291 treatment, as assessed clinically and radiographically.
Results: NVG-291 has been safe and well-tolerated through 6 completed SAD cohorts and the first two MAD cohorts. In the SAD cohorts, all adverse events (AEs) were mild and transient; the most common AE was injection site related, which was more common in the pooled NVG-291 group. Thus far in the MAD, blinded analysis shows that he most common AE was injection site related; all AEs were mild except for a single event of moderate migraine. There were no serious AEs, and no effect on vital signs or ECGs in any subjects, and NVG-291 showed promising pharmacokinetic characteristics.

Conclusions: NVG-291 appears well tolerated after administration of multiple ascending doses in healthy subjects. Upon completion this year, the Phase 1 study will establish the safety/tolerability/pharmacokinetics of NVG-291 to support advancement to the Phase 2 clinical trial in RRMS, which will assess change in clinical and advanced structural imaging measures following treatment.

Disclosure

Dr. D. Mikol is an employee and shareholder of NervGen Pharma.
J. Toews is an employee and shareholder of NervGen Pharma.
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Dr. J. Cohen reports personal compensation for consulting for Biogen, Bristol-Myers Squibb, Convelo, EMD Serono, Glaxo Smith Kline, Janssen, Mylan, and PSI; and serving as an Editor of *Multiple Sclerosis Journal.*
Dr. A. van der Walt serves on advisory boards for Novartis, Biogen, Merck and Roche and NervGen; receives unrestricted research grants from Novartis, Biogen, Merck and Roche and is funded by National Health and Medical Research Council of Australia and MS Research Australia.
Dr. R. Naismith has consulted for Abata Therapeutics, Banner Life Sciences, BeiGene, Biogen, Bristol Myers Squibb, Genentech, Genzyme, Janssen, GW Therapeutics, Horizon Therapeutics, Lundbeck, NervGen, TG Therapeutics.

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The use of magnetisation transfer ratio in demonstrating the neuroprotective effect of phenytoin in patients with acute optic neuritis

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Introduction: Acute demyelinating optic neuritis (ON) frequently occurs in multiple sclerosis (MS) and can cause permanent neuroaxonal damage to the anterior visual pathway.
Objectives: Inhibition of voltage-gated sodium channels is neuroprotective in pre-clinical models and in a phase 2 clinical trial of phenytoin treatment for acute ON.
Aims: We aimed to establish whether sodium-channel inhibition with phenytoin is also neuroprotective in acute ON using magnetisation transfer ratio (MTR), a quantitative index of macromolecular damage.
Methods: We analysed data from the phenytoin neuroprotection study, a randomized, placebo-controlled, double-blind phase 2 trial. Patients with acute ON aged 18–60 years, presenting within 2 weeks of onset, with visual acuity of 6/9 or worse, were randomly assigned (1:1) to oral phenytoin or placebo for 3 months, stratified by time from onset, centre, previous MS diagnosis, use of disease-modifying treatment, and use of corticosteroids for acute ON. Measurements from 60 patients were included in the study (28 phenytoin, 32 placebo). MTR maps of the anterior visual pathway were obtained at baseline and 6-months follow-up. Multilevel mixed models, adjusted for baseline MTR values, investigated treatment effects for phenytoin.
Results: At 6-months, affected optic nerve MTR values were higher in the phenytoin group both within the lesion (*phenytoin*: 29.27 $\pm$ 6.93 vs *placebo*: 27.73 $\pm$ 7.43; p = 0.032, 95% confidence intervals [CI] = 0.151-3.428) and post-lesion areas (*phenytoin*: 33.82 $\pm$ 5.63 vs*placebo*: 32.00 $\pm$ 4.86; p = 0.025, 95% CI = 0.335-4.919), adjusting for baseline MTR. Equivalent results were obtained comparing phenytoin with placebo for MTR follow-up minus baseline in the affected optic nerve: lesion MTR difference was -2.61 $\pm$ 9.15 in the phenytoin group versus -3.03 $\pm$ 8.99 in the placebo group (p = 0.001, 95% CI = 1.401-5.895); in the post-lesion area, the difference was -1.62 $\pm$ 6.99 in the phenytoin group versus -2.43 $\pm$ 6.32 in the placebo group (p = 0.002, 95% CI = 1.648-7.636), indicating a treatment benefit.
Conclusion: Our results support the role of phenytoin for neuroprotection in MS patients with acute ON and corroborate the results previously reported in the phenytoin neuroprotection trial. Phenytoin appears to reduce microstructural damage in the optic nerve following acute ON.

Disclosure

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AI, RR, SK, MCY, MK, RS SJH, and RK have no disclosure.

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CN045 is a novel small molecule lead for remyelinating therapies in multiple sclerosis

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Introduction: Pathological insults in MS result in loss of oligodendrocytes (OLs), demyelination, axonal degeneration and ultimately irreversible neurological disability. Currently available MS therapies focus solely on modulating the immune system. Remyelination therapies that enhance the generation of new oligodendrocytes from oligodendrocyte progenitor cells (OPCs) would restore salutatory conduction, prevent degeneration of demyelinated axons and reduce disability progression in MS. OPCs are present in demyelinated lesions. Enhancing OPC differentiation into mature OLs is considered a viable therapeutic target for promoting remyelination in MS.
Objective: To develop orally bioavailable, safe, effective and patentable small molecules that enhance remyelination in MS.
Methods: OPCs were generated from neurospheres derived from mouse embryos of transgenic mice that express EGFP driven by the PLP promoter. OPCs were cultured in 96-well plates, treated with a library of 20,000 small molecules and analyzed for PLP-EGFP expressing oligodendrocytes. Positive controls included known OPC differentiation molecules: T3, Clemastine and Beztropine. Dose response curves (EC50s) were performed for positive hits and the lead hit was tested in the cuprizone model of demyelination/remyelination. Sixty-four novel analogs were generated for the lead hit and screened in the OPC assay.
Results: We identified 42 hits in the in vitro screening of 20,000 small molecules and 18 compounds had an EC50 less than 200nM. One candidate, CN045, showed significantly higher OPC differentiation potency compared to T3, Clemastine and Beztropine and enhanced white matter and gray matter remyelination in the cuprizone mouse model of remyelination. CN045 demonstrated low toxicity and good brain penetration. To establish IP and improve pharmacokinetics of CN045, 64 novel CN045 analogs were generated and examine in the in vitro OPC differentiation assay. Eighty percent of the novel analogs retain OPC differentiation potential and several compounds were more potent than CN045.
Conclusion: CN045 is a potent small molecule that enhances OPC differentiation in vitro and remyelination in vivo. We have generated novel and patentable analogs of CN045 that retain OPC differentiation with greater potency than CN045, T3, Clemastine and Beztropine. A remyelination therapy, in combination with the current anti-inflammatory therapies, will promote myelin repair and halt neurological decline in MS patients.

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Dr. S. Medicetty is a co-founder of Cashel Neural, Inc., and he received compensation from Cashel and Cleveland Clinic.
Dr. L. Knutsen received compensation from Cashel. He also works with NMD Pharma and served on the Advisory Board of Charcot-Marie-Tooth Association
Dr. R. Hamlyn received compensation from Cashel.

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Ponesimod, mono-selective sphingosine-1-phosphate receptor 1 modulator enhances oligodendrocyte precursor cell differentiation

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Background: Sphingosine-1-phosphate receptors modulators are used clinically to treat relapsing forms of multiple sclerosis (MS). In the periphery S1P1 modulation (functional antagonism) prevents lymphocytes egress from lymph nodes, hence hampering neuroinflammation in MS. Recent findings on S1P1 modulation of oligodendrocyte precursor cells (OPCs), central nervous system resident cells suggest a potential benefit of S1P1 receptor modulation in neuroprotection.
Objective: As the Giα-coupled S1P1 is the most prominently expressed S1P receptor in OPCs, thus S1P1-monoselective modulator ponesimod may have differential direct effects on OPC compared to others in the class that are nonspecific.
Methods: C57BL/6J mouse pups (0-2 days old) were used to obtain glial cultures. Primary mouse OPCs were harvested via the shake-off method after 14 days of culture and were treated *in vitro*, all at 0.3 μM to 3 μM, with either the S1P1-mono-selective modulator ponesimod, the S1P5-mono-selective modulator A971432, a combination of ponesimod and A971432, or the dual S1P1/S1P5 modulators ozanimod or siponimod. OPC migration was evaluated in the agarose drop migration assay, while differentiation was quantified using a fluorescent immunohistochemical staining for the oligodendrocyte marker O4 and the differentiation marker myelin basic protein.*In vitro* myelination capacity was assessed in the fiber myelination assay.
Results: None of the treatments enhanced OPC migration. Moreover fingolimod-phosphate (3 μM) significantly inhibited cell migration. In terms of OPC differentiation, treatment with

ponesimod significantly increased OPC differentiation capacity compared with S1P5 monoselective modulation by A971432 and Dual S1P1/S1P5 modulation by ozanimod or siponimod which did not have any significant effects, *in vitro*based on O4 immunocytochemistry (0.3 μM and 3 μM, or in combination with A971432 0.3 μM and 1 μM). None of the S1P receptor modulators had direct effects on*in vitro* myelination capacity of primary mouse OPCs.

Conclusion: S1P1 monoselective modulator ponesimod significantly increases OPC differentiation *in vitro* which differentiates it from less specific S1P modulators such as fingolimod, ozanimod and siponimod.

Disclosure

MS, EW ad TV report no competing interest. MAT is an employee of Janssen and may own stock or stock options in Johnson & Johnson.

P323

Genetic modification of hematopoietic cells accelerates myelin repair

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Introduction: Preventing neurodegeneration-associated disability progression in patients with multiple sclerosis (MS) remains an unmet therapeutic need. As remyelination prevents degeneration of demyelinated axons, promoting this process in patients might halt the development of permanent disability. In demyelinating mouse lesions, local overexpression of Semaphorin 3F (Sema3F), an oligodendrocyte progenitor cell (OPC) attractant, increases OPC recruitment and remyelination. However, molecular targeting to MS lesions is a challenge because these are disseminated in the central nervous system.

Methods: We hypothesized that a clinically-relevant paradigm to deliver Sema3F to demyelinating lesions and increase OPC recruitment may be to use blood-derived macrophages as vehicles. Thus, we chose transplantation of genetically-modified hematopoietic stem cells (HSCs) as means of obtaining circulating monocytes that overexpress Sema3F.

Results: We first demonstrated that the supernatant from Sema3F-lentiviral vector transduced HSCs stimulates OPC migration in Neuropilin 2 (Nrp2, Sema3F receptor)-dependent fashion. We then investigated whether OPCs remain responsive to Sema3F with age. While Sema3F expression in the lesions of middle-aged and old mice was decreased, middle-aged OPCs retained Nrp2 expression and migrated in response to both recombinant Sema3F and Sema3F-transduced cell supernatant in vitro. We then investigated whether blood cells engineered to overexpress Sema3F can target demyelinating CNS lesions and improve remyelination. Thus, we transplanted Sema3F-transduced HSCs and obtained chimeric mice (with Sema3F overexpression in blood cells), in which we induced demyelinating spinal cord lesions. Transgene-carrying cells, predominantly macrophages, quickly infiltrated lesions in both control and Sema3F chimeras. While Sema3F-expressing cells did not alter the inflammatory status of the lesions nor OPC survival, it increased OPC recruitment, which accelerated the onset of remyelination.

Conclusion: Our results provide a proof-of-concept that blood cells, particularly monocyte-derived macrophages, can be used to deliver pro-remyelinating agents "at the right time and place", suggesting novel means for remyelination-promoting strategies.

Disclosure

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Therapy - Long-term treatment monitoring

P324

Improved clinical outcomes in patients treated with natalizumab for at least 11 years - real-world data from a swedish national post-marketing surveillance study (IMSE 1)

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Introduction: Natalizumab (NTZ) is a highly effective disease modulatory treatment for relapsing-remitting multiple sclerosis (RRMS). Post-marketing surveillance is important for evaluation of long-term safety and effectiveness in a real-world setting. To this end the "Immunomodulation and Multiple Sclerosis Epidemiology Study" (IMSE 1) was initiated upon NTZ launch in Sweden (Aug 2006).

Objectives/Aims: To follow-up the long-term effectiveness and safety of NTZ in a real-world setting.

Methods: Adverse events (AEs), Serious AEs (SAEs), John Cunningham virus status (JCV) and clinical effectiveness measures; Extended Disability Status Scale (EDSS), Multiple Sclerosis Severity Scale (MSSS), Symbol Digit Modalities Test (SDMT) and Multiple Sclerosis Impact Scale (MSIS-29) data is collected from the nationwide Swedish Neuro Registry (NeuroReg). Effectiveness measures were assessed using the Wilcoxon Signed Rank Test.
Results: A total of 3622 NTZ patients were included in the IMSE 1 study from August 2006 until March 2022 (72% female; mean age 36 years; 80% RRMS; mean treatment duration 49 months) and 186 had been treated for at least 132 months. Of the 132-month cohort, 73% were female, the mean age was 36 years, 88% had RRMS, and the mean treatment duration was 155 months. The majority were treated with interferons and glatiramer acetate prior NTZ (64%). 25% (47/186) discontinued NTZ treatment of which 47% (n=22) discontinued due to JCV positive (JCV+). In total, 30% (55/186) of these patients were JCV+ with a mean JCV index of 1.2±1.0 (2% missing data). Relapses before treatment were reduced from 380/1000 patient years to 43/1000 during treatment, 71% were relapse-free and 18% had 1 relapse during the entire treatment period (15% missing data). Most clinical effectiveness measures, MSSS, MSIS-29 and SDMT showed statistically significant improvement between baseline and 132 months ($p<0.05$). Over the entire observation time, 125 SAEs had been reported to the Swedish MPA including 9 cases (2 fatal) of progressive multifocal leukoencephalopathy (PML) of which 8 occurred between 2008 and 2012, and one in 2018.
Conclusions: NTZ is generally well tolerated with sustained effectiveness regarding cognitive, physical and psychological measures, as well as relapse-control. Introduction of JCV testing has led to fewer treated JCV+ patients, which likely explains a drastic drop in number of reported cases of PML.

Disclosure
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P325
Siponimod stabilises physical disability scores in people living with secondary progressive multiple sclerosis after 2 years of treatment: analysis from the novartis global managed access program

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Introduction: In the Phase III EXPAND trial, siponimod demonstrated significant reductions in the risk of confirmed disability progression (CDP) and confirmed worsening of cognitive processing speed in comparison to placebo (broad secondary progressive MS [SPMS] population). However, most regions (including European Union) approved siponimod for the treatment of active SPMS. Real-world effectiveness data for siponimod in the clinical setting are still scarce.
Objectives: To describe demographic and clinical characteristics and characterise EDSS score changes in people living with SPMS (plwSMPS) receiving siponimod under the manage access program (MAP): Global Siponimod MAP cohort (BAF2001M cohort).
Methods: The BAF2001M cohort is an umbrella program Novartis implemented to facilitate patient access to siponimod when marketing authorisation is pending (under physician request) in the absence of satisfactory alternative therapies. The program started in March 2019 and is on-going. Target population included adult patients with SPMS diagnosis and EDSS score <7 from Mar 2019-Jan 2021. From Jan 2021 onward access to the MAP required SPMS with active disease. Treatment selection and patient monitoring was based on physician assessment. No regular visits or data entry or collection were mandatory. Baseline characteristics include country, age, gender, relapse, MRI activity in the last 2 years, EDSS, and cognition evaluation.
Results: A total of 632 cases were analysed (153 excluded from the analysis due to local country restrictions). Mean age was 52.3 (SD: 8.7) years, 60% were females, and median EDSS was 5.5

(interquartile range: 4.5-6.5). Around 51% had a relapse in the last 2 years, 54% had prior cognitive evaluation, and 52% had an MRI scan in the last 2 years (48% showed activity). Mean change in EDSS from baseline was around -0.02/-0.03 at the Months 6, 12, 18, and 24 (not statistically significantly different from baseline). Approximately 94% (140/149) patients improved or were stable at Month 24. Further analysis to be presented at congress.
Conclusion: In a heterogenous cohort of 620 plwSPMS (including non-active SPMS) receiving siponimod in a real-world clinical setting, the vast majority improved or stabilised their EDSS score over 2 years. Interestingly, this patient population was older than the EXPAND study population and, with approximately half demonstrating relapse/MRI activity, supports siponimod's effectiveness in a broad SPMS population.

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P326
Safety of ocrelizumab in multiple sclerosis: Updated analysis in patients with relapsing and primary progressive multiple sclerosis

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Introduction: The long-term benefit–risk profile of ocrelizumab (OCR) in patients (pts) with multiple sclerosis (MS) can be evaluated by regular safety reporting of clinical trial (CT) and post-marketing (PM) data. Safety/efficacy of OCR have been characterised in Phase II (NCT00676715) and Phase III (NCT01247324; NCT01412333; NCT01194570) trials and related open-label extension (OLE) periods, in relapsing-remitting MS, relapsing MS (RMS) and primary progressive MS (PPMS). It is important to understand the long-term safety profile of OCR and consider the impact of COVID-19.
Aims: To report the continuity in safety by reporting longer-term safety evaluations from OCR CT and OLE periods over a 9-year follow-up period (up to November 2021).
Methods: Safety outcomes, with and without COVID-19, are reported for the OCR all-exposure population from 11 ongoing CTs in MS. Rates per 100 patient years (PY) are presented.
Results: Over more than 9 years of follow-up, 5,848 pts with MS received OCR treatment in 11 CTs (25,153 PY of exposure; November 2021). Reported rates per 100 PY (95% CI) were: Adverse events (AEs), 232.71 (230.83–234.60), [excluding COVID-19 (EX COV) 230.12 (228.25–232.01)]; infections, 69.89 (68.86–70.93), [EX COV 67.37 (66.36–68.39)]; serious AEs, 7.61 (7.27–7.96), [EX COV 6.90 (6.58–7.23)]; serious infections (SI), 2.74 (2.54–2.96), [EX COV 2.04 (1.87–2.22)]; malignancies, 0.41 (0.34–0.50); SI leading to withdrawal, 0.12 (0.08–0.18), [EX COV 0.08 (0.05–0.13)]; and AEs leading to discontinuation, 0.97 (0.85–1.10), [EX COV 0.93 (0.81–1.06)]. As of March 2022, over 250,000 pts with MS initiated OCR globally in the PM setting. Data remain generally consistent with those observed in CTs factoring in the impact of the COVID-19 pandemic.
Conclusions: AE rates in the OCR all-exposure population remain generally consistent with the controlled treatment period in RMS/PPMS populations. Serious infection and malignancy rates remain within the range reported for pts with MS in real-world registries. COVID-19 did not lead to increased treatment withdrawal. Over a 9-year follow-up period, no new or unexpected safety signal was seen in pts treated with OCR in ongoing CTs. OCR continues to exhibit a stable and favourable safety profile. Regular reporting of longer-term safety data will continue.

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Serum GFAP and long-term outcomes in high efficacy versus low efficacy early treatment in multiple sclerosis

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Introduction: High efficacy early treatment (HEET) and lower efficacy early treatment (LEET) for MS patients can differentially impact long-term disease outcomes. Serum neurofilament light chain (sNfL) and serum glial fibrillary acidic protein (sGFAP) in addition to clinical and imaging outcomes, may inform HEET vs. LEET approaches.
Objectives: Evaluate long-term effects of HEET vs. LEET evidenced by clinical, imaging, and serological outcomes.
Methods: Patients enrolled in the Comprehensive Longitudinal Investigation in Multiple Sclerosis at Brigham and Women's Hospital (CLIMB) study treated with HEET (fingolimod, natalizumab, ocrelizumab, rituximab) (n=141) or LEET (dimethyl fumarate, glatiramer acetate, interferons, teriflunomide) (n=228) within five years of symptoms onset were divided into two cohorts. Cohort A [HEET (n=85), LEET (n=70)] had sNfL and sGFAP 1-0 years before and 0.5-3 years after treatment. Cohort B [HEET (n=56), LEET (n=158)] had two samples after treatment start (0-4 and 1-5 years). A Wilcoxon test was used to compare log-transformed biomarker levels in the two groups. A Cox proportional hazards model assessed predictive associations.
Results: Clinical outcomes of cohorts A and B combined showed that LEET trended to a faster time to first relapse [HR:1.46 (CI: 1.04, 2.05); p=0.030] and time to new T2 lesion [1.35 (0.99, 1.84); p=0.062] when compared to HEET. The results were adjusted for age, sex, and EDSS at treatment initiation. In cohort A, sNfL change in the HEET group was -0.35 (SD=0.83) and -0.29 (SD=0.75) for LEET (p=0.49 for comparison between HEET and LEET). sGFAP change was -0.03 (SD=0.4) for HEET group and -0.07 (SD=0.32) for LEET group (comparison p=0.45). In cohort A, sGFAP change was associated with time to sustained progression in HEET [4.23 (1.49, 12.02); p=0.007] and time to new T2 lesion in HEET [2.8 (1.2, 6.52); p=0.017] however these associations were not present in the LEET group. In cohort B the results were not statistically significant for sGFAP or sNfL.
Conclusions: Time to first relapse and time to new T2 lesion was faster in the LEET group when compared to HEET. sNfL and sGFAP tended to decrease over time in HEET and LEET groups. Serum GFAP level during the first few months of treatment initiation was associated with disease progression and time to new T2 lesion in our HEET cohort.

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Assessing B-cell depletion and disease activity in a french multiple sclerosis cohort treated by long-term anti-CD20 antibody therapy

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Introduction: Intravenous anti-CD20 B-cell depleting therapies (BCDT) in Multiple Sclerosis (MS) are based on a fixed-schedule dosing regimen with a maintenance perfusion every six months. While BCDT is highly efficacious, long-term anti-CD20 therapy leads to a risk of severe infection. Few studies have explored the kinetics of B-cell depletion after multiple cycles of BCDT in MS

and the influence on disease activity, which may ultimately guide long-term treatment strategies by BCDT.
Objectives/Aims: To investigate whether long-term B-cell depletion by intravenous BCDT is correlated with disease stability in MS patients, and to explore whether decreased immunoglobulin levels are associated with increased risk for serious infection.
Methods: This monocentric, retrospective study included adult MS patients treated with intravenous BCDT (ocrelizumab or rituximab) for at least three cycles between January 2015 and September 2021. We evaluated demographic characteristics, clinical relapses and scores, radiological activity, biological data, and serious adverse events (SAE). B-cell depletion was defined as $CD19^+ \leqslant 1.0\%$ of the total lymphocyte count, and disease stability was defined by achieving NEDA-3 status.
Results: We included 192 patients, of which 62.5% had relapsing MS, 19.8% had primary progressive MS, and 17.7% had secondary progressive MS. Overall, 62.4% were female, with a mean age at BCDT introduction of 42.5±11.7 years and a mean BCDT treatment duration of 2.8±1.3 years. Preliminary results show that after three cycles of BCDT, 85.8% of patients showed B-cell depletion, and NEDA-3 status was achieved by 80.3% of patients. Furthermore, after three cycles, B-cell repopulation was observed in 20.4% of patients who achieved NEDA-3 status, while B-cell repopulation in those who failed to achieve NEDA-3 status was 27.3%.
Additionally, 28.4% and 9.9% showed reduced IgM and IgG levels, respectively, after three cycles of BCDT. Only 8.5% of patients reported an SAE after a mean number of cycles of 4.5±2.2, with a mean IgG and IgM level prior to an SAE of 9.4±2.75 and 0.7±0.4, respectively. Most SAE were urinary tract infections.
Conclusions: After 3 cycles of IV BCDT most patients achieve NEDA-3 status and are depleted in B cells, raising the question of delaying following infusion in order to decrease hypogammaglobulinemia and infection risk.

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DMT Persistence: we've started, when will we stop?

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Background: Real-world, long-term adherence and non-adherence data is vital to complement our understanding of disease modifying therapy (DMT), which is often based on short-term clinical trials. In this study we explored DMT persistence (days from prescription start to cessation), as well as reasons for therapy cessation (RFC) in a UK national cohort of people with MS (pwMS).
Objectives: To investigate how long patients remain on therapies in the real world (persistence) and understand why patients might discontinue therapies (RFC). Additionally, we explore the implementation of a core dataset from representative national MS centres to understand patterns of long-term DMT prescriptions.
Aims: To explore real-worldpatterns of DMT use in a MS population-based cohort and identify optimum DMT pathways for pwMS.
Methods: This cohort study included 4,415 pwMS from 12 UK MS centres, 7,490 DMT prescriptions were included in the analysis (male/female 7:18, mean 1.7, range 1-6 per patient). Prescriptions without accurate start dates/RFC were excluded (n=90). Kaplan-Meier survival analysis was used to model DMT persistence, which was used to calculate the percentage of prescriptions continuing after 2, 5 and 10 years. RFC data were collated, divided into 8 classifications: adverse event; increased risk of adverse event; lack of efficacy; onset of progressive disease; patient choice; pregnancy/pre-conceptual care; other; unknown. RFC were tabulated as percentages of annual prescriptions.
Results: 2-year persistence was highest for immune reconstitution therapies alemtuzumab (97%), ocrelizumab (96%) and cladribine (92%). Oral therapies fingolimod (73%) and dimethyl fumarate (73%), and intravenous natalizumab (80%) shared similar persistence. Injectable therapies glatiramer acetate (50%) and interferon (50%), had lowest persistence. Large variation existed in RFC between therapies, but the most common were lack of efficacy (37%) and adverse event (31%). RFC also changed between epochs, with adverse event falling from 51% in the short-term, to 15% in the long-term. Conversely, lack of efficacy rose from 22% to 45%. Potential confounding factors include variable date of DMT licensing, change in DMT algorithms over time and increasing DMT options.
Conclusion: This multi-centre study has revealed highly variable persistence between DMTs over time, which may impact real-world effectiveness. These results may inform DMT clinical decision-making and improve outcomes for pwMS.

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Cladribine treatment for highly active relapsing multiple sclerosis: real-word data for years 3 and 4 clinical outcomes

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Introduction: Cladribine is an effective immunomodulatory treatment used for relapsing forms of multiple sclerosis (RRMS).
Objectives: To describe the clinical outcomes and rates of no evidence of disease activity (NEDA) in patients with highly-active disease treated with cladribine, for years 3 and 4 of treatment.
Methods: We used the Sheba Multiple Sclerosis computerized data registry to retrospectively evaluate year-3 and year-4 clinical outcomes and NEDA-2 rates in highly active RRMS patients who completed the 2-dose 2-year cladribine treatment protocol (3.5mg/kg cumulative dose over 2 years). The first week of treatment in year 1 was considered as baseline. Data analyses were performed using Python (version 3.0) and SAS® (version 9.4 SAS Institute, Cary, NC).
Results: Sixty-one RRMS patients, 43 females, were studied for year-3 clinical outcomes, and 35 patients, 23 females, also for year-4. At the initiation of cladribine treatment, the mean±SD age was 39.6±10.74 years (45.9% of the patients were between 18-40 years), disease duration 12.7±9.08 years, Expanded Disability Status Scale (EDSS) 3.7±1.86 (54% had EDSS score >3.0), and the annual relapse rate was 1.6±0.9. The annual relapse rate decreased to 0.36 in year-3 and was 0.17 in year-4; 68.9% (42/61) of the patients were relapse-free in year-3, and 82.9% (29/35) were relapse-free in year-4. Disability at year-3 was 3.1±2.07; 83.6% (51/61) of the patients remained neurologically stable (33, 54.1%) or improved (18, 29.5%). In year-4, EDSS was 3.2±1.91, and 85.7% (30/35) of the patients remained stable (20, 57.1%) or improved (10, 28.6%). NEDA-2 was achieved for 59.0% (36/61) of patients in year-3, and for 74.3% (26/35) in year-4 of cladribine treatment.
Conclusions: In the real-world cladribine has proved to be clinically effective in year-3 and year-4 of treatment in the majority of highly-active RRMS patients.

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Rates and predictors of serious infections in MS and NMOSD patients treated with anti-CD20 therapy

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Introduction: Chronic immunosuppression with anti-CD20 therapy can increase the risk of serious infections including complicated COVID19.
Objectives and Aims: To evaluate the rates and predictors of serious infections in MS and NMOSD patients treated with anti-CD20 agents.
Methods: MS and NMOSD patients treated with ocrelizumab or rituximab at University Hospitals Cleveland Medical Center were evaluated. Patients hospitalized for any infection during their anti-CD20 therapy were identified and compared to those without infection-related hospitalizations. Significant differences were evaluated in a multivariate logistic regression model to identify predictors of serious infection.
Results: There were 184 patients treated with anti-CD20 therapy (average age 48+/-13 years, 67% females, 84% MS). Of those, 21 (11%) patients had one or more serious infection during therapy including 16 MS patients treated with ocrelizumab and 5 NMOSD patients treated with rituximab. The most common serious infections were complicated COVID19 (9), bacterial skin infections (5), bacterial pneumonia (3), urosepsis (3), ocular infection (1), and disseminated shingles (1). Compared to those without serious infections, patients with serious infections had a higher average time on anti-CD20 therapy (1087.57±5 days vs 796.28±35 t= -2.61, P=0.005) and were more likely to have total lymphopenia (80% vs 40%; P=.004). There was a trend towards higher rates of hypogammaglobulinemia in patients with serious infections (24% vs 10%; P=.07). Logistic regression identified total lymphopenia (<1.0 x109/L) as an independent predictor of serious infection in patients treated with anti-CD20 therapy.
Conclusion: Serious infections are rare in MS and NMOSD patients treated with anti-CD20 therapies. Those with serious infections were exposed to treatment longer and more frequently had lymphopenia and hypogammaglobulinemia. Total lymphopenia during therapy is an independent risk factor for serious infections.

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Rituximab in paediatric onset multiple sclerosis – a european multicenter experience

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Introduction: Paediatric onset multiple sclerosis (POMS) is associated with manifestation of physical disability and cognitive impairment at a young age. The chimeric anti-CD20 antibody rituximab (RTX) is frequently used off-label in multiple sclerosis (MS). However, studies in POMS are scarce.
Objectives: To report the use of RTX in POMS.
Aims: To report the use of RTX in POMS.
Methods: Retrospective review of POMS patients from Austria, Sweden and Germany who received RTX for POMS between 04/1991 and 11/2021. Annualized relapse rates (ARR), Expanded Disability Status Scale (EDSS) scores and magnetic resonance imaging (MRI) scans were assessed before and after RTX start. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events.
Results: Overall, 61 patients (43 female, 42 treatment-naive) received a median (interquartile range (IQR)) of 5 (3-7) RTX infusions during a median (IQR) follow-up (FU) duration of 21 (12-52.5) months. The median (IQR) age at MS onset was 14.9 (13.4-16.3) years; the median age at RTX initiation was 16.3 (14.8-17.1) years. The administered doses were 500 mg in 31.1%, 375 mg/m^{2}in 26.2%, and 1000 mg in 21.3% of patients. B cell depletion was successfully achieved in 96.5% of patients. The median (IQR) annualized relapse rate decreased from 0 (0–0.89) to 0 (0–0) and the median (IQR) EDSS score improved from 1.0 (0.0-2.0) to 0.0 (0.0-1.5). The median (IQR) annualized rate of new T2 lesions on MRI decreased from 10.0 (1.27-28.48) to 0 (0-0.05). While 50% exhibited gadolinium-enhancing lesions at RTX start, no contrast enhancement was detected at last FU. Overall, 62.2% displayed no evidence of disease activity during RTX and most refractory activity was limited to the first year and the first FU MRI.
AEs were observed in 60.7% and were graded mild to moderate. Transient infusion reactions occurred in 47.5% but decreased with subsequent infusions. Infections were recorded in 19.6%. Hypogammaglobulinemia and lymphopenia were the most frequent laboratory abnormalities in 22.6% and 7.1% of patients, respectively. Five patients discontinued RTX due to refractory disease activity or AEs and two patients were lost to FU. This corresponds to an overall drug survival rate of 91.8%.
Conclusions: RTX was generally safe and well tolerated in this cohort of 61 POMS patients. Larger and prospective trials with a longer FU duration are required to further define the long-term risk/benefit profile of RTX in POMS.

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Long-term effectiveness of extended interval dosing of natalizumab in multiple sclerosis

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Introduction: Review of TOUCH database showed that EID dramatically reduced the risk of NTZ-associated Progressive Multifocal Leukoencephalopathy (PML). Randomized control trial demonstrated EID to maintain excellent efficacy of NTZ over 72wks.Long-term (LT) effectiveness of NTZ EID is not known.
Objectives: To evaluate the effectiveness of extended interval dosing (EID) of natalizumab (NTZ), at every 6 weeks, in patients who were on EID for ⩾2yrs.
Aims: To evaluate percentage of patients who maintain no new disease activity on MRI while on EID NTZ for ⩾2yrs.
Methods: RRMS patients treated at NYU MS Care Center on EID NTZ for more than 2 years were reviewed. LT EID

definitions were based on preplanned analyses specified for the 2017 TOUCH study: LT-EID1: 20 infusions in the last 24mo of treatment; LT-EID2: consecutive EID infusions for ⩾12mo; LT-EID3: patients with ⩽10 infusions/yr over the course of treatment for at least 2yrs of treatment. Descriptive statistics were used to summarize demographics, clinical characteristics, and disease activity.

Results: 228 patients on NTZ met the criteria for LT-EID analysis (EID1: 174; EID2: 178; EID3: 53). Mean age at start of NTZ 38.1±11.9yrs; 68% female; disease duration at start of NTZ 6.4±6.3yrs. For LT-EID1, total number of infusions was 55.4±24.8 over 61.3±32.1mo; the average number of MRI brain/yr was 2.0; and 77% pf patient had no disease activity. For LT-EID2, total number of infusions was 53.9±26.5 over 53.1±27.4mo; the average number of MRI brain/yr during was 1.8; and 78% pf patient had no disease activity. For EID3, total number of infusions was 40.5±19.1 over 66.4±32.3mo; the average number of MRI brain/yr was 0.9; and 78% pf patient had no disease activity.

Conclusions: LT NTZ EID up to 5.5 years shows maintenance of drug efficacy. Limitations of the study include selection bias (patients not doing well less likely to continue EID), and immortal time bias (patients with breakthrough on standard dose less likely to transition to EID).

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Long-term safety and efficacy of ozanimod in relapsing multiple sclerosis: interim analysis of the DAYBREAK open-label extension study

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Introduction: Ozanimod, an oral sphingosine 1-phosphate receptor 1 and 5 modulator, is approved in multiple countries for the treatment of adults with either relapsing forms of multiple sclerosis (RMS) or moderately to severely active ulcerative colitis.

Objectives: To report the safety and efficacy of extended exposure to ozanimod from an ongoing open-label extension (OLE) trial.

Methods: Patients with RMS who completed a phase 1, 2, or 3 ozanimod trial were eligible to enrol in DAYBREAK (NCT02576717), where they received ozanimod 0.92 mg/d. The primary objective was to evaluate safety in the overall population; treatment-emergent adverse events (TEAE) were monitored. Efficacy was evaluated with annualised relapse rate (ARR), calculated via negative binomial regression and pooled for all parent-trial treatment groups. Number of new/enlarging T2 and gadolinium-enhancing (GdE) magnetic resonance imaging (MRI) brain lesions were reported for patients who entered the OLE from an active-controlled phase 3 trial.

Results: In total, 2639 patients completed the parent trials; this interim analysis (datacut 1 February 2022) included 2494 patients with mean (range) ozanimod exposure of 56.4 (0.03–74.7) months (11732.2 patient-years) in the OLE. In the OLE, 2199 patients (88.2%) had any TEAE, 352 (14.1%) had a serious TEAE (SAE), and 89 (3.6%) discontinued due to a TEAE. Similar rates of TEAEs and SAEs occurred when assessed by parent trial treatment group. The most common TEAEs (based on preferred terms) were nasopharyngitis (20.6%), headache (16.9%), upper respiratory tract infection (11.9%), COVID-19 infection (11.5%), and lymphopenia (10.5%), which were generally similar to parent trial observations (excluding COVID-19 infection). Adjusted ARR in the OLE was 0.099 (95% CI, 0.083–0.119). After 60 months of treatment, 68% of patients were relapse free in the OLE. Three- and 6-month confirmed disability progression was observed in 15.9% and 14.0% of patients in the OLE, respectively. Mean number of new/enlarging T2 lesions per scan at 60 months was similar, regardless of parent trial treatment group (range, 0.77–0.98), as was mean number of GdE lesions at month 60 (range, 0.057–0.065).

Conclusion: The safety and tolerability profile of ozanimod in DAYBREAK was consistent with prior reports. Ozanimod treatment demonstrated sustained efficacy on clinical and MRI measures of disease activity and on disability progression.

Disclosure

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Natalizumab treatment satisfaction in the TONiC-MS study: preliminary resultssupport from NIHR, MNDA, Walton Neuroscience Charity, Biogen, Novartis, Roche, Teva

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Background: It is important to understand patients' perceptions and treatment satisfaction with disease modifying therapy in multiple sclerosis (MS), particularly if that therapy changes. Natalizumab is one therapy where a subcutaneous (s.c.) route of administration is now available as an alternative to the established intravenous (i.v.) preparation.
Objective: To determine, in people with MS (PwMS), perceptions of and satisfaction with natalizumab treatment as they switch from i.v.to s.c. preparations.
Method: Specially designed questionnaires, including a Patient Preference Questionnaire (PPQ), were administered prospectively to PwMS at 4 monthly intervals, nested within the Trajectories of Outcome in Neurological Conditions (TONiC) study, a multicentre UK study capturing factors affecting quality of life. No influence on any clinical decision to switch route of natalizumab administration during the period of observation was intended.
Results: 95 patients, treated at 18 hospitals, had baseline i.v. data by May 2022 and approximately 10% (n=9) had made the switch to s.c. natalizumab. Mean age was 49 years and 85% were female. 97% had EDSS⩽6.5. Median duration of i.v. treatment was 9 years; 52% had received natalizumab as their first disease modifying therapy otherwise the remainder had switched from platform therapies. Infusions occurred monthly for 50% of respondents and every 6 weeks for 44%. 52% had to travel for over 1 hour to the treatment centre. Infusions normally took 1-2 hours (87%) and 53% reported no post-treatment observation. 43% normally required ⩾2 attempts at cannula insertion, of whom 30% had experienced an infusion treatment which required more than 5 attempts. 2 people had a portacath in situ specifically for natalizumab administration. Worry about successful cannulation was reported by 25%. 62% indicated liking the company of other patients during their treatment session. Of the 9 switchers, all expressed either a 'fairly strong' or 'very strong' preference for s.c. natalizumab, over i.v, on the PPQ.
Conclusion: This is the first UK real-world study on natalizumab patients' perceptions and treatment satisfaction with natalizumab. The representativeness of the sample is discussed but these preliminary results highlight cannulation challenges experienced by some i.v. patients and a strong preference, in those who elected to switch, for s.c. natalizumab.

Disclosure

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Longitudinal retinal changes during first line versus high-efficacy therapy for patients with multiple sclerosis

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Introduction: Different disease-modifying therapies (DMT) for multiple sclerosis (MS) have disparate effects on disability outcomes. With optical coherence tomography (OCT) retinal changes can be measured at micrometers' level.
Objective: The aim of this study is to investigate changes of EDSS, MRI lesions and OCT parameters in MS patients during 1st line DMT, then during switched high-efficacy DMT, with comparison to baseline without therapy.
Materials and Methods: This is a prospective longitudinal observational study. Eighteen MS patients were followed up for 6.83 (4.15 – 8.33) years, 12 of them were untreated at baseline. All patients underwent1st line DMT and then switched to high efficacy DMT. Neurological status, MRI lesions, and OCT measures were registered.
Results: GCIPL thickness was significantly reduced during 1st line DMT (73.75 μm, $p<0.01$) compared to baseline (76.38 μm), which was diminished during high efficacy DMT (73.27 μm, $p<0.05$). Time-adjusted analysis showed a significant reduction of GCIPL thickness by 0.22 μm per year, and pRNFL thickness by 0.48 μm per year. MRI contrast-loading lesions were significantly decreased during high efficacy DMT ($p<0.01$). However, brain parenchymal fraction (BPF) was decreased regardless of high efficacy DMT.
Estimated models showed similar results. EDSS and MSSS showed no significant changes over time. EDSS was estimated with increment by 0.02 per year and MSSS was estimated with decrement by 0.07 per year.
Conclusion:GCIPL decline was most profound during 1st line DMT which was diminished during high efficacy DMT. MRI contrast lesions had vanished during high efficacy DMT.

Disclosure

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Therapy - Risk management for disease modifying treatments

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Natalizumab wearing-off symptoms: effect of extend interval dosing during Sars-CoV-2 pandemic

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Introduction: Many patients treated with Natalizumab experience end of dose interval (EDI) symptoms towards the end of the administration cycle.
Objectives and aims: During the pandemic, to minimize patients accesses to the hospital and reduce exposure to Sars-CoV-2, we advised and asked patients undergoing treatment with Natalizumab if they wanted to be shifted from a Standard Interval Dosing (SID of 4 weeks) to and Extended Interval Dosing (EID of 5-6 weeks), regardless of their JCV index. Our main objective was to study prevalence and incidence of End of Dosing Interval (EDI) symptoms when Extended Interval Dosing (EID) was adopted, considering the variable prevalence of the wearing off effect.
Methods: We enrolled 87 patients, from May 2020 to January 2021, evaluated at baseline and during a 6 months follow-up with a survey focused on End of Dosing Interval Symptoms(EDIs), Fatigue Severity Scale (FSS), Expanded Disability Status Scale (EDSS) and Magnetic Resonance Imaging.
Results: Among the 87 patients, 32(36.8%) reported End of Dose Interval (EDI) symptoms. Most common EDI symptom was fatigue (93.7%). Of note, among the patients with an EID (71), 16.9% patients reported a new onset of fatigue, where none was present before adopting the EID. Mean EDSS was higher in the group reporting EDI symptoms (3.6 EDI vs 2.2 non-EDI, $p<0.05$).*Sphincterial functions* were the ones that differed the most between the EDI-symptoms group and the non-EDI-symptoms group (1.4 EDIs vs 0.62 non-EDIs, $p<0.05$), among EDSS different components.
Conclusions: The present study confirms that fatigue is the most common Natalizumab wearing-off symptom and 16.9% of patients develop a new onset of fatigue adopting an EID. Interestingly, there is a strong correlation between higher EDSS and fatigue in an EID setting. An increase of people suffering from fatigue is to be expected after adopting an EID, especially in the people with a higher EDSS and impairment of sphincterial functions. EID in our study does not compromise safety and efficacy of Natalizumab.

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Rebound of clinical disease activity after fingolimod discontinuation? A nationwide cohort study of patients in Denmark

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Introduction: Withdrawal of fingolimod may lead to increased risk of clinical and radiological disease activity. When the level of disease activity after withdrawal of a disease-modifying treatment is higher than the level before initiating this disease-modifying treatment, rebound is considered to have occurred.
Aims and objectives: We investigated whether disease rebound occurred after fingolimod discontinuation in a large complete population of patients with relapsing-remitting multiple sclerosis (RRMS) in Denmark. We further identified clinical and demographical factors associated with disease reactivation after fingolimod discontinuation.
Methods: The study population consisted of 992 patients with RRMS treated with fingolimod for six months or more. We estimated annualized relapse rates (ARR) before, during and after treatment by fitting negative binomial regression models. We estimated overall ARRs and ARRs stratified by disease activity before fingolimod discontinuation. Using multivariable Cox regression, we analyzed the association between demographic and clinical variables at fingolimod discontinuation and time to first relapse during six months of follow-up after discontinuation.
Results: During the 12 months before fingolimod initiation, the overall ARR was 0.74 (95%CI=0.69-0.80). From fingolimod initiation until six months before discontinuation, the overall ARR was 0.30 (95%CI=0.26-0.33). During the last six months of fingolimod treatment, the overall ARR was 0.58 (95%CI=0.52-0.66). Overall ARRs were 0.56 (95%CI=0.47-0.66) during the first three months and 0.32 (95%CI=0.25-0.40) during the subsequent three months after fingolimod discontinuation. ARRs were higher among patients who discontinued fingolimod due to disease activity than among patients who discontinued fingolimod for other reasons in all time periods except during the period from three to six months after fingolimod discontinuation where the two groups had similar ARR levels.
During follow-up, we identified 117 relapses among the 992 patients who discontinued fingolimod. Lower age, female sex and disease activity before discontinuation, but not prior treatment with DMT, were statistically significantly associated with an increased risk of a relapse.
Conclusions: We did not find evidence for disease rebound after fingolimod discontinuation. A higher risk of disease reactivation was seen in those with disease breakthrough before fingolimod cessation, in women and younger patients.

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Consensus recommendations on the use of follow-on disease-modifying treatments for multiple sclerosis

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Introduction: As patents for multiple sclerosis (MS) therapies expire, follow-on disease-modifying treatments (FO-DMTs) have started to emerge. FO-DMTs have the potential to reduce healthcare costs. However, unintended nocebo effects may occur when switching from reference product (RP) to FO-DMT due to adverse expectations of people with MS (PwMS) and clinicians. Well-being and safety of PwMS should take priority.
Objectives: To identify best practices for development and use of FO-DMTs by agreeing on principles and consensus statements through appraisal of the published clinical evidence. We focused this consensus on structurally complex drugs, i.e., non-biologic complex drugs and biosimilars rather than small-molecule generics.
Aims: To empower PwMS and clinicians to critically weigh the evidence for efficacy and safety for FO-DMTs, aiding informed shared decision-making and avoiding nocebo-related harms when switching.
Methods: Following a systematic review we formulated 5 overarching principles and 13 consensus statements concerning FO-DMTs, with a focus on the regulatory framework in Europe,

but commented also on other regions. The principles and statements were voted on by a 33-member multidisciplinary panel from 17 European countries, Argentina, Canada, and the United States.

Results: More than 80% of panellists voted in favour of all principles and consensus statements. In brief, we agreed that: (1) FO-DMTs approved within highly regulated areas can be considered as effective and safe as their RPs, (2) it is appropriate for regulators to evaluate FO-DMTs case by case, and not to require Phase 3 trials in every instance, (3) long-term pharmacovigilance and data transparency are needed, (4) there is lack of evidence for multiple and cross-switching among FO-DMTs, and that (5) education is imperative to address remaining concerns around FO-DMTs, and instrumental to achieve the expected economic benefits, ie, improved affordability of DMTs and increased access to care.

Conclusion: The available information supports the use of FO-DMTs in MS. The consensus statements may aid shared decision-making. While the consensus focused on Europe, the results may contribute to enhanced quality standards for use of FO-DMTs elsewhere.

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Ocrelizumab dosing according to CD19+ cell count monitoring in multiple sclerosis: a tertiary centre audit during the SARS-CoV-2 pandemic

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Introduction: In March 2020, to prevent the risk of infection from SARS-CoV-2 in people with multiple sclerosis (MS) on Ocrelizumab, notably associated with an immunosuppressed state, the Association of British Neurologists (ABN) advised delaying the infusions until the recovery of CD19+ cells to over 1% of the total lymphocyte population. The indication is based on observations from multinational experience using Rituximab, suggesting that an Ocrelizumab infusion may remain effective at controlling MS for longer than 6 months.

Objectives: We will analyse data on the delayed time intervals between Ocrelizumab infusions, the rate of relapses and signs of disease activity or progression reported for 209 patients in the audited period.

Aims: We aim at assessing the efficacy of dosing Ocrelizumab according to CD19+ cell count in terms of MS control.

Methods: The study was designed as a clinical audit. 209 patients under the care of the MS centre of the Queen Elisabeth Hospital Birmingham were included in the audit. The protocol suggested by the ABN was applied to all of them from mid-March 2020 onwards. 2 years after, we collected data on the time intervals between the infusions, the relapses and radiological findings reported for the 209 subjects in the audited period.

Results: A total of 424 Ocrelizumab infusions were administered. 123 (29%) were first infusions. 301 (71%) were either second, third, fourth, fifth or sixth infusions. Of those 301 infusions, 235 (78,07%) were administered after 8 months or more

from the preceding one, whereas 66 (21,92%) were performed at a time interval of 6-7 months. Of 209 patients, 8 (3,82%) experienced a clinical relapse not supported by radiological signs of disease activity or progression. 4 patients (1,91%) presented clinical manifestations of a relapse confirmed by radiological findings of disease activity or progression. For 1 patient (0,47%) the magnetic resonance imaging showed evidence of increased lesion load not associated with any new clinical sign or symptom. In addition, 4 patients (1,91%) reported subjective feelings of worsening MS that they attributed to infusions being delayed and were re-established on standard sixth-month interval infusions.

Conclusions: Ocrelizumab dosing according to CD19+ cell count monitoring remained effective at controlling MS in the majority of the 209 patients included in the audit while preventing unnecessary exposure to SARS-CoV-2 infection related to hospital attendance.

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Updated post-approval safety of cladribine tablets in the treatment of multiple sclerosis, with particular reference to liver safety

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Introduction: Several integrated analyses have reported on the safety of cladribine tablets (CladT; 3.5mg/kg cumulative dose over 2 years) during the clinical development programme for relapsing multiple sclerosis (RMS). As of July 2021, an estimated 35,668 patients have received CladT with 49,783.5 patient-years of exposure since approval in 2017.

Objectives: To provide continual presentation of relevant new safety data concerning CladT as they become available.

Aims: To update on post-approval safety profile of CladT in patients with RMS, including liver safety.

Methods: Serious and non-serious adverse events (AEs) from post-approval sources (including spontaneous individual case safety reports, non-interventional post-marketing studies, and reports from other solicited sources) are presented to July 2021. For AEs of special interest, adjusted incidences per 100 patient-years are reported; crude values are shown for liver AEs.

Results: Adjusted incidence rates for AEs of special interest were as follows: severe lymphopenia (72 cases), 0.14 (95% confidence interval: 0.11–0.18); herpes zoster (362 cases), 0.73 (0.66, 0.81); tuberculosis (16 cases), 0.03 (0.02, 0.05); severe infections (479 cases), 0.96 (0.88, 1.05); progressive multifocal leukoencephalopathy, 0; opportunistic infections (9 cases), 0.02 (0.01, 0.03); malignancies (108 cases [including 11 haematological malignancies]), 0.22 (0.18, 0.26); and congenital anomalies (2 cases), 0.004 (0.001, 0.016).

Liver AEs (generally enzyme elevations) were uncommonly reported in temporal association with CladT. Most cases of liver enzyme elevations were Grade 1 (mild, 19 cases) or Grade 2 (moderate, 6 cases). One Grade 3 case (severe; resolved within 2 weeks of onset) and one Grade 4 case (fatal, attributed to isoniazid toxicity) were reported. Time to onset of liver AEs varied; most cases occurred within 8 weeks of initiating the first course of treatment in Year 1.

Conclusions: Cumulative to July 2021, the safety profile of CladT is consistent with findings from the clinical development programme. Liver toxicity, while uncommon, was noted as an important identified risk of CladT as part of a cumulative post-approval safety review and further guidance on monitoring of liver function is now provided as part of updated prescribing information.

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Multiple sclerosis reactivation after fingolimod discontinuation for planning pregnancy: a monocentric experience

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Introduction: Multiple sclerosis (MS) mainly affects young women of child-bearing age. Fingolimod (Fg) is an effective disease-modifying therapy contraindicated during pregnancy. MS reactivation after Fg cessation in young patients with pregnancy projects and its management has not been well studied.
Objectives: To describe the incidence, characteristics and management of MS reactivation after stopping Fg to plan a pregnancy.
Methods: We conducted a monocentric, retrospective study from the EDMUS local database on female patients with remittent-recurrent MS, who stopped Fg therapy for planned or ongoing pregnancy between 2013 and 2020. The primary objective was to assess the incidence of disease reactivation, defined as the occurrence of at least one relapse after stopping Fg, and to characterize this reactivation (delay, clinical and radiological data, outcome). We described if treatments were received during conception to relay Fg therapy, to assess the efficacy of routine management in planning pregnancy.
Results: 24 patients were included for analysis, with a median age of 24 [21-28] years and a median MS duration before Fg introduction of 55 [29-79] months. The median EDSS at Fg discontinuation was 1.5 [1.1-2.4] and the median annualized relapse rate was 0 [0-0], suggesting well-controlled MS. Fg was discontinued in 21 (88%) patients to plan a pregnancy, and in 3 (12%) patients for ongoing pregnancy. 15 (63%) patients did not receive a relay therapy, 7 (29%) received glatiramer acetate and 2 (8.3%) had interferon. 20 (83%) patients presented a disease reactivation, with a median delay of 4.5 [2.6-5.5] months after Fg stopping. 16 (76%) relapses were pre-conceptional, 1 (5%) occurred during the first trimester and 3 (14%) during the second trimester. Of the 12 available MRI at the time of the relapses, 11 (92%) showed new lesions and 10 (83%) were gadolinium-enhanced. 15 (75%) relapses included motor flare-ups and the median EDSS after disease reactivation was 2 [1.5-3.5], suggesting substantial severity of relapses. 13 patients (54%) gave full-term birth, 3 (12.5%) suffered from spontaneous miscarriage and 8 (33%) gave up pregnancy planning.
Conclusion: In our cohort, most patients experienced MS reactivation after Fg cessation. Relapses and the risk of disability worsening may postpone the pregnancy planning. Escalating treatment before conception to prevent reactivation should be individually balanced with the potentially teratogenic risk.

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Humoral and T- cell response to multiple COVID-19 booster vaccinations in people with MS

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Introduction: People with multiple sclerosis (PwMS) treated with anti-CD20 therapies and fingolimod are less likely to

successfully produce a humoral response to COVID-19 vaccines 1 and 2.
Objectives: To measure the humoral and/or cellular response to COVID-19 booster vaccinations in a cohort of PwMS who were previously seronegative after their initial COVID vaccine course.
Aims: To determine whether there is a benefit of COVID-19 booster vaccinations for people with MS who are known to have had an attenuated response to initial vaccines.
Methods: We studied a cohort of PwMS all of whom were seronegative for anti-SARS-CoV-2 spike protein IgG after the 1st and 2nd COVID-19 vaccines, including PwMS treated with ocrelizumab (n=53), fingolimod (n=15), other DMTs (n=9) and no DMT (n=2). Dried blood spot +/- whole blood samples were obtained from participants at 2-8 weeks after their 3rd (n=79) and 4th (n=40) COVID-19 vaccines. Samples were used to measure anti-SARS-CoV-2 spike protein IgG (ELISA) and T-cell response (IFN-g release assay measured on whole blood).
Results: Overall 27/79 (34%) who were seronegative after COVID vaccine 2 seroconverted after vaccine 3. Seroconversion rates were 17% for PwMS treated with ocrelizumab, 47% for fingolimod and 100% for other DMTs. A further 2/30 (7%) of those who remained seronegative after vaccine 3 seroconverted after vaccine 4. Anti-SARS-CoV-2 T-cell responses were measurable in 26/40 (65%) after vaccine 3 and 13/19 (68%) after vaccine 4 but were conspicuously absent in people treated with fingolimod. Overall, 75% of participants showed either humoral or cellular response after receiving 4 COVID vaccinations. PwMS with laboratory evidence of prior COVID-19 infection had higher measurable T-cell responses.
Conclusion: Booster vaccinations for COVID-19 are associated with incremental benefits in measurable immunity in those with attenuated responses to the initial vaccine course. Overall, three quarters of those who were seronegative after COVID vaccines 1 & 2 had a measurable immune response after COVID vaccine 4. This data supports the use of booster vaccinations in pwMS at risk of attenuated vaccine response.

Disclosure
Potential Conflicts of Interest: Biogen, Merck, Novartis, Roche, Sanofi/Genzyme, Teva all manufacture multiple sclerosis disease modifying therapies that were used in this study, or which could be affected by the study. The following authors have received speaker fees, consultancy fees and/ or travel expenses to attend educational meetings from one or more of these companies: ECT, DB, RD, GI, KEH, NE, GG, AK, NPR, KS, SJ. MSand AG are co-founders of and hold equity in ImmunoServ Ltd, which provided T-cell analysis. NV, AR, VA, RC, KG, AG, AH, MJ, ASK, SL, SJM, MU, MW have no conflicts of interest.
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Effective humoral and cellular immunity in mRNA-COVID-19 multiple sclerosis vaccinees treated with alemtuzumab

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Introduction: The National multiple sclerosis (MS) Society and other expert organizations recommended that all MS patients should be vaccinated against COVID-19. However, the impact of disease-modifying therapies on the efficacy to mount appropriate immune response is currently under investigation.
Objective: To characterize the humoral and cellular immunity in mRNA-COVID-19 MS vaccinees treated with alemtuzumab.
Methods: We prospectively measured (1) SARS-COV-2 IgG response using a quantitative anti-spike protein-based immunoassay (Euroimmun, Lubeck, Germany, cut-off IgG level >35.2 BAU/ml), (2) memory B-cells specific for SARS-CoV-2 RBD, and (3) memory T-cells secreting IFN-g and/or IL-2, in response to SARS-CoV-2 peptides by ELISpot/Fluorospot assays, in MS patients vaccinated with BNT162b2-COVID-19 vaccine before, one and three months after the second vaccine dose. Patients were either untreated (N=31, 21 females, or under treatment with alemtuzumab (N=12, 9 females, median time from last dosing 15.9 months, range 1.8-28.7 months). The percent of subjects that developed protective antibodies, the antibody titer, and the cellular B and T cell responses were evaluated.
Results: None of the patients had clinical SARS-CoV-2 or immune evidence for prior infection. Positive humoral IgG response was demonstrated in 100% of untreated MS patients and in 83.3% of MS patients treated with alemtuzumab. Spike IgG titers were similar between untreated and alemtuzumab treated MS patients, both at 1 month (median 1320.7, 25-75 IQR 850.9-3152.8 vs. median 1291.9, 25-75 IQR 590.8-2950.9, BAU/ml, respectively) and at 3 months (median 1388.8, 25-75 1064.6–2347.6 vs. median 837.2, 25-75 IQR 739.4-1868.5, BAU/ml, respectively), after the second vaccine dose. In untreated and alemtuzumab-treated MS patients specific SARS-COV-2 memory B cells were detected in 41.9% and 41.7% of subjects at 1 month, and in 32.3% and 25% at 3 months following vaccination, respectively. Specific SARS-COV-2 memory T cells were found in 48.4% and 41.7% untreated and alemtuzumab-treated MS patients at 1 month, and in 41.9% and 41.7% untreated and alemtuzumab MS patients at 3 months, respectively.
Conclusions: Alemtuzumab treatment enabled effective humoral and cellular immune responses at 1 month and 3 months following COVID-19 vaccination.

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Humoral immune response to COVID-19 mRNA vaccines in patients with relapsing multiple sclerosis treated with ofatumumab

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Introduction: Ofatumumab (OMB), a fully-human anti-CD20 monoclonal antibody (Ab), is indicated for the treatment of adults with relapsing multiple sclerosis (RMS). As OMB induces B-cell depletion, it is important to understand if OMB-treated patients (pts) can mount a protective immune response to the COVID-19 vaccine.

Objective: Assess humoral immune response (HIR) to mRNA COVID-19 vaccines in OMB-treated pts with RMS.

Methods: This was an open-label, single-arm, multicentre, prospective pilot study (NCT04847596) of pts with RMS aged 18-55y receiving 2 doses of an mRNA COVID-19 vaccine after treatment with OMB 20mg for ⩾1mo. Pts who received a 3rd/booster vaccine dose were also eligible. Exclusion criteria included prior COVID-19 diagnosis, recent major infections and prior sphingosine 1-phosphate receptor modulator or natalizumab treatment. The 1st post-vaccination immune assay was performed ⩾14d after full vaccination course (2 or 3 doses), with the 2nd assay conducted 90d after the 1st assessment (assays conducted by local laboratories). Primary endpoint was proportion of pts achieving an HIR, defined as a positive response on the SARS-CoV-2 qualitative IgG Ab assay. Secondary endpoints were adverse events (AEs) and serious AEs.

Results: 26 pts (median [range] age: 42 [27-54]y) were included; 81% were female, 96% were White and 35% were Hispanic/Latino. Median (range) OMB treatment duration at screening was 237d (50-364). 15 pts (58%) received 2 vaccine doses; 11 (42%) received a 3rd/booster dose. HIR to COVID-19 vaccines was achieved by 14/26 pts (54% [95%CI: 33%-73%]) at the 1st post-vaccination assay. In pts who received a booster; 7/10 achieved an HIR and 6/7 aged <50y achieved HIR. Prior ocrelizumab use or age ⩾50y led to a decreased HIR while length of OMB treatment and COVID-19 mRNA vaccine type did not impact HIR. At the 2nd assay, 13/26 pts (50% [95%CI: 30%-70%]) achieved an HIR (10 pts maintained and 3 additional pts achieved HIR; 2 pts who achieved HIR at the 1st assay were negative at the 2nd assay; 2 pts had missing assays). Overall, 5/26 pts (19%) reported ⩾1 AEs, including COVID-19 infection (n=4), herpes zoster infection (n=1), *S. pharyngitis* (n=1) and headache (n=1). No serious AEs were reported.

Conclusion: These findings suggest that most OMB-treated pts with RMS mount an HIR after COVID-19 mRNA vaccination and may help inform the coordination of vaccination and treatment of RMS pts with OMB.

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The impact of ocrelizumab on immunoglobulin levels and the risk of infection

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Introduction: In the Phase III clinical trials of ocrelizumab (OCR) in patients with relapsing and primary progressive MS, those treated with OCR had higher rates of infections compared to interferon-β1a and placebo. The European Medicines Agency updated OCR prescribing information to include an association between reduced serum immunoglobulins (Ig) and serious infections. The US prescribing information now suggests Ig monitoring and to consider discontinuing OCR when recurrent serious infections occur.
Objective: To determine if low IgM, IgG levels, age at the start of OCR treatment greater than 55 and duration on OCR are risk factors for overall infections.
Methods: Chart reviews was performed at the start of OCR treatment and every 6 months thereafter on adult persons with MS in our OCR registry. Patients with ⩾1 IgM/IgG value, who received ⩾2 doses of OCR were included. IgM and IgG levels obtained within a month of each infusion. GEE regression models were used to investigate the relationship between IgM or IgG and infection. GLM analyses were used to assess age > 55 and progressive MS as predictors for infection.
Results: 444 patients were included.323 (73%) were female; median age at OCR start was 50 (range 19-80) years, 151 (34%) age > 55yo.Median disease duration was 10 [0, 39] years, and 301 (68%) of patients had been on a previous DMT. Median time on OCR was 31.5 months (range 5.5-89.8). Baseline median IgM level was 82 mg/dL (range 22-294) (n=184). Overall median IgM level during treatment was 55 mg/dL (range 1.3-1860). Of 2684 OCR courses, for 737 (28%) courses IgM levels were below forty-five. Baseline median IgG level was 874 mg/dL (range 0-1740) (n=203). Overall median IgG level during treatment was 814 mg/dL (range 0-1742). The number of IgG levels below 680 was 596 (22%), below 400 was 70 (3%), and below 300 was 33 (1%). Infections occurred between 737 (28%) of the courses. In univariate and multivariate analyses risk of infection did not increase with age, baseline levels, IgM < 45, IgG < 680, IgG <400, or IgG <300g/dl. In a univariate analysis, OCR duration of 2 years or more increased the risk of infection and the number of infections although the association is not significant in the multivariate analysis. All multivariate models indicate that women have 2 times the odds of infection. Also, the interval from diagnosis to initiating OCR was significantly and independently associated with infection.
Conclusions: Despite concerns for greater infection risk due to depressed Ig levels in OCR-treated patients, this is not supported by the results of our study, nor was age >55. Women and longer disease duration are predictive risks for infection. Our results call into question the use of Ig levels as a guide to discontinuing OCR therapy.

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Cellular immune responses to SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis: an Israeli multi-center experience following 3 vaccine doses

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Objectives/Aims: Disease modifying therapies (DMTs) affect immune responses to SARS-CoV-2 exposure or vaccination in patients withmultiple sclerosis(PwMS).Humoral responses were shown to be significantly compromised inPwMStreated with anti-CD20 therapies and S1P inhibitors.We evaluated the effect of DMTs(and specifically anti-CD20)on cell-mediated immune responses to 2 and 3 SARS-CoV-2 vaccinations in PwMS.
Methods: 522 PwMS and 68 healthy controls vaccinated with BNT162b2-Pfizer mRNA vaccine against SARS-CoV-2, were recruited in a nation-wide multi-center study. Blood was collected at 3 time-points: 2-16 weeks and ~6 months post 2nd vaccination and 1-16 weeks following 3rd vaccination.The cellular responseswere evaluatedby quantifying IFNgamma secretion in blood incubated with COVID-19 spike-antigen.
Results: 75% PwMS were seropositive post 2nd or 3rd vaccination. IgG levels decreased by 82% within 6 months from vaccination ($p<0.0001$), but were boosted 10.3 fold by the 3rd vaccination ($p<0.0001$), and 1.8 fold compared to ⩽3m post 2nd vaccination ($p=0.025$). Patients treated with most DMTs were seropositive post 2nd and 3rd vaccinations,with the exception ofocrelizumab- and fingolimod-treated patients(antibody positivity between38%to 56%). A time interval of ⩾5 months between ocrelizumab infusion and vaccination was associated with higher IgG levels ($p=0.039$ post-2nd vaccination; $p=0.036$ post-3rd vaccination), and with higher proportions of seropositive patients.Anti-spike proteinT-cell responses were detected in96% of PwMStreated with ocrelizumabpost 2nd and 3rd vaccination.The mortality rates and the proportion of patients with severe COVID-infection, were at similar levels in patients treated with ocrelizumab and those under other DMDs.
Conclusion: PwMS treated with most DMTs developedeffective-humoralresponses in general. In patients treated with anti-CD20

therapies, who had reduced antibodies following repeated vaccinations, strongT-cell responseswere mounted and provided a good level of protection against severe disease or death from COVID.

Disclosure
Nothing to disclose

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S1P1 receptor modulators used as a disease-modifying treatment in multiple sclerosis increase invitro**melanoma cell lines proliferation at a therapeutic dose**

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Introduction: S1P1 receptor modulators (S1P1-RM) are oral Disease-Modifying Therapies (DMTs) for Multiple Sclerosis. Several authorities have raised doubts about S1P1-RM being responsible for an increased risk of melanoma in multiple sclerosis patients.
Objectives: We studied the *invitro*effects of S1P1-RM on different melanoma cell lines.
Aims: To compare available S1P modulators on the proliferation of human melanoma cells
Methods: Four drugs, all S1P modulators fingolimod (Gilenya*), siponimod (Mayzent*), ozanimod (Zeposia*), and ponesimod (Ponvory*), are approved in Multiple Sclerosis (MS). We tested all at different concentrations, including the one prescribed for therapeutic use (0.5,1.6,5.5,18,60 μmoL) on different human melanoma cell lines (501mel cells, 1205LU cells and M249R cells) to analyze cell proliferation monitored with the IncuCyte ZOOM live cell microscope (Essen Bioscience). For live imaging, cells were transduced with NucLight Red lentivirus reagent (Essen Bioscience). Images were taken every two hours over three days. As a measure of cell proliferation, confluency and number of nuclei were quantified by IncuCyte software. Measuring normal melanocyte proliferation was performed by counting DAPI-stained nuclei.
Results: Cell proliferation increased for Ozanimod used at therapeutic doses for all melanoma cell lines compared to controls (58 ±23 vs 34 ±15, $p<0.001$). Siponimod (45 ±6 vs 28 ±1, $p<0.001$) and Fingolimod (35 ±2 vs 28±1, $p<0.001$) increased proliferation for M249R cells at therapeutic doses and had no significant effect on other melanoma cell populations. In all three melanoma cell lines, Ponesimod increased proliferation at 5.5μM doses (67 ±25 vs 49 ±26, p=0.017) but decreased it at 18μM doses (16 ±14 vs 49 ±26, $p<0.001$).
Conclusion: These data suggest an increased proliferation of various melanoma cell lines with S1P1-RM treatments used at therapeutic concentrations for MS. Clinical trials and post-marketing surveillance data are mandatory to confirm these*in vitro*results. In addition to the safety alerts reported with real-world data, these results should raise the question of increased dermatologic surveillance in MS patients treated with S1P1-RM.

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Single-dose immunisation with live attenuated vaccines is an effective option before treatment initiation in MS patients

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Background: The standard immunisation scheme for Varicella zoster vaccine (VVZ) and Mumps-Measles-Rubella (MMR) consists of two doses at least 4 weeks apart, but single-dose immunisation may also be effective and can reduce delays in immunosuppressive treatment initiation, especially in highly active patients with MS (PwMS).
Objectives: To evaluate the immunogenicity of a single-dose attempt vs the standard immunisation scheme with VVZ and/or MMR in PwMS.
Methods: Retrospective observational study based on an ongoing prospective cohort of PwMS who required immunisation against VVZ and/or MMR between July 2016 and April 2022. Patients who received at least one dose of VVZ/MMR and who had available post-vaccination serology were included. Seroprotection rates (proportion of patients with protective titters: 165 mUI/mL

for varicella and 16.5 UA/mL for measles) and antibody (IgG) geometric mean titers (GMTs) were compared between two strategies.

Results: A total of 96 patients were included, 68 (70.8%) were women, with a mean age of 36.7 years (SD 8.9) and mean disease duration of 6.8 (SD 7.3) years. Only 19 patients (19.7%) were under DMTs at the time of vaccination: interferon (N=10), glatiramer acetate (N=6), teriflunomide (N=1) and dimethyl fumarate (N=2). A total of 28 patients received VVZ, 65 MMR and 3 both. A single-dose immunisation attempt was done in 60 (62.5%) patients and 36 (37.5%) received the standard scheme. No differences were observed in the type of vaccine, demographic and clinical characteristics, except for a higher annual relapse rate in the single dose attempt (ARR 0.84 (SD 0.8) vs 0.52 (SD 0.6); p= 0.002). In the single-dose attempt group, 40 had protective antibodies resulting in a seroprotection rate of 66.7% (IC95% 53.3-78.3) as compared to 97.2% (IC 95% 85.5-99.9) in the regular scheme ($p<0.001$). In the seroprotected patients, GMTs were similar for both schemes (187.1 vs 196.9 UA/mL; p=0.7 for measles and 1455.7 vs 1465.6 mUI/mL; p=0.9 for VVZ). An additional dose was administered in the 20 patients no seroprotected after the single-dose attempt resulting in a 95% (IC95% 86.1-99) seroprotection rate.

Conclusions: A single dose-attempt of VVZ and/or MMR following confirmation by post-vaccination serology could be sufficient to provide protection in almost two thirds of patients. It could be included in the routine clinical practice to achieve a rapid immunisation, especially in highly active patients who need immunosuppressive therapy.

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Exploratory magnetic resonance imaging endpoints from NOVA: a randomized controlled study of the efficacy of 6-week dosing of natalizumab vs continued 4-week treatment for multiple sclerosis

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Introduction: Primary and secondary magnetic resonance imaging (MRI) outcomes in NOVA (NCT03689972) suggest no clinically meaningful difference for relapsing-remitting multiple sclerosis patients who are stable on every-4-week (Q4W) dosing who switch to natalizumab every-6-week (Q6W) dosing compared with patients who continued Q4W treatment. Exploratory volumetric MRI endpoints in NOVA included change from baseline (BL) to week 72 in gadolinium-enhancing (Gd+), T2 hyperintense and non-enhancing T1 hypointense lesion volumes, and change in normalised whole brain volume (WBV), cortical gray matter (CGM), and thalamic regional brain volumes.

Objective: To evaluate exploratory MRI endpoints in patients previously treated with natalizumab Q4W for ⩾12months who switched to Q6W compared with those who continued Q4W over 72 weeks in NOVA.

Methods: NOVA patients randomised to natalizumab Q6W or Q4W with BL and ⩾1 post-BL MRI assessment were included. Treatment group differences (Q6W minus Q4W) in least square mean (LSM) change from BL in Gd+, T2 and T1 lesion volumes; in LSM percent change in WBV; and LSM change in CGM and thalamic regional volumes at 72 weeks were analysed with a mixed model of repeated measures adjusted for BL body weight, duration of natalizumab exposure at BL, geographic region, and respective BL MRI volumes.

Results: This analysis included 247 Q6W and 242 Q4W patients. At 72 weeks, the treatment group difference (95% confidence interval [CI]) in LSM change from BL was 0.07 mL (−0.04, 0.17; P=0.200) for T2 lesion volume and 0.02 mL (−0.08, 0.11; P=0.759) for T1 lesion volume. Gd+ lesion volume could not be assessed as there was only 1 patient in each treatment group with Gd+ lesions at 72 weeks. The between-group difference (95% CI) in LSM percent change from BL in WBV was −0.04% (−0.15, 0.07; P=0.441). The between-group difference (95% CI) in LSM change from BL was 219.01 µL (−740.17, 1178.19; P=0.654) for CGM and −10.07µL (−45.85, 25.72;P=0.580) for thalamic regional volume.

Conclusions: There were no differences in the NOVA exploratory MRI volumetric outcomes between RRMS patients who were stable on Q4W dosing who switched to natalizumab Q6W dosing compared with patients who continued Q4W. These results provide additional evidence that the majority of patients stable on Q4W dosing can switch to Q6W dosing with no clinically meaningful loss of efficacy.

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Safety and efficacy of teriflunomide rapid loading dose in the treatment of multiple sclerosis following cell trafficking therapy (SETL – MS)

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Background and objectives: Without a potent but measured approach to the de-escalation of therapy from cell-trafficking agents (fingolimod and natalizumab) patients continue to be at an increased risk of disabling rebound disease within 6 months following therapy discontinuation. Teriflunomide with a rapid load (TRL) regimen is an appealing and promising approach to assist in this situation as an established safe and efficacious treatment for relapsing forms of MS. TRL has been shown to be safe and well tolerated in healthy controls and extrapolating from similar loading regimens with its parent compound leflunomide in patients with other autoimmune diseases (rheumatoid arthritis). We decided to apply this strategy as it can establish levels equivalent to steady state serum concentration within days compared to months with the usual daily regimen and assess its tolerability and efficacy in preventing rebound disease .
Methods: we studied 40 stable patients on cell-trafficking agents who needed to discontinue treatment for various reasons (cancer, pregnancy desire, risk of Progressive multifocal leukoencephalopathy) who were deemed inactive (no relapses nor new lesions in the previous 2 years). They received Teriflunomide rapid load (TRL) between June 2018 until December 2021 . TRL was initiated once lymphocyte count had reached at least 0.8 x 10^9per liter . TRL comprised 70 mg daily for 5 days followed by the usual 14 mg daily thereafter. Clinical symptoms, liver enzymes and cell counts were closely monitored.
Results: 4/39 patients (10.3%) had clinical rebound, but none required hospital admission, compared with 18% in our historical cohort and 31% requiring admission respectively with mean EDSS (Expanded Disability Status Scale) of 8.5. Mean EDSS in TRL cohort was 4.25, median EDSS 4.0, whereas the mean EDSS was 5.4 and median EDSS was 6.5 in historical cohort.
No patients had reported gastrointestinal symptoms. Only 1/39 patients had an increase of liver enzymes (x 3 ULN) along with similar hematological effects (9% neutropenia compared with 16% in clinical trials). Hair thinning data was not collected.
Conclusion: the use of TRL is a promising approach and risk mitigation strategy to reduce the risk of rebound disease after discontinuation of cell trafficking agents, while maintaining tolerability and safety.

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Therapy - Tools for detecting therapeutic response

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Role of serum neurofilament light chain concentration in the prediction of treatment response in multiple sclerosis

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Introduction: Multiple sclerosis (MS) has a highly variable course and the cornerstone of management is prevention of disability accrual by timely initiation of effective therapies.
Objective: We sought to determine if a pre-existing model of treatment response prediction could be improved by utilizing an emerging MS biomarker, neurofilament light (NfL) chain.
Aims: To assess the contribution of blood NfL levels to the prediction of treatment response when added to the Crystal Ball model which is a previously published and externally validated algorithm that uses only individual clinical and demographic information.

Methods: Data from 3 centers (Swedish MS registry, Swiss MS Cohort by University Hospital Basel and Prague General Hospital) were collated to include patients with relapsing MS, recorded Expanded Disability Status Scale and blood NfL at baseline, while being treated with or commencing a disease modifying therapy. We used principal component analysis to reduce the dimensionality of the data similar to the original Crystal Ball study. Cox proportional hazards models with three principal components and with vs. without NfL were used to model the risk of relapses, 6-month confirmed disability worsening and 9-month confirmed disability improvement in the pooled cohort while adjusting for therapy category and treatment duration. The accuracy of the NfL and no-NfL models was compared using bootstrap validation and Uno's C-index.
Results: 1716 patients across 12 MS therapies were pooled into 3 groups (platform injectable therapies, oral therapies and monoclonal antibodies) for the final analysis (68% female, mean age 38±11). The accuracy of the prediction of treatment response in the models without NfL was comparable to the original study. Addition of NfL did not further increase the predictive accuracy (For relapse: model with NfL=0.629 (95% CI:0.628 – 0.631) vs. model without NfL=0.630 (95% CI:0.628 – 0.631), for disability worsening: model with NfL=0.676 (95% CI:0.674 – 0.678) vs. model without NfL=0.676 (95% CI:0.674 – 0.678), for disability improvement: model with NfL=0.831 (95% CI:0.829 – 0.832) vs. model without NfL=0.829 (95% CI:0.827 – 0.830).
Conclusion: blood NfL does not substantially contribute to differentiating individual response to MS therapies among patients with various clinical and demographic characteristics. Clinical and demographic information remains the most useful indicator of future individual response to MS therapies.

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Expression of peripheral blood IFN-inducible genes predicts treatment outcome in patients with secondary progressive multiple sclerosis treated with IFN-beta-1a

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Introduction: Patients with secondary progressive multiple sclerosis (SPMS) responding to interferon-beta-1a treatment display peripheral blood transcriptional inflammatory profile comprised with the expression of IFN-inducible genes including IFI44, IFI6, IFIT1, IFIT3 and MX1.
Objectives: Evaluate the ability of peripheral blood IFN-inducible genes to predict treatment response in SPMS patients treated with IFN-beta-1a.
Methods: The expression of IFI44, IFI6, IFIT1, IFIT3 and MX1 IFN-inducible genes was measured in peripheral blood samples obtained from SPMS patients treated with IFN-beta-1a by RT_PCR. Patients were followed for 2 years and response to treatment was evaluated. Good response was defined as no disability worsening during the follow up. The best classification model for prediction of treatment outcome was established by Partek software (www.partek.com). Predictions were verified on an additional independent cohort of SPMS patients treated with IFN-beta-1a and followed for 2 years.
Results: The expression of peripheral blood IFN-inducible genes in 20 SPMS patients, mean age±SE 51.9±8.8 years, 17 females, baseline Expanded Disability Status Scale (EDSS) 4.0, 25-74% IQR 4.0-6.0 was higher in 10 treatment-responding patients ($p<0.05$), as compared to the 10 non-responding patients, in which after 2 years of follow up the median EDSS increased from 5.25 (IQR 4.75-6.5) to 6.5 (IQR 6.0-7.0). The best classifier was based on Diagonal Linear Discriminant Analysis algorithm that was further verified on 20 independent SPMS patients (mean age±SE 46.1±9.1, F/M ratio 17/3, baseline EDSS 4.8 IQR 4.0-6.0, 10 responders, 10 non-responders). Using the classifier,the 70.0% overall correct classification rate with positive predictive value of 75% to diagnose treatment responder were obtained.
Conclusion: Higher expression of IFN-inducible genes in SPMS patients can predict responders to IFN-beta-1a treatment with 70% accuracy.

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Hippocampal Glx in RRMS: a potential therapeutic indicator in fingolimod and injectables

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Background: Disease-modifying therapies (DMTs) can reduce relapses and mitigate the long-term damage in people with relapse-remitting MS (pw-RRMS). Magnetic resonance spectroscopic (MRS) studies have shown a positive effect of DMT on neurometabolites in pw-RRMS, which correlates with maintaining axonal metabolic function. Hippocampal demyelination and dysregulation of a major excitatory neurotransmitter (glutamate+glutamine; Glx) are associated with memory impairment in pw-RRMS. To date, evaluating the longitudinal DMT effect on hippocampal metabolism in pw-RRMS has not been investigated.
Objective: We measured morphologic and hippocampal neurometabolites in pw-RRMS on oral (fingolimod) and injectable DMTs and compared them to non-MS healthy controls (HCs).
Methods: A total of 65 pw-RRMS on fingolimod (N=36) or injectable (glatiramer acetate (GA) or interferon (IFN), N=29), were age and sex matched to HCs (N=44). All MRI and hippocampal MRS (voxel size=30x15x15mm^3) were acquired from pw-RRMS and HCs cohorts at baseline and 2 years follow-up. Segmentation of brain MRI/S was performed by FSL/SPM12. All pw-RRMS underwent cognitive, fatigue and mental health assessment as well as Expanded Disability Status Scale (EDSS).
Results: Individual and combined pw-RRMS cohorts showed similar statistically significant volumetric differences compared to HCs: GM (-4%), WM (-5%) and CSF (+28%). Pre- and post-mean hippocampal Glx levels were significantly altered in the MS cohorts ($p \leqslant 0.05$): fingolimod (1.47 ± 0.51 vs 1.06 ± 0.39) and injectable (1.33 ± 0.06 vs 1.16 ± 0.04) but HCs remained stable (1.161 ± 0.46 vs 1.158 ± 0.35). However, post-hoc tests revealed fingolimod is associated with a larger statistically significant reduction in hippocampal Glx($p=0.003$) compared to injectable ($p=0.01$) and a trend to be lower compared to HCs($p=0.09$). Hippocampal NAA levels showed statistically significant increase in fingolimod cohort ($p \leqslant 0.0001$) compared to HCs over the 2-yrs follow-up.
Conclusions: Fingolimod has a stronger impact on hippocampal Glx and NAA brain profiles than injectable DMTs. Our results suggest that MRS might be used as therapeutic indicator.

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Bayesian prediction of individualised treatment response in multiple sclerosis

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Introduction: Personalised decisions to start disease modifying therapy (DMT) in relapsing-remitting multiple sclerosis (RRMS) require a better understanding of why individual treatment responses are so variable. Whilst factors including DMT type, number of relapses and enhancing MRI lesions are associated with clinical response at the *group-level*, we do not have a tool that combines this information to make clinically useful predictions of treatment response at the *individual-level*.
Objective: To use clinical and radiological data to predict NEDA-3 (no evidence of disease activity) in patients initiating DMTs for RRMS.

Methods: We analysed observational data from RRMS patients who initiated glatiramer acetate, dimethyl fumarate, fingolimod, natalizumab or ocrelizumab between 2002–2022 at a UK centre. We predicted NEDA-3 at 1 and 2 years with 14 clinical and radiological predictors using Bayesian multiple logistic regression models. The accuracy gain of these 'comprehensive' models over simpler ones incorporating fewer predictors was evaluated by an out-of-sample measure of individualised predictive accuracy – the pairwise difference in leave-one-subject-out expected log posterior density (ELPD-LOO; higher is better)

Results: A total of 1986 patients (71% female; mean age 39.2 years (±10.2); disease duration 8.4 years (±7.0); median EDSS 2.5 [range 0-8.0]; 43% DMT naïve) initiated different DMTs (glatiramer acetate=547; dimethyl-fumarate=670; fingolimod=336; natalizumab=177; ocrelizumab=256). Overall, 76% and 52% achieved NEDA-3 at year 1 and 2 respectively.

Cross-validated prediction accuracy of the 'comprehensive' model (reference ELPD-LOO=0, SEM=0) was substantially better than a simpler model of average treatment effect (ELPD-LOO=-43.8, SEM ± 11.0), and similar to a simpler model with clinical but no radiological information (ELPD-LOO=-4.7, SEM ± 4.9). A similar pattern was observed with NEDA-3 at 2 years - the average treatment effect model performed worse (ELPD-LOO=-26.3, SEM ± 10.1) whilst the clinical information only model was similar (ELPD-LOO=-4.5, SEM ± 6.1) to the 'comprehensive' model

Conclusions: Routinely acquired clinical and radiological information can be used to predict NEDA-3 more accurately than current group-level estimates of DMT efficacy. Further work will incorporate more complex information such as serum biomarkers and genetics, seek to predict a wider array of clinical outcomes and validate this model in unrepresented populations

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Stability of longitudinal DTI metrics in MS with treatment of injectables, fingolimod and dimethyl fumarate

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Introduction: Diffusion tensor imaging (DTI) can detect microstructural changes in white matter of people with relapse-remitting multiple sclerosis (pw-RRMS) leading to progressive disability.
Objectives: This study uses selected DTI metrics to evaluate normal-appearing white matter (NAWM) as well as white matter-lesion (WML) to identify changes over time in pw-RRMS on different treatments compared to age and sex-matched healthy controls (HCs).
Methods: 78 pw-RRMS (29 on injectables, 36 on fingolimod and 13 on dimethyl fumarate (DMF)) were age and sex-matched to 43 HCs. Structural and diffusion scans on a 3T MRI were performed at baseline (BL) and 2-year follow-up (2-YFU). Primary outcome was change in DTI parameters, while secondary outcome was correlation with clinical parameters like EDSS, cognition, fatigue and mental health. Volumetric data and white matter fractional anisotropy (FA), mean, radial and axial diffusivities (MD, RD, AD) were estimated using our MRTrix in-house pipeline.
Results: While significant differences were observed in most clinical parameters between pw-RRMS and HC at BL and 2-YFU ($p<0.01$), no statistically significant differences in average changes over time for any DTI metrics have been observed. We also could not find any significant differences in changes over time between treatment groups in both NAWM and WML. MD, RD and AD in NAWM and WML correlated negatively with most cognitive domains at both time points, while FA correlated positively at baseline but only for NAWM at 2-YFU ($p<0.05$). FA correlated negatively with disability in NAWM and WML over time, while MD and RD correlated positively only in NAWM.
Conclusions: This is the first DTI study comparing the effect of different treatments on MRI parameters over time in a stable cohort. While there was a strong correlation of DTI metrics with most clinical symptoms of MS, in particular cognition scores, there were no differences in DTI metric changes over time between injectables, fingolimod and DMF in the absence of relapses.

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Treating the depression or the disease? Pseudo-trial with the UK MS register

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Introduction: Repurposing of treatments outside of their initial scope for treating the symptoms of MS is an area of active research. However, clinical trials for a drug already approved for treating other disease are expensive and unlikely to be undertaken by pharmaceutical companies. The UK MS Register (UKMSR) is a rich source of longitudinally collected patient reported outcome measures (PROs) such as the Multiple Sclerosis Impact Scale (MSIS-29), the Hospital Anxiety and Depression Scale (HADS) and both MS and non-MS specific medication treatment information.
Objectives/Aims: We use a recently developed pseudo-trial 'streak' methodology with longitudinal PROs to assess the effectiveness of antidepressant treatments on the progression of physical disability.
Methods: Progression of physical disability was defined as 10-point change in the MSIS-29 motor score (normalised 0 – 100), a clinically significant change; as described in the literature; we also looked at a 10-point improvement. The 'streak' of MSIS-29 questions consists of a continuous chain of at least 3 responses with a minimum of 30 days and maximum of 270 days between responses. A treatment cohort was defined such that the 'streak'

started within 180 days of treatment and once established propensity score matching by first MSIS motor and psychological score, Age, Gender, Diagnosis, and time since onset was used to create a control. Kaplan-Meier survival analysis for improvement and worsening events was performed and compared treatments using a log-rank test to determine significant differences between control and treatments cohorts.
Results: 360 pwMS were found to be eligible for the treatment arm of the 'pseudo-trial' (170 Tricyclic Antidepressants (TCA), 153 Selective serotonin reuptake inhibitors (SSRI), and 37 Serotonin and norepinephrine reuptake inhibitors (SNRI)) and an equal amount were matched for the control arm. There was a significant difference in worsening (p=0.028); notably fluoxetine was more likely to have worse outcomes and Sertraline better outcomes compared to control. Improvement was also significantly (p=0.01) Sertraline illustrating better outcomes than all other selected treatments and there was no difference between other treatments and control.
Conclusion: Preliminary studies in repurposing antidepressants to treat the symptoms of MS in this 'pseudo-trial' show a promising signal for further testing Sertraline in clinical trials.

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P358
Correlations between early MRI parameters and long-term clinical outcomes in phase 3 and open-label extension studies of ozanimod in relapsing multiple sclerosis

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Introduction: The ability of early magnetic resonance imaging (MRI) parameters to predict long-term clinical outcomes of relapsing multiple sclerosis (RMS) is not fully understood.
Objectives: To explore the predictive value of early MRI parameters on long-term clinical outcomes in patients with RMS treated with ozanimod in phase 3 and open-label extension (OLE) trials.
Methods: This post hoc analysis pooled data from patients treated with ozanimod 0.92 mg/d in SUNBEAM (NCT02294058) and RADIANCE (NCT02047734) who entered the DAYBREAK OLE (NCT02576717), in which all patients received ozanimod 0.92 mg/d. Early MRI parameters included observed (baseline [BL]) and % change in (month 12 [M12]) whole brain volume (WBV), thalamic volume (TV), and cortical grey matter volume; BL and M12 gadolinium-enhancing (GdE) lesion count and T1 and T2 lesion volumes; and M12 new/enlarging T2 lesion count. Clinical outcomes included number of relapses in the OLE, as well as cognitive processing speed (Symbol Digit Modalities Test [SDMT]) and disability (Expanded Disability Status Scale [EDSS]) at OLE month 48 (M48). Spearman correlation coefficients (ρ) for MRI parameters vs clinical outcomes were calculated and ranked by absolute values.
Results: Of the BL MRI outcomes, SDMT scores at OLE M48 correlated most strongly ($\rho > 0.46$-< 0.49) with T1 lesion volume (inverse correlation) and TV; EDSS at OLE M48 correlated less strongly with these MRI parameters ($\rho > 0.38$-< 0.42). For EDSS scores at OLE M48, the strongest correlations ($\rho > 0.41$-< 0.42) were observed with BL TV and WBV (inverse correlations). SDMT and EDSS correlated poorly with BL GdE lesion count ($\rho < 0.11$). Of the M12 MRI outcomes, SDMT and EDSS scores correlated most strongly with T1 and T2 lesion volumes (SDMT, $\rho > 0.44$-< 0.50, inverse correlations; EDSS scores, $\rho > 0.34$-< 0.39). Relapses during the OLE were poorly correlated with BL and M12 MRI parameters ($\rho < 0.19$).
Conclusions: MRI lesion volumes and TV had stronger correlations with SDMT than with EDSS long term, suggesting these imaging measures may be better predictors of cognition than physical disability over the long term. These results may be used to improve predictive models of long-term clinical outcomes and response to treatments in RMS.

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Cognitive functions in persons with multiple sclerosis treated with fingolimod: 2-years follow-up study

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Background: Cognitive impairment has been frequently reported in pwMS. There is limited information on the efficacy of fingolimod in longitudinal studies.
Objective: To evaluate the proportion of cognitive impairment at baseline and cognitive worsening or improving over 1 and 2 years in pwMS treated with fingolimod.
Methods: 454 pwMS (mean age 37.29, EDSS 1.66, disease duration 9.17, female 73.1%, male %26.9%) receiving fingolimod were assessed by neurological examinations and cognitive tests at baseline, at month (M) 12, and at M24. Age, sex, and education-matched healthy controls were also evaluated cognitively at baseline, using The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery.Cognitive Impairment Index identified subjects with improving or deteriorating cognitive performance above or below 1 SD of the healthy group over the follow-up period.
Results: In the study group, the mean EDSS scores did not change significantly, and only 11 pwMS had a relapse over 2 years (baseline; 1.66 vs at M24; 1.92). CI at baseline on SDMT scores was reported at 24.2%, and 17.3% at 12M, and also the rate was similar 24M (24.5%). CI at baseline on CVLT-II was calculated at 26.7%, 20.6% at 12M, and 14.7% at 24M. CI at baseline on BVMT-R was shown at 29.5%, 20.7% at 12M, and 14.8% at 24M. The number of pwMS scored at or above the control was assigned for each test at follow-up. At baseline, the rate over CVLT-II scores was 73.3%, 75.8% for SDMT, and 70.5% for BVMT-R. At 12M, the proportion over CVLT-II scores was 82.6%, 82.6% for SDMT, and 79.3% for BVMT-R. At 24M, the rate over CVLT-II scores was 85.2%, 75.4% for SDMT, and 85.2% for BVMT-R. Among pwMS receiving fingolimod, the proportion of patients who remained cognitively intact were stable during a 2-years follow-up.
Conclusion: Our findings support that fingolimod treatment may provide nonprogression based on low relapse rate, stable EDSS scores, and the prevalence of unchanged cognitive performance at follow-up. Even if the rates of CI remained unchanged over 2 years period, it could be assessed as the actual effectiveness of treatment on cognition.

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Therapy - Symptomatic treatment

P360
Carbohydrate restriction improves motor and visual deficits in a mouse model of multiple sclerosis

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Introduction: Optic neuritis is a common sequela of multiple sclerosis (MS). Steroids are the primary treatment but provide only symptomatic relief. Carbohydrate restriction using ketogenic diets (KD) is gaining popularity as a therapeutic strategy based on pilot clinical trials.

Objectives: Identify the efficacy of nutritional interventions as disease modifying therapies in MS.
Aims: Establish if the KD mitigates visual and motor deficits in the experimental autoimmune encephalomyelitis (EAE) mouse model of MS.
Methods: EAE was induced in C57BL/6J male and female mice by immunization with the myelin oligodendrocyte glycoprotein (MOG_{35-55})peptide antigen. Two treatment paradigms were tested. In the preventive regimen, mice were acclimated to the KD or a control diet (CD) for 2 weeks, immunized with MOG_{35-55}, and sustained on each diet for 3 additional weeks.For the interventional regimen, KD or CD feeding began after symptom onset. The KD contains 77.1% fat, 22.4% protein, and 0.5% carbohydrate (CHO)) whereas the CD has 10.4% fat, 20.4% protein, and 69.3% CHO. Mice were scored daily for motor deficits and visual acuity. Blood glucose and ketone levels were tracked longitudinally. Mice were euthanized for post-mortem tissue analyses to quantify retinal ganglion cells (RGCs) and analyze optic nerves for myelination and inflammatory infiltrates. Plasma cytokines and fatty acids were also measured. Spleens were processed for immune profiling by flow cytometry.
Results: The interventional KD restored motor and visual functions, while mice in the KD preventive studies were largely resistant to EAE pathologies. The KD preserved RGCs near the optic nerve head, the site of greatest RGC dropout in MS patients, and preserved myelination of the optic nerve, concomitant with restricting lymphocyte and microglial infiltration.The KD also decreased proinflammatory cytokines and chemokines, reduced arachidonic acid, and increased multiple anti-inflammatory omega-3 fatty acids in the plasma. Curiously, EAE mice pretreated with KD exhibited splenomegaly and enlarged lymph nodes with a corresponding increase in TER119+ pre-erythrocytes in the spleen.
Conclusions: These findings support a model in which reducing dietary carbohydrates using a KD promotes a systemic anti-inflammatory milieu that mitigates autoimmune-induced demyelinating visual and motor deficits, further supporting ongoing clinical trials using this dietary strategy to treat MS patients.

Disclosure
nothing to disclose

37: RWE and MS registries

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Emulating randomized clinical trials in relapsing-remitting multiple sclerosis with nonrandomized real-world evidence: an application using data from the MSBase registry

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Introduction: Real-world clinical evidence (RWE) about potential benefits of disease-modifying treatments (DMTs) in Relapsing-Remitting Multiple Sclerosis (RRMS) patients has consistently increased in the last decade. Regulators are evaluating the use of RWE to assess the effectiveness of DMTs. To mimic as closely as possible a randomized controlled trial (RCT) and calibrate the RWE studies against a known treatment effect would be helpful to understand if RWE can support causal conclusions in selected circumstances.
Objectives: To emulate the TRANSFORMS[1] trial comparing Fingolimod (FTY) vs Interferon β-1a intramuscular (IFN) using observational data and to compare results with those obtained in the trial.
Methods: All RRMS patients collected within the MSBase Registry in the period 2011-2021 who received intramuscular Interferon β-1a or Fingolimod (0.5 mg) and with the same inclusion and exclusion criteria of the RCT were extracted. Patients had to be in the range 18-55 years of age, have had at least one relapse during the previous year or two in the previous 2 years and an EDSS of 0 to 5.5. The primary endpoint was the annualized relapse rate (ARR) in the first 12 months from treatment start. Patients were 1:1 propensity-score (PS) matched on age, sex, edss, relapses in the previous 1 and 2 years, disease duration and naïve status. Relapse-rate ratio (RR) was calculated by mean of a negative binomial regression.
Results: A total of 1232 RRMS patients (439 in IFN and 793 in FTY) were selected. After PS, 238 patients in each group were matched (age: 34.6±9.3; female gender: 74.8%; disease duration: 4.6±6.0; edss: 2 (IQR: 1-2.5); ARR previous year: 1.31±0.63; naïve patients: 73.1%). The ARR was 0.39 (95%CI: 0.30-0.47) in IFN and 0.21 (95% CI:0.15-0.27) in FTY with a significant

difference between the two groups (RR:0.54, 95%CI:0.38-0.78; p=0.001). Results were very close to those obtained in the RCT: 0.33 (95%CI:0.26-0.42) in IFN and 0.16 (95% CI: 0.12-0.21) in FTY with a RR of 0.48 ($p<0.001$).

Conclusions: Applying the same inclusion and exclusion criteria of the RCT and appropriate methodology we were able to replicate the results of the RCT with only small differences. Further analyses will investigate the reasons of the residual heterogeneity.

References: *1. Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis. Cohen J, et al. NEJM 2010; 362: 402-415.*

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Natalizumab treatment of multiple sclerosis in Denmark — a nationwide study with 14 years of follow-up

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Introduction: Natalizumab is a high-efficacy treatment in multiple sclerosis (MS), and is in Denmark widely used for treatment in patients with high disease activity, who are JCV (John Cunningham Virus)-antibody negative. Real-world evidence regarding long-term effectiveness and safety is warranted.

Objectives: We performed a nationwide study evaluating the prescription patterns, therapeutic effectiveness, and adverse events in patients treated with natalizumab.
Methods: A nationwide cohort study using the Danish MS Registry including all patients initiating natalizumab between June 2006 and April 2020. Patient characteristics, annualized relapse rates (ARRs), 24-week confirmed Expanded Disability Status Scale (EDSS) score worsening, any MRI activity (defined as any new T2- or Gadolinium-enhancing lesions), and reported adverse events were evaluated. Further, prescription patterns and outcomes across different time periods ("epochs") were analysed.
Results: In total, 2424 patients were enrolled, with a mean follow-up time of 3.6 years. With more recent epochs, patients at treatment initiation were younger, had lower EDSS scores, had fewer pre-treatment relapses and were more likely to be treatment naïve. At 13 years of follow-up, 36% had a confirmed EDSS worsening. On-treatment ARR was 0.30, corresponding to a 72% reduction from pre-initiation. MRI activity was rare, 6.8% showed any activity within 2-14 months from treatment start, 3.4% within 14-26 months, and 2.7% within 26-38 months. Approximately 14% of patients reported adverse events, with cephalalgia constituting the majority. During the study, 62.3% discontinued treatment, of which the majority (40.6%) was due to JCV antibodies. Discontinuations due to disease breakthrough (9.0%), natalizumab-antibodies (9.3%) or adverse events (8.9%) were less common.
Conclusions: Natalizumab is increasingly used early in the disease course. Most patients treated with natalizumab are clinically and radiologically stable with few adverse events. JCV antibodies constitute the main cause for discontinuation.

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Characterizing activity between cycles in patients with multiple sclerosis under cladribine treatment in real word setting: data from Argentina

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Cladribine is an innovative disease modifying therapy (DMT) for relapsing-remitting multiple sclerosis (RRMS). The total dose of cladribine is divided into two cycles separated by one year. In this period, presence of clinical and/or radiological activity has been reported. Its frequency and predictive factors are unknown.
Objective: to analyze the frequency, characteristics, and predictors of MS activity between the 1st and 2nd cycle in people with MS (pwMS) under cladribine treatment.
Methods: retrospective cohort study conducted between February and March 2022, which included RRMS patients under cladribine treatment that received a complete dose. Demographical, clinical (EDSS, relapses) and paraclinical (magnetic resonance imaging –MRI- and blood test) data of last year prior to cladribine treatment, year between 1st and 2nd cycle and years after complete dose were collected by treating physician.
Results: 110 pwMS were included, 70.9 % female, mean EDSS: 2.22 ± 1.6, mean age: 37.1 ± 9.5 years, mean disease duration: 7.57 ± 5.6 years, mean time lapse under cladribine: 23.7 ± 10.1 months, 42.7 % naïve of previous DMT. Of 110 pwMS, 26.4 %

showed clinical and/or radiological activity between cycle 1 and 2, 17.3 % only clinical and 23.6 % only MRI activity; mean of MS activity presence: 4.7 ± 3.7 months after cycle 1. We did not find statistical differences between those who had MS activity between cycles and those who did not in the following: prior DMT used, EDSS and number of relapses in the year prior to starting cladribine, disease duration and lymphocyte count in months 3 and 7 post cycle 1. In pwMS followed up for at least one year after the second cycle, we found an association between the activity between cycles and after 2nd cycle ($p<0.01$, $X^2 9.9$). Furthermore, MS activity between cycles was independently associated with the presence of MS activity after 2nd cycle (OR= 1.7, p= 0.003).

Conclusion: MS activity between 1st and 2nd cycle is associated with activity after the 2nd cycle and shows no relationship with disease activity in the prior year to starting cladribine. Future evidence with larger numbers of patients will be needed to confirm these findings.

Disclosure

Nothing to disclose

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Achieving No Evidence of Disease Activity-3 (NEDA-3) in cladribine and monoclonal antibodies treated multiple sclerosis patients

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Background: Cladribine and monoclonal antibodies (mab; natalizumab, alemtuzumab, ocrelizumab and rituximab) are high efficacy therapies (HETs) used mainly in patients with highly active multiple sclerosis (HAMS).

Objective: We aimed to determine the proportion of HAMS patients under HETs failing to meet NEDA-3 at 1 and 2 years, and to identify factors associated to failing to meet NEDA-3 at 2 years.

Methods: This retrospective cohort study based on Argentina Multiple Sclerosis patient registry, RelevarEM (NCT 03375177), includes all HAMS patients patients who received HETs. Logistic regression model was used to predict factors related to NEDA-3 at two years, $p< 0.05$ was considered significant.

Results: Three hundred and twenty three HAMS patients were included, 22% and 32% of patients failing to meet NEDA-3 at 1 year and 2 years, respectively. Patients who achieved NEDA at 2 years had shorter duration of MS ($p < 0.01$) and shorter time between first treatment and current treatment ($p = 0.01$). On the other hand, naive patients had reached NEDA more frequently ($p < 0.01$). In a multivariable logistic regression model, being a naïve patient (Odds Ratio (OR) 3.78, 95% confidence interval (CI) 1.50-9.86, $p < 0.01$) was an independent risk factor to reach NEDA-3 at 2 years. No association was found between HETs and NEDA-3 at 2 years when adjusted for potential confounders (mab adjusted OR 1.73; 95% CI 0.51- 6.06, p 0.57).

Conclusion: We found a high proportion of patients who achieved NEDA-3 at 1 and 2 years. Treatment- naïve patients had a higher risk of achieving NEDA-3 at 2 years

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SISTER – subcutaneous: Non-interventional, observational, prospective, German multicentre, open label study over 12-months for tysabri patient preference – experience from real world – preliminary results of the 1ST interim analysis

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Background: Natalizumab (NTZ) is approved for the treatment of relapsing remitting multiple sclerosis (RRMS). The conventional route of administration (ROA) is an intravenous (IV) 300mg infusion. Since May 2021 subcutaneous (SC) injection of NTZ (2x150mg prefilled syringes) is available in Germany. This new route of administration allows shorter and simpler application, improves patient convenience, and reduces healthcare-associated costs.
Objectives: Primary objective is to collect and descriptively compare data on patients' preference of ROA between SC and IV NTZ at months 6 and 12. Secondary and additional objectives include immunogenicity, disease specific parameters (annualised relapse rate, expanded disability status scale [EDSS]), and pharmaco¬economic aspects.
Methods: This is an ongoing, non-interventional, observational, prospective, multicentre open label study conducted in Germany in routine medical care. NTZ is prescribed in accordance with the marketing authorisation and the SmPC with an observation period of one year. Approx. 500 RRMS pts at approx. 50 sites are included in 3 cohorts: Pts switching from current IV to SC NTZ administration (switcher IV to SC, ~300 patients), pts who newly start NTZ either IV or SC (new starter IV/SC, ~100 pts each). Data are collected at baseline, and every 3/6 months. We report the preliminary baseline results of the 1st interim analysis (abstract data cut-off Feb-2022).
Results: Up to February 2022, 116 switcher (mean age 39.3±9.5 years, 84.5% females, mean EDSS 2.0±1.5), 11 new starter IV (mean age 35.4±12.7 years, 100% females, mean EDSS 2.6±1.7), and 14 new starter SC (mean age 30.4±6.1 years, 100% females, mean EDSS 0.6±0.7), were enrolled. The most frequent MS therapies prior to NTZ were fingolimod (23 pts, 20.7%), dimethyl fumarate (18 pts, 16.2%), and glatiramer acetate (17 pts, 15.3%). Anti-JCV-Ab status was negative in 81.5% (110 pts). In total, 90.5% (114 pts) chose the SC route and 98.4% (121 pts) expressed satisfaction with their choice. The most frequent reason for patients' SC preference were shorter duration of administration and convenience.
Conclusion: This study will provide valuable insight into patients' preference for NTZ ROA in routine care and complement currently available data from clinical studies with real-world data on subcutaneous natalizumab.

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Real-world evidence of anti-CD20 monoclonal antibodies in chilean patients with multiple sclerosis

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Introduction: Real-world evidence studies regarding the effectiveness and safety of disease-modifying therapies are useful for clinical practice and for assessing the risk-benefit of some health policy interventions.
Objectives: To evaluate safety and effectiveness outcomes in year 1 and year 2 in patients receiving antiCD20 monoclonal antibodies. Methods: Longitudinal observational study of MS patients under regular care at the Programa de Esclerosis Multiple UC in Chile who received at least one dose of ocrelizumab or rituximab between June 2018 and April 2022.
Results: A total of 229 patients were included, 219 using Ocrelizumab and 10 using Rituximab. 163 patients had relapsing-remitting MS (RRMS), 68% female, mean age at antiCD20 34.3+8.5 years, mean disease duration 5.6+5.4 years, and median baseline EDSS 1.5(0-6.0). 35 had primary progressive MS (PPMS), 54% female, mean age at antiCD20 47+12 years, mean disease duration 6.3+6.3 years and median EDSS 4.0(1.0-7.0). 31 had secondary progressive MS (SPMS), 64% female, mean age at antiCD20 50.4+9.7 years, mean disease duration 16.4+10.1 years

and median EDSS 6.0(1.0-7.0). Before antiCD20, mean annualized relapse rate (ARR) was 0.7+0.5 for RRMS, and 0.2+0.4 for PPMS and SPMS patients, and MRI activity (newT2/Gd+) was observed in 84.8% of RRMS, 60% of PPMS and 40.7% of SPMS patients. Mean ARR in years 1 and 2 was 0 in RRMS and PPMS, 0.05+0.2 in year 1 and 0 in year 2 for SPMS. NewT2/Gd+ in years 1 and 2 were observed in 11.4% and 8.3% in RRMS, 21.4% and 0 in PPMS, and 0 in SPMS. Year 1 and 2 EDSS progression was observed in 0% and 3.6% of RRMS, 0 and 15.4% in PPMS, and 18.1% and 21.4% in SPMS. Years 1 and 2 NEDA3 was obtained in 82.6% and 94.6% of RRMS, 70% and 87.5% of PPMS and 90% and 87.5% of SPMS. Infusion Reactions were observed in 35% during the first dose, decreasing with each infusion (13.5% in the fourth infusion), all were considered mild. The most frequent year 1 adverse event were COVID-19 (n=5), upper tract infection (n=4), diarrhoea (n=4) and urinary tract infection (n=4). The most frequent year 2 adverse events were COVID-19 (n=4) and skin infection (n=3). One patient with previous history of breast cancer developed a tumour recurrence during the second year of treatment.

Conclusion: This study supports robust effectiveness outcomes in a real-world cohort, with a consistent safety profile in patients receiving care at a specialized MS Unit.

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Real-world experience with ocrelizumab in primary Progressive multiple sclerosis: Insights from the MSOCR-P cohort, a MSBase Registry sub-study

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Introduction: MSOCR-P is a five-year prospective cohort study of primary progressive multiple sclerosis (PPMS) patients built as a secondary data use of the international, real-world MSBase registry. It aims to enrol 500 patients with PPMS, newly treated or untreated with Ocrelizumab (OCR), and to assess disability progression trajectories in clinical practice setting. Patient recruitment began in November 2017.

Objective: This MSOCR-P interim analysis aims to describe baseline characteristics of enrolled PPMS patients and report initial disability outcomes.

Methods: Eligibility criteria are diagnosis of PPMS (McDonald Criteria 2010), age $\geqslant$ 18 years, EDSS $\leqslant$ 8, with $\geqslant$ 2 visits recorded in MSBase and $\geqslant$ 1 year of follow-up prior to study entry, OCR naïve or OCR treatment $\leqslant$ 24 weeks prior baseline. Descriptive statistics were used to present baseline patient characteristics including demographics, disease history, prior disease modifying therapies (DMT), and EDSS. Disability outcomes were analyzed in all patients with follow-up of $\geqslant$ 6 months.

Results: As of October 2021, 277 patients were included the MSOCR-P study, mainly from Australia, Turkey, Belgium,

Kuwait and Spain. Of these, 69 patients (42.0% females) were treated with OCR at baseline and 208 (53.4% females) were OCR-naïve. Mean (SD) age and median (IQR) disease duration were 54.4 (10.7) and 11 (6.2,16.7) years in the OCR naïve cohort vs. 50.7 (10.6) and 8.6 (5.0,12.7) in the OCR treated cohort. Both cohorts had a similar median baseline EDSS 6 (IQR 4-6.5). Among the 208 OCR naïve at baseline, 81 (38.9%) were on DMTs in the 12 months pre-baseline (mainly with fingolimod 17.3% and rituximab 18.5%) and 84 (40.4%) switched to OCR post-baseline. Median follow-up was on OCR therapy was approximately 2.3 yrs and OCR discontinuation was recorded in 16.3% (25/153) of patients at last follow-up. Disability outcomes will be presented as 24-week confirmed EDSS progression in the OCR naïve and OCR treated cohorts.

Conclusion: This study characterizes an international population of OCR naïve and newly OCR treated PPMS patients in a real-world clinical setting. Enrolled patients are middle aged, more frequently females, with disease duration since symptom onset of ~10 years and relatively disabled. Comparative analysis of confirmed EDSS progression rates between OCR treated and untreated patients will require longer follow up duration and higher cumulative event rates.

Disclosure

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T. Kalincik served on scientific advisory boards for BMS, Roche, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

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M. Barnett served on scientific advisory boards for Biogen, Novartis and Genzyme and has received conference travel support from Biogen and Novartis. He serves on steering committees for trials conducted by Novartis. His institution has received research support from Biogen, Merck and Novartis.

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Utilization, safety, and tolerability of ocrelizumab: data from the providence ocrelizumab registry

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Introduction: The Providence Ocrelizumab (OCR) Registry (POR) was established to monitor long-term treatment and safety outcomes after the approval of OCR in the US in 2017.
Objective: To evaluate OCR treatment outcomes using real-world data from a community-based MS population.
Methods: Adult MS patients who have been prescribed and received at least one dose of OCR were eligible. Chart reviews were done at OCR start date and every 6 months by a trained RN. Expanded Disability Status Scale (EDSS) scores were determined by the treating provider on the OCR start date and yearly, thereafter.
Results: Of the 509 patients enrolled from March 2017 to April 2022, 74.2% were female; mean (SD) age was 52.1 (12.6) years; 82.7% had RMS, 11.0% had SPMS, and 6.7% had PPMS. Median time on OCR was 34.3 [17.2, 49.6] months. The RMS cohort had an annualized relapse rate (ARR) of 0.32 prior to starting OCR. Among all patients who had $>$ 1 dose of OCR (n=449), ARR was 0.05 (SD 0.23) with 5 patients having 2 or more relapses. Median EDSS scores at 12 months were 3.0 [2.0, 4.5] (n=205) for RMS patients, 6.5 [6.5, 7.5] (n=33) for SPMS, and 6.5 [6.5, 7.5] (n=19) for PPMS. Infusion reactions occurred in 33% of patients during dose 1, becoming less frequent with subsequent doses. Respiratory infections have occurred in 37.5% of patients followed by urinary tract infections (UTI) (36.7%). 10% of patients have developed documented COVID-19. Of the 70 patients hospitalized, 27 patients had multiple hospitalizations. Over half of the hospitalizations were due to infections. 66% of these patients were 55 years or older. One hundred and twenty-nine (25.3%) patients have stopped OCR with a median time to discontinuation [IQR] of 20.5 [11.2,34.7] months; 63 patients stopped due to side effects with recurrent infections being the main reason for stopping followed by fatigue/malaise. There have been 12 deaths, including 2 from COVID-19. There were no significant changes in Beck Depression Inventory (BDI). Modified Fatigue Inventory (MFIS), had significant improvement at 12 months (mean difference -3.6 ($\pm$14.2), (p=0.01). No change in the MFIS of the 17 patients switching from natalizumab.
Conclusion: Our study showed that OCR was effective in controlling relapse and disability worsening and reported similar rates of infusion reactions compared to earlier phase III clinical trials. However, a quarter of our patients have stopped OCR, the majority stopping due to recurrent infections.

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The real-world safety and effectiveness of ocrelizumab in patients with primary progressive multiple sclerosis – a confidence study interim analysis

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Introduction: As of October 2021, 225,000 patients with relapsing (RMS) or primary progressive multiple sclerosis (PPMS) around the world have initiated treatment with the CD20$^+$ B-cell-targeting humanized monoclonal antibody ocrelizumab (OCR).
Objectives: Large, observational studies can add value to further assess the long-term safety profile and effectiveness of OCR in the real-world.
Aims: To describe safety and effectiveness in patients with PPMS treated with OCR over a maximum observation time of 3.5 years in regular clinical practice.
Methods: CONFIDENCE (ML39632, EUPAS22951) is an ongoing non-interventional, post-authorization safety study that is aiming to enroll 3,000 RMS and PPMS patients newly treated with OCR and 767 patients newly treated with other selected disease-modifying therapies in Germany, following them for up to 10 years. Safety was described in all patients with PPMS treated with OCR (SAS population). Effectiveness was described in patients from the SAS with $\geqslant$1 post-initiation assessment visit (FAS), and was analyzed by mean change in Expanded Disability Status Scale (EDSS), 24-week confirmed disease progression (CDP) and Treatment Satisfaction Questionnaire for Medications© (TSQM).
Results: As of 8 Oct 2021, 489 patients with PPMS were included in the SAS. Patients were a mean (standard deviation) 51.3 (10.0) years old and had 846.3 patient years (PY) of exposure, with a mean observation time of 1.72 (0.90) years. AEs occurred in 42.1% of patients (66.4 AEs/100 patient years [PY]) and SAEs occurred in 9.6% of patients (9.1 AEs/100 PY). As expected, AEs were most often classified as 'infection and infestation' (16.7 AEs/100 PY; 2.2 SAEs/100 PY). No new safety signals were observed in this analysis.
The FAS included 473 patients. The mean baseline age was 51.2(9.9) years. Baseline EDSS was 4.43 (1.60), with a mean change of 0.34 (0.77) over 18 months. Over the same time period, 75.9% of patients were free of CDP. TSQM global satisfaction was a mean 66.2 (20.1) at baseline and 70.1 (20.0) at 18 months.

Conclusions: The majority of patients with PPMS treated with OCR in CONFIDENCE were over 50 years old and/or had significant disability at baseline (EDSS ⩾4.0). Over 18 months of observation, most patients had a stable EDSS and approximately 76% were CDP free. No new or unexpected AEs were observed during this analysis.

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- **SG Meuth** receives honoraria for lecturing, and travel expenses for attending meetings from Almirall, Amicus Therapeutics Germany, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva. His research is funded by the German Ministry for Education and Research (BMBF), Bundesinstitut für Risikobewertung (BfR), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Gemeinsamer Bundesausschuss (G-BA), German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, German Foundation Neurology and Alexion, Almirall, Amicus Therapeutics Germany, Biogen, Diamed, Fresenius Medical Care, Genzyme, HERZ Burgdorf, Merck Serono, Novartis, ONO Pharma, Roche, and Teva.
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The real-world safety and effectiveness of ocrelizumab in patients with relapsing multiple sclerosis – a confidence study interim analysis

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Introduction: As of October 2021, 225,000 patients (pts) with relapsing (RMS) or primary progressive multiple sclerosis (PPMS) globally have initiated treatment with the $CD20^+$ B-cell-targeting humanized monoclonal antibody ocrelizumab (OCR).
Objectives: Large, observational studies can add value to further assess the long-term safety profile and effectiveness of OCR in the real-world.
Aims: To describe the safety of OCR treatment in pts with RMS over a maximum observation time of 3.5 years in clinical practice, and the effectiveness of OCR in RMS pts who were treatment naïve (TN) and those with prior MS-specific therapies (PMST).
Methods: CONFIDENCE (ML39632, EUPAS22951) is an ongoing non-interventional, post-authorization safety study aiming to enroll 3,000 RMS and PPMS pts newly treated with OCR and 767 pts newly treated with other selected disease-modifying therapies in Germany, following them for up to10 years. Safety was described in all pts with RMS treated with OCR (SAS population). Effectiveness was described in pts from the SAS with ⩾1 post-initiation assessment visit (FAS), and was analyzed by the annual relapse rate (ARR), 24-week confirmed disease progression (CDP) and Treatment Satisfaction Questionnaire for Medications© (TSQM).
Results: As of 8 Oct 2021, 2130 pts with RMS were included in the SAS with 3563 patient years (PY) of exposure and a mean (SD) observation time of 1.67 (0.95) years. The mean age was 41.3 years (11.4). Overall, 46.2% of pts experienced an adverse event (AE) (89.8 AEs/100 PY; 10.4 serious AEs/100 PY). As expected, AEs were most often classified as 'infection and infestation' (24.7 AEs/100 PY; 2.3 serious AEs/100 PY). No new safety signals were observed.
The FAS included 2023 pts (TN, 350; 1 PMST, 494; 2 PMST, 484; ⩾3 PMST, 695). From 0–12 months ARR in TN pts was 0.12 (0.46) and 0.26 (0.64) in pts with ⩾3 PMST. From 12–24 months ARR in TN pts was 0.08 (0.40) and 0.15 (0.47) in pts with ⩾3 PMST.
Over 24 months, 87.0% of pts were CDP free. The rates were highest in TN pts (89.5%) and lowest in pts with ⩾3 PMST (85.6%). The overall mean baseline TSQM global satisfaction score was 70.1 (20.0) at baseline and 75.8 (19.8) at 24 months.
Conclusions: Overall, ARR in pts with RMS remained low over 24 months of OCR treatment. Pts treated at an early line experienced numerically lower rates of relapses and CDP than pts with ⩾3 PMST. No new or unexpected AE were observed during this analysis.

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- **Mathias Buttmann** received honoraria for lecturing, consulting and/or travel expenses for attending meetings from Bayer, Biogen, Boehringer, Bristol Myers Squibb, Coloplast, Daiichi-Sankyo, Das Fortbildungskolleg, Merck, Novartis, RG Ärztefortbildung, Roche, Sanofi and Teva
- **SG Meuth** receives honoraria for lecturing, and travel expenses for attending meetings from Almirall, Amicus Therapeutics Germany, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva. His research is funded by the German Ministry for Education and Research (BMBF), Bundesinstitut für Risikobewertung (BfR), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Gemeinsamer Bundesausschuss (G-BA), German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, German Foundation Neurology and Alexion, Almirall, Amicus Therapeutics Germany, Biogen, Diamed, Fresenius Medical Care, Genzyme, HERZ Burgdorf, Merck Serono, Novartis, ONO Pharma, Roche, and Teva.
- **P Dirks** is an employee of F. Hoffmann-La Roche AG and shareholder of F. Hoffmann-La Roche AG.
- **J C Eggebrecht** is an employee of Roche Pharma AG and shareholder of F. Hoffmann-La Roche AG
- **S Hieke-Schulz** is an employee of Roche Pharma AG.
- **J Leemhuis** is an employee of Roche Pharma AG and shareholder of F. Hoffmann-La Roche AG.
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Drivers of therapy switch in relapsing multiple sclerosis: a study from the Italian MS Registry

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Background: Different studies have recently focused on patients with relapsing multiple sclerosis (RMS), a term that comprises active relapsing remitting (RR) and secondary progressive (SP) MS patients.

Objectives: To assess the characteristics of RMS patients in the Italian Multiple Sclerosis Register (IMSR), evaluating disease modifying therapy (DMT) switches due to disease activity.

Methods: RRMS and SPMS patients with ⩾5-year follow-up and ⩾3 EDSS scores were extracted from the IMSR. In order to evaluate the percentage of patients switching DMT due to disease activity, we have first determined the proportion of active patients during DMT exposure, defined with at least one relapse in the last

2 years of follow up. The effect of demographic, clinical and DMT exposure on the risk of treatment switch was assessed using multivariable logistic regression models.
The role of DMTs exposure was assessed in 2 different models including: last recorded DMT or last DMTs grouped according to their efficacy and mechanism of action (MoA) (moderate efficacy (ME), high efficacy (HE) DMTs, anti-CD20 drugs).
Results: After applying the inclusion criteria, we retrieved a cohort of 21,174 RRMS and 1153 SPMS patients. Using a clinical definition, we identified 4161 RR (19.7%) and 578 SP (50.1%) active patients, of whom 2694 (56.8 %) switched DMT. RMS patients were significantly younger (median (IQR) years: 36.50 (29.10-44.80) years vs 39.60 (32.80-48.00), $p<0.0001$), less disabled (median (IQR) EDSS score: 2.00 (1.00-3.50) vs 2.50 (1.50-4.00), $p<0.0001$), more frequently affected by a RR disease course (89.8% vs 85.2%, $p<0.0001$) in comparison with not active patients. The multivariable logistic regression model performed revealed that Alemtuzumab (OR 0.08 95% CI 0.02-0.37), Natalizumab (OR 0.48 95% CI 0.30-0.76), Ocrelizumab (OR 0.1 95% CI 0.02-0.45) and Rituximab (OR 0.23 95% CI 0.06-0.82) were protective factors against treatment switch due to relapses in comparison with patients exposed to Interferon beta products. Our model also revealed that the use of HE DMTs was a protective factor against the treatment switch due to a relapse (OR 0.43 95% CI 0.31-0.59), especially considering anti-CD20 drugs (OR 0.14 95% CI 0.05-0.37) in comparison with the use of ME DMTs.
Conclusions: Clinical disease activity is an important trigger of treatment switch in RMS patients. HE DMTs, especially those with anti-CD20 MoA, significantly reduce the risk of disease activity in RMS.

Disclosure
The authors Pietro Iaffaldano, Giuseppe Lucisano, Tommaso Guerra, Francesco Patti, Eleonora Cocco, Giovanna De Luca, Vincenzo Brescia Morra, Carlo Pozzilli, Mauro Zaffaroni, Patrizia Sola, Claudio Gasperini, Giuseppe Salemi, Roberto Bergamaschi, Giacomo Lus, Matilde Inglese, Silvia Romano, Paolo Bellantonio, Maria Gabriella Coniglio,Giorgia Teresa Maniscalco, Antonella Conte, Alessandra Lugaresi, Marika Vianello, Paolo Agostino Confalonieri, Marco Capobianco, Ilaria Pesci, Franco Granella, Rocco Totaro, Girolama Alessandra Marfia, Maura Chiara Danni, Paola Cavalla, Paola Valentino, Umberto Aguglia, Sara Montepietra, Elisabetta Ferraro, Alessandra Protti, Daniele Spitaleri, Carlo Avolio, Elio Scarpini, Davide Maimone, Gioacchino Tedeschi, Maria Sessa, Marco Rovaris, Francesca De Robertis, Augusto Rini, Bonaventura Ardito, Damiano Paolicelli, Maria Pia Amato, Massimo Filippi, Maria Trojano report no conflicts of interest with respect to the contents of the current study, but note that the patients in the study were treated with a number of disease modifying drugs and that authors report have received advisory board membership, speakers honoraria, travel support, research grants, consulting fees, or clinical trial support from the manufacturers of those drugs, including Actelion, Allergan, Almirall, Bayer Schering, Biogen, Celgene, Excemed, Genzyme, Forward Pharma, Ipsen, Medday, Merck, Merz, Mylan, Novartis, Sanofi, Roche, Teva, and their local affiliates. Mihaela Nica is employee of Novartis S.p.A., Origgio, Italy.

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Proof of concept for 2-stage models of heterogeneous treatment effects derived from the real-world MS PATHS research network

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Introduction: Published 2-stage models of heterogeneous treatment effects (HTE) in multiple sclerosis (MS) are derived from clinical trials (CT). They show potential for improving personalized medicine but have limited generalizability due to restrictive inclusion criteria.
Objectives: To establish proof of concept for 2-stage HTE models for relapse inclusive of all MS disease-modifying therapies (DMTs) and MS patient types using real-world data (RWD) and compare with published CT models.
Methods: Analyses included MS patients who initiated DMT, had ⩾1 year follow-up, and completed baseline data in the MS PATHS observational study. DMT groups were based on efficacy: high (natalizumab, ocrelizumab, alemtuzumab, ofatumumab, rituximab), moderate (fumarates, S1PR modulators, and cladribine) and low (teriflunomide, interferons, glatiramer acetate). Patients were split into training (70%) and test (30%) sets stratified by treatment group. In the first stage, baseline relapse risk scores were derived by logistic LASSO regression with baseline covariates as inputs; performance was assessed by area under the receiver operator curve (AUROC). In the second stage, propensity score weighting using overlap weight was performed. The propensity score model was derived using multinomial logistic regression, with baseline relapse risk score used as one of the covariates. Covariate balance was measured by standardized mean differences (SMD). Average treatment effect (ATE) and HTE were calculated with low-efficacy DMT as the reference.
Results: Analyses included 1600 MS patients on DMTs: 1,067 high, 322 moderate, and 211 low-efficacy groups; 64% were relapsing remitting. The relapse risk model achieved AUROC=0.75 on the test set. Pre-adjustment 8/21 covariates had SMD >20%; after adjustment, all SMDs were <20%. In the ATE model, moderate- and high-efficacy groups had better relapse outcomes compared to low, with the high- efficacy group approaching statistical significance (p=0.058). HTE curves showed consistently worse outcomes for low- versus moderate- and high-efficacy DMTs, regardless of risk. At low risk, moderate and high efficacy groups were similar. As relapse risk increased, advantages for high-efficacy treatment became apparent, mirroring published models from CT, but did not reach statistical significance.
Conclusions: 2-stage models of HTE in MS PATHS replicated CT findings providing proof of concept for expanding this methodology into RWD.
Study Support: Biogen.

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Long-term effectiveness of natalizumab for RRMS: Dutch and global interim results from TYSABRI observational program

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Introduction: The TYSABRI Observational Program (TOP) is an ongoing observational study of natalizumab treatment in relapsing-remitting multiple sclerosis (RRMS) patients. Country-specific data on relapse and disability outcomes, alongside global data, can provide information on natalizumab's effectiveness in local practice.
Methods: Annualised relapse rate (ARR) was analysed in TOP Netherlands (n=300) and global (N=6321) cohorts using data from July 2007 to November 2021. A subgroup analysis assessed ARR in patients with one prior disease modifying therapy (DMT) in the Dutch (n=143) and global (n=2757) cohorts. Another subgroup analysis assessed ARR in patients with EDSS <3.0 and EDSS $\geqslant 3.0$ at baseline in the Dutch (n=107 and n=174, respectively) and global (n=2252 and n=3947, respectively) cohorts. Cumulative probabilities of 24-week confirmed disability worsening and improvement will also be presented.
Results: Mean on-natalizumab duration was 58.99 doses for the Dutch cohort and 55.66 doses for the global cohort. ARR decreased in Dutch patients from 1.67 in the year prior to treatment initiation to 0.17 on natalizumab ($P<0.0001$), consistent with a global decrease from 2.00 to 0.18 ($P<0.0001$). In patients with one prior DMT, ARR decreased in Dutch patients from 1.63 in the year before initiation to 0.13 on natalizumab ($P<0.0001$), similar to the global decrease from 2.03 to 0.16 ($P<0.0001$). In Dutch patients with EDSS <3.0 at baseline, (n=107) ARR reduced from 1.72 to 0.14 ($P<0.0001$) and in patient with EDSS $\geqslant 3.0$ (n=174) reduced from 1.66 to 0.20 ($P<0.0001$). This is similar as the global cohort: patients with EDSS <3.0 at baseline (n=2252) ARR reduced from 2.00 to 0.15 ($P<0.0001$) and in patients with EDSS $\geqslant 3.0$ (n=3947) reduced from 1.99 to 0.20 ($P<0.0001$).
Conclusions: The significant reduction in ARR on natalizumab was similar in the TOP Netherlands and global cohorts, including in the subset of patients with one prior DMT and in patients with EDSS <3.0 or $\geqslant 3.0$ at baseline. These findings support the real-world effectiveness of natalizumab.

Disclosure Support: Biogen.

Disclosures: OG, GH will be added to the poster; AD and EW are employees of and may hold stock and/or stock options in Biogen

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Teriflunomide routine clinical practice in patients with relapsing-remitting multiple sclerosis: final results of the TAURUS MS II study

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Introduction: Teriflunomide is a once-daily oral immunomodulatory agent for the treatment of relapsing–remitting multiple sclerosis (RRMS). The efficacy and safety of teriflunomide was shown in phase 2 and phase 3 studies. In Germany, the non-interventional studies (NIS) TAURUS MS I and II studies confirmed the effectiveness, tolerability and patient satisfaction in patients receiving teriflunomide in a real-world setting. Patient recruitment for the TAURUS MS II study started in September 2017 and was completed by end of March 2020.
Objective/aims: To report the final data on effectiveness and treatment satisfaction with teriflunomide according to pre-treatments 24 month after end of recruitment in the TAURUS-MS II study.
METHODS:TAURUS MS II isaprospective, NIS conducted in Germany. Patients with a diagnosis of RRMSare observedfor two years. Dataarecollected approximately 4 weeks after initiation of teriflunomide and approximately 3, 6, 12, 18 and 24 months thereafter. Collected data include patient demographics, treatment effectiveness (Expanded Disability Status Scale [EDSS] score, number of relapses), safety (adverse events) as well as patient - and healthcare-professional reported outcomes.
Results: The followingdata are derived from the 12-month-interim analysis conducted in 2021:Of 1000 patients enrolled, 676 (67.6%) patients were included in the analysis.Patients were predominantly female (65%) and had a mean age of 43 years.About two-thirds (67%) of patients had received a pre-treatment including 26.3% with more than one previous therapy. Most used therapies before study entry were interferons (28.8%), glatiramer acetate (15.2%) and dimethyl fumarate (14.3%). The majority of patients (85.4%) was relapse-free during their first year of teriflunomide treatment. Regarding safety, infections were reported for 4.9% of patients during the first year of follow-up. The finalanalysis of TAURUS MS II is currently being performed and will be presented.
Conclusions: The following final analysis of TAURUS MS II will provide an up-to-date insight in the real-world use of teriflunomide therapy in Germany. Especially the impact of pre-treatments on effectiveness and patient satisfaction over 24 months in a real-world setting will be addressed.
Study funding: Sanofi

Disclosure

BA Kallmann: Honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities

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Study funding: Sanofi

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Two years efficacy and safety results from real world experience for cladribine tablets in management of relapsing multiple sclerosis in Qatar

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Objectives: To study safety and efficacy of Cladribine tablets (Clad T) treatment in RMS patients over 2 years in a real-world clinical setting.
Aims: To describe the efficacy and safety in Real-world experience in an Arab Population.
Methods: This is a retrospective single-centre observational study in Qatar. Medical records of Relapsing Multiple Sclerosis (RMS) patients who received at least one year treatment of Cladribine treatment between January 2018 through December 2021 were reviewed. Demographic and clinical aspects, EDSS, previous disease-modifying drugs (DMD) and annual relapse rate (ARR) were recorded. MRI data of patients who completed at least first-year course of Cladribine tablets were assessed as well adverse events.
Results: A total of 49 RMS patients (46 RRMS, 3 SPMS) were included, from those 34 (69%) were females. Mean age at Clad T initiation was 32 (18-59), mean disease duration is 7.6 (1-25) years. 25 patients (51%) were treatment naive, and 24 patients (49%) had one or more disease modifying therapy (DMT) before treatment. The most common reason for treatment with cladribine was disease activity (68 %), pregnancy planning (11%), compliance (10%) and side effects (11%). Prior DMTs included DMF (40%), Fingolimod (16%), Teriflunomide (16%), Natalizumab (12%), Interferon Beta (12%) and Ocrelizumab (5%). By December 2021, 32 patients finished the two courses of the drug. The Median follow-up period of the total cohort was 32 months. 26/32 (81.25%) patients were relapse free post treatment compared to 25% pretreatment. Annualised relapse rate (ARR) was reduced by 92% (0.08 vs 0.97). 75% of patients were free of Gd+ T1 lesions post treatment compared to 37.5% at the baseline. Majority of MRI findings (7/8) were observed in the 1st year of treatment and only one patient experimented radiological activity after the second-year course. 31 patients (96.8%) had no 3 months confirmed EDSS progression. Only mild Adverse events were reported and single case of herpes zoster, urinary tract infection and oral candidiasis. All COVID-19 cases (n=12) were mild and didn't need hospitalization. Grade 3 lymphopenia was recorder for 5 patients (1.5%) and no grade 4 was observed.
Conclusion: Our real-world experience confirms good efficacy, tolerability, and safety of cladribine tablets in consistency with data from phase 3 clinical trials and other real-life studies. Reported adverse events showed lower frequency of lymphocytopenia.

Disclosure
Dr Beatriz Garcia-Cañibano: Served on Advisory Board and received speaker/travel honoraria from Merck®, Novartis®, Bio
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Therapy - Symptoms Management (including cognition, fatigue, imbalance)

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Functional connectivity modifications in monoaminergic circuits occur in fatigued MS patients treated with fampridine and amantadine

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Introduction: Fatigue is a common and disabling symptom in multiple sclerosis (MS). Different pharmacological agents have been tested for treating MS fatigue, with no clear evidence supporting their efficacy. Symptomatic treatments for fatigue rely on drugs reinforcing monoaminergic synaptic transmission. Therefore, monoaminergic network abnormalities may have a role in fatigue pathogenesis.
Objectives: To investigate changes over time of fatigue severity and concomitant modifications of resting state (RS) functional connectivity (FC) abnormalities in monoaminergic networks in 45 fatigued MS patients after different symptomatic treatments.
Methods: S patients were randomly, blindly assigned to treatment with fampridine (n=15), amantadine (n=15) or placebo (n=15) and underwent clinical, neuropsychological and 3T RS fMRI at baseline (T0) and after four weeks (W4) of treatment. Fifteen matched healthy controls (HC) were acquired twice. Dopamine-, noradrenaline- and serotonin-dependent RS FC patterns were derived by independent component analysis (ICA), constrained to PET atlases for dopamine, noradrenaline and serotonin

transporters, previously obtained in HC. Changes in modified fatigue impact scale (MFIS) score and monoaminergic-dependent RS FC were assessed.
Results: S patients showed baseline abnormalities*vs* HC in all three networks, with decreased monoamine-related RS FC in temporal, occipital, insular and cerebellar regions, and increased RS FC in frontal, parietal and subcortical areas. At W4, MFIS scores decreased in all patients' groups, with no time-by-treatment interaction. At W4, fampridine and amantadine patients showed increased dopamine- and noradrenaline-dependent RS FC in the insular cortex, as well as increased serotonin-dependent RS FC in the precuneus/posterior cingulate cortex. Amantadine patients also showed increased dopamine- and noradrenaline-dependent RS FC in the anterior cingulate cortex (ACC). Conversely, placebo patients mostly showed increased noradrenaline-dependent RS FC in the precuneus and middle cingulate cortex. In fampridine and placebo groups, there were trends towards significant correlations between RS FC modifications and MFIS improvements (r=-0.49:-0.52, p=0.07-0.08).
Conclusions: Fatigue improved in all MS groups. Concomitant monoaminergic-dependent RS FC modifications were found in insular, ACC and parietal regions for fampridine and amantadine MS patients, and in medial parietal regions for placebo patients.

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Cognitive improvements in ocrelizumab-treated patients with relapsing-remitting multiple sclerosis: 96-week CASTING study data

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Background: Cognitive impairment is highly prevalent in people with multiple sclerosis (PwMS) and is associated with reduced quality of life. The Symbol Digit Modalities Test (SDMT) measures cognitive processing speed and can be used as a screening test for cognitive impairment in PwMS.
Aims: To report changes in SDMT scores over 96 weeks in ocrelizumab (OCR)-treated patients with relapsing-remitting MS (RRMS) in the Phase IIIb CASTING trial (NCT02861014).
Methods: Patients (Expanded Disability Status Scale score $\leqslant$4.0) with a suboptimal response to one or two prior disease-modifying therapies received intravenous OCR 600 mg every 24 weeks for 96 weeks. SDMT was measured at baseline, Week 48 and Week 96. Scores were translated to z-scores with a cut-off of −1 to define cognitive impairment; baseline z-score $\leqslant$−1 defined the cognitively impaired subgroup and baseline z-score $>$−1 the minimally impaired subgroup. In both subgroups an increase of $\geqslant$4 SDMT points was considered a clinically relevant improvement, and a decrease of $\geqslant$4 SDMT points was considered clinically relevant worsening.
Results: Overall baseline mean z-score was −1.36. From baseline to Week 96, mean SDMT score changed from 53.8 to 55.2 (p=0.0047) in the overall population (N=680), and from 46.5 to 49.5 (p<0.001), and 65.6 to 64.1 (p=0.0073) in the impaired (N=392) and minimally impaired (N=245) subgroups, respectively. From baseline to Week 96 in the overall population, 29.0% (n/N=197/680) of patients had an improvement of $\geqslant$4 points, 22.6% (n/N=154/680) had worsening of $\geqslant$4 points and 32.8% (n/N=223/680) remained stable. In the impaired subgroup, 38.3% (n/N=150/392) of patients had an improvement of $\geqslant$4 points, 18.6% (n/N=73/392) had worsening of $\geqslant$4 points and 33.4% (n/N=131/392) remained stable. In the minimally impaired subgroup, 19.2% (n/N=47/245) of patients had an improvement of $\geqslant$4 points, 33.1% (n/N=81/245) had worsening of $\geqslant$4 points and 37.6% (n/N=92/245) remained stable.
Conclusions: There was a significant improvement in SDMT score over 96 weeks in patients with RRMS treated with ocrelizumab, mainly observed in the cognitively impaired subgroup. An increased proportion of patients in the cognitively impaired subgroup experienced clinically relevant improvements in SDMT score over 96 weeks, compared with the less impaired subgroup.

Disclosure
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A randomized, controlled trial of low-fat diet for fatigue in multiple sclerosis

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Introduction: Fatigue is a common and disabling symptom of multiple sclerosis (MS). A dietary intervention to improve fatigue is desirable given the minimal risk of adverse events.
Objectives and aims: To determine if a low-fat diet was effective at ameliorating fatigue in people with MS (PwMS), as measured by Modified Fatigue Impact Scale (MFIS) through a randomized controlled trial (RCT). Primary outcome was reduction in fatigue assessed via MFIS at 14 weeks. Secondary outcomes included evaluation of blood markers of inflammation, lipid metabolism, and clinical outcomes including cognitive function, mobility, and body composition. Additional outcomes included changes on actigraphy, gut microbiome and blood metabolomics.
Methods: This was a two-arm open-label, RCT where PwMS were assigned to a low-fat diet or wait-list control group. The diet group received 1-2 weeks of nutrition counseling followed by strict adherence to the diet for 12 weeks. The control group was offered the same nutrition counseling after 14 weeks. We measured diet adherence using monthly Food Frequency Questionnaire and 24-hr food recall. The principal statistical analysis used linear mixed models, with a random effect for subject to account for the within-subject correlation, in an intent-to-treat (ITT) framework to determine the effect of diet on the outcomes of MFIS and Fatigue Severity Scale (FSS). Sensitivity analysis was conducted by excluding potential outliers in both groups.
Results: A total of 39 participants were recruited with 20 in the diet group and 19 in the wait-list group. At baseline participants mean age was 50 years ($\pm$12 years), mean BMI was 31 kg/m^2($\pm$7 kg/m^2), and mean EDSS score was 3.8 ($\pm$1.4). Mean MFIS decreased by -4.00 (95% CI: -12.04, 4.04) and mean FSS decreased by -0.41 (95% CI: -1.18, 0.36) from baseline to the end of the RCT in diet group compared to wait-list. Sensitivity analysis strengthened the magnitude of association with a mean MFIS decrease of -13.93 (95% CI: -20.65, -7.20) and mean FSS decrease of -1.22 (95% CI: -1.94, -0.50) in diet group compared to wait-list. Percent calories from fat, assessed by 24-hr food recall, decreased by 10.56% (95% CI: -18.50%, -2.97%) in diet group compared to wait-list. Additional data analysis is under process.
Conclusions: This 12-week long low-fat dietary intervention reduced the fatigue score significantly in the PwMS compared to controls. Studies with a larger sample size and longer follow-up are needed.

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Therapy - Neurobiology & Rehabilitation

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Abnormal thalamic functional connectivity correlates with cardiorespiratory fitness and physical activity in progressive multiple sclerosis

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Introduction: Patients with progressive multiple sclerosis (PMS) have insufficient levels of physical activity (PA) and cardiorespiratory fitness (CRF), which showed some associations with measures of structural MRI damage. Functional MRI (fMRI) correlates of reduced PA/fitness have never been explored. Given the role of thalamus in motor planning, sensory processing and cognition, abnormal thalamic resting state (RS) functional connectivity (FC) might explain PA/fitness levels in these patients.

Objectives: To assess thalamic structural and functional MRI alterations and investigate their correlations with PA/CRF levels in PMS patients.

Methods: Ninety-one PMS patients performed a cardiopulmonary exercise test and wore an accelerometer for 7 days to assess PA/CRF levels. They also underwent, together with 37 matched healthy controls (HC), a structural and RS fMRI acquisition at 3.0T, which was used to derive whole-brain and thalamic atrophy and thalamic RS FC. Between-group comparisons of MRI measures and their correlations with PA/CRF variables were assessed.

Results: PMS patients had significant whole-brain and subcortical atrophy compared to HC (all $p<0.001$). Patients also showed decreased intra- and inter-thalamic RS FC, decreased RS FC of the thalamus with caudate nucleus, cerebellum and bilateral anterior cingulate cortex (ACC), and increased thalamic RS FC with the bilateral hippocampus and some occipital regions. Lower CRF levels correlated with lower normalized white matter volume (r=range 0.28;0.31, p=range 0.003;0.01), with decreased thalamic RS FC with the left ACC (r=range 0.22;0.28, p=range 0.01;0.04), and with increased thalamic RS FC with the left hippocampus, left calcarine cortex, and right lingual gyrus (r=range -0.26;-0.21, p=range 0.01;0.04). Lower PA correlated with decreased inter-thalamic RS FC (r=0.27, p=0.02), and with increased thalamic RS FC with the right hippocampus (r=-0.3, p=0.01) and left lingual gyrus (r=-0.23, p=0.04).

Conclusions: Only white matter atrophy correlated with CRF variables. Conversely, abnormal RS FC in the thalamic network showed various maladaptive associations with PA and fitness status in people with PMS. Given its extensive correlation with PA and CRF, thalamic RS FC might be used as an outcome to monitor physical impairment and efficacy of rehabilitative and disease-modifying treatments in PMS patients.

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Disease-modifying effect of circuit class therapy in patients with relapsing-remitting multiple sclerosis

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Introduction: Physical therapy plays an essential role in the long-term multidisciplinary management of patients with multiple sclerosis (MS) and has shown to be beneficial in improving gait impairment and alleviating fatigue. Recent evidence suggests that physical exercise in MS is not just a symptomatic therapy but seems to have also a disease-modifying effect.
Aims: Our study aimed to assess the efficacy of 12-week intensive circuit class therapy (ICT) on MS progression by comparing 2 years before and after the ICT in relapsing-remitting MS patients with lower disability (EDSS up to 4).
Methods: Twenty-two MS patients underwent 12-week circuit class therapy (1 hour once a week) and were motivated to continue exercising on regular basis in their home environment for the next two years. Median EDSS 2.5 (0 to 4). Twenty-four MS patients served as a control group. Median EDSS 1 (1 to 3.5). All patients were treated with disease-modifying therapies.
Patients were clinically evaluated at three-month intervals for 4 years (2 years before and after the ICT in the exercising group) to assess any further clinical attacks or EDSS progression. The brain MRI was performed once a year.
Results: Significant improvement was found in the annualized relapse rate (ARR) in the exercising group: 0.5 (0 to 1.5) before and 0 (0 to 1.5) after the ICT (p=0.01). No significant AAR change was found in the control group:0 (0 to 0.5) both in the first and second 2-years interval (p=0.30).
The prevalence of new or enlarging T2 lesions after the ICT in the therapy group (24%) was significantly lower than before ICT in the same patients (61%; p=0.001). No significant difference was found between the first (27%) and second 2-years interval (32%) in the control group (p=0.37).
No significant differences in EDSS change were found between the first and second 2 years in either ICT (p=0.29) or the control group (p=0.32).

Conclusions: The study showed a positive impact of ICT on AAR and MRI progression in exercising patients and thus confirmed the disease-modifying effect of exercise in MS.

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Therapy - Others

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COVID-19 antibody response by vaccine type and lymphocyte count in RMS patients on ponesimod: results from Phase 2 long-term extension study AC-058B202

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Background: Various factors may impact the humoral response to coronavirus disease 2019 (COVID-19) vaccination in multiple sclerosis (MS) patients treated with sphingosine 1-phosphate receptor modulators, including ponesimod.
Objective: To characterize the SARS-CoV-2 humoral response by vaccine type and pre-vaccination lymphocyte count in relapsing MS (RMS) patients who have received COVID-19 vaccination while on ponesimod treatment.
Methods: Patients in the Phase 2 extension study AC-058B202 receiving ponesimod 20 mg who reported COVID-19 vaccination were included in this analysis. Blood samples collected before and at least 3 weeks after vaccination were evaluated with Human SARS-CoV-2 PreSpike IgG (spike antibody) enzyme-linked immunoassay (Nexelis). A responder to vaccination was defined as seroconversion in case of negative pre-vaccination antibody testing, or a 4-fold antibody concentration increase in case of positive pre-vaccination antibody result. Responder analysis was performed by vaccine type and by pre-vaccination lymphocyte count.
Results: 49 COVID-19-vaccinated patients had both pre- and post-vaccination blood samples available for analysis. These patients were on uninterrupted ponesimod treatment during the course of vaccination. Response to COVID-19 vaccination varied by vaccination type: of 32 participants who received mRNA vaccines, 29 (90.6%) met responder criteria. Of 7 participants who received viral vector vaccines, 5 (71.4%) were responders. Of 6 participants who received inactivated virus vaccines, 2 (33.3%) were responders. Of 4 participants who received mixed or unspecified vaccine types, 4 (100%) were responders. Response to COVID-19 vaccination also varied by lymphocyte count: of 16 participants with pre-vaccination lymphocyte count $<500/mm^3$, 9 (56.3%) were responders. Of 32 participants with lymphocyte count $\geqslant 500/mm^3$, 30 (93.8%) were responders.
Conclusion: Humoral response to COVID-19 vaccines in RMS patients on ponesimod in the Phase 2 study varied by vaccine type and pre-vaccination lymphocyte count. In patients who received mRNA COVID-19 vaccines and/or who had pre-vaccination lymphocyte count $\geqslant 500/mm^3$, most ($>90\%$) met antibody concentration responder criteria.

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Treatment of acute optic neuritis and multiple sclerosis relapses: an international survey of clinician perspectives and practice

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Introduction: Acute optic neuritis (AON) is a common presentation in demyelinating diseases such as multiple sclerosis (MS). AON study results are often extrapolated to MS relapses in general. The landmark Optic Neuritis Treatment Trial (ONTT), conducted in the 1980s, showed faster recovery but no sustained functional outcome benefit with intravenous methylprednisolone (IVMP) vs. placebo or low dose oral prednisone (LDOP). Structural outcomes and high dose oral prednisone (HDOP) were not assessed. Most subsequent studies have similarly not shown

long-term benefits from steroids. Debate persists about optimal management.

Objectives: To survey clinician-reported AON treatment decision-making.

Aims: Update understanding of AON management and perspectives to guide future research.

Methods: In March-May 2022, a 25-question multiple-choice anonymous survey was emailed to all members of CMSC, ACTRIMS, and IMSVISUAL. Results are summarized with descriptive statistics.

Results: The 302 respondents included neuroimmunologists (75%), general neurologists (16%), and neuro-ophthalmologists (4%); regionally from Asia/Pacific (As/P, 6%), Canada (8%), Europe (29%), Latin America (LA; 9%), Middle East/N. Africa (MENA, 9%), and the US (40%). Most respondents (70%) extend ONTT results to MS relapses. 97% endorse that corticosteroids for typical ON have beneficial effects including faster recovery (92%), improvement in clinical function (55%), neuroprotection (12%), and/or reduced conversion to clinically definite MS (10%); steroid benefit perspectives varied by specialty. Typical AON treatment options include IVMP (89%), HDOP (47%), LDOP (4%), IV immunoglobulin (10%), plasmapheresis (28%) or no treatment (11%). HDOP usage varied by region: 9-19% (MENA, LA, As/P), 45-60% (Europe, US) to 85% (Canada). Overall, 65% almost always treat AON with steroids, ranging by region from Canada (50%) to LA (85%). Lastly, 90% endorsed an evidence gap, and that a study assessing sensitive structural and functional outcomes of steroid treatment in AON would be impactful for their practice.

Conclusions: There is significant heterogeneity in interpretation of the ONTT and other AON studies, and differing approaches to AON treatment including some variation by region. Most clinicians endorse an AON treatment evidence gap—and notably, most use AON data to guide treatment of MS relapses in general. An AON study with broader treatment interventions and sensitive outcomes may help address this gap.

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Autologous hematopoietic stem cell transplantation for MS. The Dutch experience of patients going abroad

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Introduction: Autologous hematopoietic stem cell transplantation (aHSCT) is not provided in the Netherlands, resulting in numerous Dutch patients with MS going abroad at their own expense to fee for service clinics for aHSCT.
Aim: To gain insight into the number of people and their diagnosis who have undergone an HSCT abroad, and in the number of people who have plans to go.
Methods: Via (social) media communities and the Dutch MS society, patients with MS were requested to fill out a questionnaire about aHSCT treatment abroad.
Results: 481 patients responded to the call (386 female, 80%). Of these, 135 (28,1%) had undergone aHSCT (treated group) and 346 (71,9%) had considered treatment (planned group).
Of the planned group, 10.9% ultimately decided not to undergo aHSCT, and 176 (51.9%) patients indicated that they are waiting with their final decision until aHSCT in the Netherlands has been approved.
The treated group consisted of 51 (38%) patients with RRMS, 46 (38%) with SPMS, and 31 (34%) with PPMS. The planned group consisted of 241 (70%) patients with RRMS, 50 (14%) with SPMS, and 41 (12%) with PPMS.Most patients were treated in Russia 76 (57%) or Mexico 42 (31%). Eight were treated in India (6%) and the remaining 6% elsewhere.
Most patients rely on social media to choose a particular clinic. Within the treated group, 77% decided for aHSCT regardless of their treating neurologist's opinion.
Within the treated group, two patients died during treatment (India), and two underwent euthanasia in a later stage after aHSCT. In the treated group, 125 (93%) patients indicated that, in hindsight, they would make the same decision. Four patients indicated that it was too early after the treatment to answer this question. Two patients regretted their decision. 84% reported no new disease activity since aHSCT and 57% improvement in disability.
In none of the cases, the health insurance contributed to financing the treatment.
Conclusions: Many Dutch MS patients seek aHSCT treatment abroad, usually regardless of the advice of their treating physician. While in the past years many patients had progressive MS in recent years there seems to be a shift towards RRMS.
Expert coaching with the attention to aftercare of people going abroad for this high-risk treatment could contribute to better safety. A central registration is neededfor the registration of side effects and with the ultimate goal to organize reimbursement for selected cases.

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Treatment preferences among health care providers in the United States in selecting disease modifying therapies for multiple sclerosis: a discrete choice experiment study

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Introduction: The multiple sclerosis (MS) treatment landscape has several available disease modifying therapies (DMTs).
Objectives: This study aimed to assess implicit and explicit treatment preferences among US healthcare providers (HCPs) in selecting DMTs for MS patients based on clinical and logistical product attributes.
Methods: A 45-minute web-enabled questionnaire including a Discrete Choice Experiment (DCE) was approved by an Institutional Review Board and fielded with HCPs in February 2022. Qualifying HCPs were board-certified or eligible, practicing for 3-35 years, spent ⩾70% of time in direct patient care, and treated ⩾5 MS patients with DMTs. Relative importance of treatment attributes was captured using direct assessments via a 9-point scale (1='not at all important' and 9='extremely important'). The DCE included both clinical and logistical treatment attributes to ensure that HCPs made holistic decisions in evaluating DMTs. The DCE was analyzed using a hierarchical Bayesian model. DCE results are reported as mean relative attribute importance scores.
Results: The study recruited 145 HCPs (100 neurologists and 45 advanced practice clinicians). Direct assessments suggested that safety (mean importance rating = 7.8), relative risk reduction (RRR) in relapses (7.6), and RRR in disability progression (7.5) were the most important attributes in selecting DMTs. In contrast, derived importance from the DCE suggested that logistical attributes such as dose frequency (18%), dose titration (10%), formulation (9%), and volume of calls (9%) were also important considerations when selecting DMTs, along with efficacy (17%), safety (10%), and GI tolerability (9%). Other attributes considered less important were patient monitoring (6%), time for treatment initiation (4%), type of MS (4%), and vaccine requirements (4%).
Conclusions: HCPs stated that clinical attributes were most important in making MS treatment decisions. However, when implicit and explicit treatment decision making was considered

via the DCE, logistical attributes such as dose frequency, formulation, titration, and volume of calls were often of equal importance to clinical attributes. These results highlight the criticality of logistical considerations in MS treatment decisions and suggest that along with a safe and efficacious treatment, HCPs also aim to minimize potential logistical burden on their patients and their practice.

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IVIG treatment for acute MOGAD attacks- a retrospective multicenter observational study

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Background: Acute relapses in MOGAD are generally managed with high-dose corticosteroids (CS). However, some patients do not respond well to CS and require additional treatments. The potential benefit of Intravenous immunoglobulins (IVIG) has been anecdotally reported, but its effect has not been evaluated in a large cohort of patients.
Objective: To describe efficacy outcomes of IVIG treatment during acute MOGAD attacks.
Methods: This was a retrospective observational study involving 6 tertiary neuroimmunology centers in 4 countries (USA, UK, Israel, and Germany). Data collection included: patients' age, disease duration, chronic immunosuppression, EDSS, and visual acuity (VA) before the attack; type of attack, EDSS and VA at the nadir of attack before IVIG treatment, dose and duration of IVIG treatment, and additional acute treatments; EDSS and VA at the end of IVIG treatment and at follow up visits³3 months after treatment.
Results: 36 patients and 37 attacks were included in the final analysis. 19 (53%) were females. The median age was 18.5 years (range 5-74 years), and the median disease duration was 4.5 years (range 0.75-15.5 years). Twenty-seven patients (75%) were not on immunosuppressive medications. Four patients (11.1%) received oral CS maintenance therapy at the time of the attack. The most common type of attack treated with IVIG was optic neuritis (unilateral, n=14, bilateral, n=4), followed by ADEM (n=7), multifocal (n=5), myelitis (n=4), brainstem (n=2), and other encephalitis (n=1). In most cases (n=34, 92%), IVIG was administered as a second-line treatment due to lack of response to high- dose CS and/or plasma exchange. In 3 attacks (8%), IVIG was administered as first-line treatment. A significant improvement in both the EDSS and VA measures was observed at the first follow up compared to nadir [median EDSS at nadir=4(range 1-9.5), at follow up=1.5 (range 0-7), $p<0.0001$; median converted LogMar VA at nadir=2.2 (range 0.1-3), at follow up= 0.2 (range 0-3), $p<0.0001$].
Conclusions: IVIG may be an effective treatment option for acute MOGAD attacks. Further prospective studies are warranted to validate our results.

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Disease activity after short-term interruption of ponesimod versus teriflunomide in relapsing multiple sclerosis patients

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Introduction: Cases of severe disease reactivation have been reported after natalizumab and fingolimod discontinuation. In the Phase 3 OPTIMUM study, ponesimod – a selective S1P1 receptor modulator – demonstrated superiority to teriflunomide in reduction of annualized relapse rate, as well as magnetic resonance imaging (MRI) activity. The objective of this post-hoc analysis was to evaluate disease activity after short-term interruption of ponesimod, versus after washout of teriflunomide.
Methods: In OPTIMUM, patients with relapsing MS were randomized (1:1) to 20 mg ponesimod or 14 mg teriflunomide daily for up to 108 weeks. Patients who completed the 108-week double-blind treatment period and underwent accelerated elimination procedure were eligible to enter open label extension study (OLE) and receive ponesimod 20 mg once daily. The PP group (ponesimod in OPTIMUM/ponesimod in OLE) was compared with the TP group (teriflunomide in OPTIMUM/ponesimod in OLE) for disease activity, as measured by 1) time to first confirmed relapse, 2) number of patients with confirmed relapses at 3 and 6 months after ponesimod initiation in OLE, and 3) combined unique active lesions (CUAL) at first MRI assessment in OLE at Week 48.
Results: Of 1133 patients randomized in OPTIMUM, 877 (77.4%) patients (439 PP and 438 TP) were enrolled in OLE, where they started (TP) or re-initiated (PP) treatment with ponesimod 20 mg. Duration of treatment interruption ranged from 13 to 51 days (median 16 days). In time to first confirmed relapse analysis at 3 months, PP group had median time of 49.5 days, while TP group had median 41.0 days. In time to first confirmed relapse analysis at 6 months, PP group had median time of 70.0 days, while TP group had median 44.0 days. By OLE Month 3, 27 PP versus 46 TP patients had confirmed relapses (Kaplan-Meier [K-M] estimates 6.5% and 10.8%, log-rank p=0.018). By OLE Month 6, 44 PP versus 55 TP patients had confirmed relapses (K-M estimates 11.6% and 13.5%, log-rank p=0.207). In CUAL analysis of MRI at OLE Week 48 compared to end of treatment in OPTIMUM, mean number of CUALs was 1.638 in the PP group (n=210) and 1.693 in the TP group (n=231) (p=NS)
Conclusion: These findings suggest that disease activity observed after interruption of ponesimod does not exceed the disease activity observed after washout of teriflunomide, which is a DMT not associated with "rebound" after treatment interruption.

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COVID-19 infections and vaccinations among patients receiving ozanimod in the daybreak open-label extension trial

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Introduction: COVID-19 emerged in late 2019. It is unclear whether selective sphingosine 1-phosphate (S1P) receptor modulators affect clinical outcomes of COVID-19 in patients with relapsing multiple sclerosis (RMS), including those who received SARS-CoV-2 vaccination.

Objectives: To characterise COVID-19 outcomes and vaccine breakthrough infections during ozanimod use, an $S1P_1$ and $S1P_5$ modulator, for treatment of RMS in an ongoing open-label extension (OLE) study.

Methods: DAYBREAK (NCT02576717), an OLE study of ozanimod 0.92 mg/d, began 16Oct2015. Patients who completed a phase 1–3 ozanimod RMS trial were eligible; >90% are from Eastern Europe. In this post hoc analysis, COVID-19 events from 1Nov2019 to 28Jan2022 in DAYBREAK were identified by MedDRA 24.1 COVID-19 SMQ (narrow scope). Each patient's most recent infection and all postvaccination infections were characterised.

Results: Of 2181 patients in DAYBREAK during the analysis period, 319 (14.6%) developed COVID-19 (274 confirmed, 45 suspected). COVID-19 was nonserious in 291 (91.2%). During COVID-19, ozanimod was continued in 220 (69.0%) patients, interrupted in 94 (29.5%), and permanently discontinued in 3 (0.9%); action was unknown in 2 (0.6%) patients. At data cutoff, 285 (89.3%) had recovered (including 195 who had continued ozanimod), 6 (1.9%) recovered with sequelae, 5 (1.6%) were recovering, 16 (5.0%) had not recovered, and 5 (1.6%) died; a sixth COVID-19–related death due to lung abscess occurred after recovery with sequelae from COVID-19 infection. Of 1984 patients in DAYBREAK on 11Dec2020, when COVID-19 vaccines emerged, 596 (30.0%) received ⩾1 vaccine dose (415 [69.6%] mRNA; 99 [16.6%] replication-defective viral vector; 65 [10.9%] inactivated SARS-CoV-2; 26 [4.4%] other); 504 (25.4%) were fully vaccinated. COVID-19 occurred in 39/596 (6.5%) vaccinated patients and 213/1388 (15.3%) unvaccinated patients; 3 postvaccination cases (including 1 case after 2 mRNA doses) were serious. Of 39 patients with postvaccination infections, 28 (71.8%) recovered (including 2/3 serious cases), 1 (2.6%) recovered with sequelae, 3 (7.7%) were recovering, and 7 (17.9%, including the third serious case) had not recovered at data cutoff. There were no COVID-19–related deaths among vaccinated patients.

Conclusion: COVID-19 cases were largely nonserious, and the majority of infected patients recovered while continuing ozanimod. Few vaccinated patients developed COVID-19; most who did recovered without sequelae.

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A multi-stakeholder survey on multiple sclerosis multidisciplinary care: The situation in Belgium and lessons for the global community

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Introduction: Multiple sclerosis (MS) is a multifaceted disease requiring a multidisciplinary approach. Due to lack of clear evidence, the Belgian health care system does not implement standardized reimbursed MS multidisciplinary teams (MDT).
Objective: To frame the current care for People with MS (PwMS) in Belgium and to identify needs and future perspectives.
Methods: Online surveys were sent out to PwMS, MS specialist nurses and MS-neurologists. The survey for PwMS asked for specific MS parameters (e.g. MS type, treatment, availability of an MDT and MS nurse) and their view on current care. The topics in the surveys for MS nurses and neurologists were employment status, education, job content, MS care organization, future perspectives. Statistics include demographic data, T/Mann-Whitney U/Fisher exact tests.
Results: We received responses from 916 PwMS, 22 MS nurses and 62 neurologists. The PwMS cohort is representative with a mean age of 46±12.7, mainly relapsing remitting MS (60,8%) and a mean patient determined disease step of 2.5±2.05, which did not differ with or without nurse/MDT. Whilst 45.5% of the MS nurses are employed in a university hospital, 75.8% of the neurologists work in a general hospital. 65.3% and 60.4% of the PwMS reported to have access to an MDT or an MS nurse. The funding for MS nurses is diverse (hospital budget 19.4%, grants 4.8%, clinical trials 11.3%, budget within association 21%). Considering symptomatic treatment, the proportion of PwMS who receive spasticity ($X^2(1, 748)=4.15$, P=.042) and gait treatment ($X^2(1, 748)=4.43$, P=.035) is higher with access to a nurse and treatment for bladder problems was higher in PwMS with access to an MDT ($X^2(1, 810)=4.96$, P=.047). Work adjustments were higher with a nurse ($X^2(1, 748)=5.64$, p=.018) and MDT ($X^2(1, 810)=9.64$, P=.002) availability. PwMS were significantly more likely to be in order with driving regulation with access to a nurse ($X^2(1, 748)=25.35$, P<.001) or MDT ($X^2(1, 755)=27.64$, p<.001). Finally, 69% and 75% neurologists working without a nurse or MDT state a need of such support, mainly in centres with a follow up of over 200 PwMS. Preference for care at a hospital network level was advocated by a majority of neurologists (61%).
Conclusion: Belgian neurologists offer a variety of multidisciplinary initiatives for MS. Alignment and reimbursement are much needed as our data may suggest MDT's and nurses might provide better support for symptomatic care, work and legal aspects.

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Comparing the risk and severity of infusion-related reactions in patients premedicated with cetirizine versus diphenhydramine prior to ocrelizumab infusions (PRECEPT)

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Introduction: In the phase III trials, at least one infusion-related reaction (IRR) occurred in 34% of patients. Pre-medication with methylprednisolone, an analgesic/antipyretic, and an oral antihistamine commonly diphenhydramine (DPH) was recommended to minimize IRRs. Since drowsiness is commonly associated with DPH, newer antihistamines such as cetirizine (CTZ) may be tolerated better without an increase in IRRs.
Objective: The primary objective of this study is to evaluate whether CTZ is non-inferior to DPH in limiting the proportion and severity of reactions from OCR infusions (IRR). The secondary objective of this study is to evaluate patient reported outcomes after receiving CTZ or DPH as premedication for OCR infusions.
Methods: Adult patients with relapsing or progressive MS, starting OCR were eligible to enroll. Patients were randomized 1:1 to DPH 25mg or CTZ 10mg.
Patients completed Modified Fatigue Impact Scale (MFIS) and Multiple Sclerosis Impact Scale (MSIS-29) prior to starting OCR and after the 2nd dose. Stanford Sleepiness Scale (SSS), Visual Analogue Scale-Fatigue (VAS-F), and Treatment Satisfaction Questionnaire for Medication (TSQM) were completed prior to starting OCR and within 2 hours after each OCR infusion.
Results: 19 of the 20 patients have completed the study. 75 % were female; median age at OCR start was 47.5 (range 29-63); 17 (85%) with RRMS. IRRs occurred in 14 (67%) patients following the 1st two infusions of dose 1, 6 (60%) in CTZ group and 8 (73%) in DPH group. IRRs occurred in 5 (18%) patients with dose 2, 3 (23%) in the CTZ group and 2 (13%) in the DPH group. MFIS and MSIS-29 at screening were higher in the patients randomized to DPH, with no significant change after the 2nd dose. There was significant difference in VAS-F Fatigue domain favoring patients pretreated with CTZ (p= 0.001), but no difference in the Energy domain. Patients on CTZ achieved significant improvement in SSS across the 4 assessments (p= 0.001). While there was no significant difference of TSQM Global Satisfaction, subscales of effectiveness, side effects and convenience favored CTZ, p-, 0.02, 0.04, 0.06, respectively. Incidence of AEs were balanced between groups. 1 SAE was reported in the DPH group but it was not related to DPH. No discontinuation due to AEs.
Discussion: IRRs were similar across arms with no significant difference in the number of AEs related to the premedication. However, patient reported outcomes favored CTZ.

Disclosure
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RIMS - Biological effect of rehabilitation

P390

The effect of aerobic training on neuro-specific blood-based biomarkers in people with multiple sclerosis – a secondary analysis of a randomized clinical trial

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Background: Neuro-inflammation and neurodegeneration are pathological hallmarks of multiple sclerosis (MS). Exercise might have neuroprotective effects in MS but current literature is inconclusive. Brain derived neurotrophic factor (BDNF), neurofilament light (NfL), and glial fibrillary acidic protein (GFAP) are potential blood-based biomarkers for neurogenesis, axonal damage and astrocytosis, respectively. We hypothesize that exercise has a neuroprotective effect reflected by increased BDNF and decreased NfL and GFAP levels.
Objectives: To investigate the effect of aerobic training (AT) compared to a control intervention on neuro-specific blood-based biomarkers (i.e. BDNF, NfL, GFAP) in people with MS (pwMS).
Methods: In the TREFAMS-AT (Treating Fatigue in Multiple Sclerosis - Aerobic Training) trial, 89 pwMS were randomly allocated to either 16-week AT with 3 sessions/week or a control group (CG) (3 visits to an MS-nurse). In this secondary analysis, blood-based biomarker concentrations were measured using Simoa technology. Pre- and post-intervention concentrations between groups were compared, using an analysis of covariance (ANCOVA). Confounding effects of age, sex, MS severity measured by expanded disability status scale (EDSS), disease duration, use of disease modifying medication, and Body Mass Index were taken into account.
Results: Blood samples of 55 participants (mean age 45.6 years, 71% female, median disease duration 8 years, median Expanded Disability Status Scale 2.5) were available. Median [interquartile range (IQR)] baseline values for BDNF (ng/mL): AT 20.1 [15.6-25.0] and CG 21.4 [17.4-28.0], NfL (pg/mL): AT 8.8 [5.3-14.2] and CG 9.8 [7.6-12.2], and GFAP (pg/mL): AT 97.2 [72.8-137] and CG 98.3 [87.5-136]. ANCOVA demonstrated no significant between-group differences between AT and CG for BDNF (β = 0.11 ng/mL, 95%CI [-3.78 to 4.00]), NfL (β = -0.10 pg/mL, 95%CI [-0.71 to 0.50]), and GFAP (β = 0.01, 95%CI [-0.43 to 0.40]), adjusted for confounders.
Conclusion: Aerobic exercise therapy did not result in significant improvements of neuro-specific blood-based biomarkers in pwMS.

Disclosure Conflict of interest
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RIMS - Physical exercise and lifestyle changes

P391
Psychometric properties of the modified reaching performance scale in persons with multiple sclerosis

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Introduction: A valid and reliable assessment tool to describe the quality of a reach-to-grasp movement pattern can provide valuable insights into motor performance deficits in persons with MS (pwMS). The Reaching Performance Scale (RPS), developed for stroke, is an attractive scale to assess reaching movement patterns. Nevertheless, it has not been validated in pwMS.
Objectives: Firstly, to investigate the content and modify the RPS for application in patients with MS. Secondly, to investigate the psychometric properties (within- and between-session reliability and concurrent validity) of this modified Reaching Performance Scale (mRPS) for pwMS.
Methods: Forty-five pwMS executed the RPS that measured movement patterns and compensations during reach-to-grasp tasks. The content validity was determined by an expert panel based on observations of 45 subjects. The reliability of the mRPS was investigated based on five repetitions performed within one day, and between two days. For the concurrent validity, clinical measures at two levels of the International Classification of Functioning were correlated with the mRPS: Fugl-Meyer Assessment of the Upper Limb (FMA-UL), maximal isometric hand grip strength (HGS), Action Research Arm Test (ARAT), Box and Blocks Test (BBT), Nine Hole Peg Test (NHPT) and Trunk Impairment Scale 2.0 (TIS 2.0) and finally perceived performance by the Manual Ability Measure-36 (MAM-36).
Results: The subscale of trunk displacement of the original RPS was modified for its use in pwMS. The mRPS, specifically developed for pwMS, had excellent agreement scores for the within-session reliability (range of K between 0.85 and 0.98) and moderate-to-excellent agreement scores for between-session reliability (K: 0.66-1). Regarding validity, the mRPS was highly

correlated with the ARAT (rho=0.74, p<0.001), and moderately correlated with the trunk performance (TIS 2.0, rho= 0.61, p<0.001), hand function: (BBT: rho=0.64, p<0.001; NHPT: rho=-0.61, p<0.001) and perceived performance (MAM36 rho= 0.53, p<0.001).
Conclusion: The mRPS is a reliable measurement tool to evaluate the movement pattern and motor compensations used during reaching in pwMS. Concerning concurrent validity, the mRPS measures different aspects of performance, namely compensation, that are not identified in other clinical measures that evaluate mostly task completion. Therefore mRPS fills a gap in clinical evaluation – that of quantifying movement quality during reaching.

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P392
Fear of falling impacts participation in instrumental activities of daily living, leisure activities and social activities in people with multiple sclerosis

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Background: Fear offalling (FOF)is an important risk indicator for health related outcomes and quality of life in patients with multiple sclerosis (MS). However, its relationship with participation level in this population is not clear.
Aim: The aim of this study is to explore the relationship between fear of fall and participation levels including participation in instrumental activities of daily living, leisure activities and social activities in people with MS.
Methods: One hundred patients with MS were evaluated. Fear of falling was assessed using the Fall Efficacy Scale-International (FES-I). Participation levels in instrumental activities of daily living, leisure activities and social activities were assessed using the Activities Card Sort (ACS). In addition, age, gender and the Patient-Determined Disease Step (PDDS) were collected from patients.
Results: Stepwise regression analysis demonstrated that fear of fall predicts participation in instrumental activities of daily living after adjusting for age, gender and PDDS ($R^2 = 0.353$, $P < 0.0001$), accounting for 35.5% of the variability of the fear of fall around its mean. Similarly, regression analysis showed that fear of fall predicts participation level in leisure and social activities after adjusting for age, gender and PDDS ($R^2 = 0.273$, $P < 0.0001$ for leisure activities; $R^2 = 0.252$, $P < 0.0001$ for social activities).
Conclusions: Fear of fall can be an important determining factor affecting participation in instrumental activities of daily living, leisure activities and social activities.

Disclosure
All authors have nothing to disclose

P393
High-intensity resistance training in fatigued persons with multiple sclerosis - a randomized controlled trial

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Introduction: Exercise studies among fatigued persons with multiple sclerosis (PwMS) with fatigue as primary endpoint are currently lacking.
Objectives/aims: The objective here was to explore effects on fatigue, mood, health-related quality of life and inflammatory markers of a high-intensity resistance training (HIRT) programme in fatigued PwMS.
Methods: A total of 71 PwMS scoring ⩾53 (i.e., at least moderate fatigue) on the Fatigue Scale for Motor and Cognitive Functions (FSMC) were randomized to participate in supervised HIRT twice (group A, n=35) or once (group B, n=36) a week for 12 weeks. A non-randomized group (n=69) matched for FSMC score served as non-intervention control. Linear repeated-measurement intention-to-treat analyses were used for evaluating within-group (time) and between-group (time x group) effects, except for inflammatory markers where multivariable linear regression models were used. The study was registered at ClinicalTrials.gov (NCT04562376).
Results: Three of the 11 participants who dropped-out were lost to follow-up. Session and content adherence were fulfilled for 50 (70%) and 52 (73%) of participants, respectively. Between-group differences were non-significant for primary and most secondary endpoints, while the time effects were all significant. Mean difference in FSMC score (95% confidence intervals) was -10.9 (-14.8; -6.9) in group A and-9.8 (-13.2; -6.3) in group B. Corresponding values for combined intervention groups vs non-intervention control were -10.3 (-12.9; -7.7) and 1.5 (-0.6;3.6), respectively, a significant between-group effect (p<0.001). Secondary endpoints also improved, but only Hospital Anxiety and Depression Scale anxiety and MS Impact Scale-29 psychological subscales favoured the twice weekly over once weekly HIRT group. As an exploratory endpoint, changes in plasma inflammatory protein markers were associated with reduced FSMC scores.
Conclusion: Once or twice weekly HIRT leads to clinically relevant reductions in self-reported fatigue scores among fatigued PwMS, with improved fatigue scores being associated with changes in plasma inflammatory protein levels. These findings provide evidence for recommending HIRT for fatigued PwMS.

Disclosure
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P394
Monitoring the progression of the multiple sclerosis: not all the outcome measures are the same over time

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Introduction: Multiple Sclerosis (MS) is a progressive neurodegenerative disease which affects the cognitive and the motor domain. The exacerbation may present in different way outlining three main types of courses: relapsing-remitting (RR), secondary progressive (SP) and primary progressive (PP). RR is the most common course, characterized by defined attacks; SP follows the initial RR course and then it presents a continue progression; PP does not show relapses or remissions, but a continue worsening of the neurological symptoms. Validated and standard outcome measures are fundamental to monitor the progression of the disease.
Objectives/Aims: The aim of this study is to understand how different scales monitor the progression of the pwMS during a follow up of 3 years in order to understand which is the best scale able to detect the change over time.
Methods: We recruited 320 patients with diagnosis of MS according to McDonald criteria. The mean age was 61,2±12,2 year-old with a mean EDSS of 5,9±1,8.Data about EDSS, FIM, MFIS, Abilhand for the motor and disabilities domain, HADS for the emotional one and PASAT, SDMT and MOCA for the cognitive function have been exported from the PROMOPROMS database. We selected patients with 3 yearly visits. An ANOVA test for repeated measures has been performed to compare the 3 visits.
Results: In our data, EDSS and FIM can detect changes in 3 years in all the courses of the disease significantly (PPp=0,0005; RRp=0,0005; SPp=0,02). Abilhand and MFIS detect the change after 3 years only for RR courses (Abilhand p=0,04, MFISp=0,02). HADS shows no significant resultats along the years. PASAT and MOCA are significant for RR and SP forms (PASAT–RR p<0,0001; SPp=0,007; MOCA–RR p<0,0001; SPp=0,01), while SDMT does not show any significance.
Conclusion: These scales are useful to define the needs and the disabilities in a precise moment, but our data show that not all the scales are good to detect changes over time.Different disease courses can affect this aspect. EDSS and FIM are confirmed to be reliable to detect the progression of the disease over 3 years, instead Abilhand and MFIS work better in the RR course. Moreover, the emotional and the cognitive fields behaves very different and we had some results for the RR and SP courses. Further studies are needed to calculate multivariate statistical analyses and to provide precise information about the progression of the different courses and functional domains of the disease

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P395
Balance assessment using stabilometric platform in multiple sclerosis: a preliminary FNIRS study

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Introduction: Balance impairments are common in people with Multiple Sclerosis (PwMS). However, so far, no studies have examined brain activation while performing balance tasks in PwMS.
Aims: The present ongoing study aims at investigating cortical activity between Healthy Subjects (HS) and PwMS using functional near-infrared spectroscopy (fNIRS).
Material and methods: We recruited 9 PwMS with mean+standard deviation age of 40+9.4 years and Expanded Disability Status Scale (EDSS) of 2.1+1.3 points, and 9 HS with age 34+11.6 years. Participants underwent fNIRS recording while performing balance tasks on a stabilometric platform. We employed the NIRSscoutX system to measure oxy-(HbO) and deoxy-hemoglobin (HBr) levels with 16 sources and detectors for a total of 44 measurement channels. Investigated areas were frontal, occipital, and temporal cortices. In a block-design, we compared cortical activity during standing on foam in the following conditions: eyes open (EO), eyes closed (EC), and during dual task (Stroop test_Reading (ST_R) and Stroop test_Interference (ST_I)) while concurrently measuring the centre of pressure displacement in terms of Area (mm^2).
Results: No difference was found between PwMS and HS in Area during EO condition (PwMS=414.8+223.4, HS=267.7+95.1, p=0.2). We observed statistically significant differences between groups in Area during EC (PwMS=2779.4+1961.9, HS=1134.8+345.0, p=0.05), ST_R (PwMS=359.0+257.1, HS=181.7+53.1, p=0.03), and ST_I (PwMS= 378.7+285.9, HS=171.6+41.0, p=0.03). PwMS and HS showed comparable cortical activity in EO and EC, while cortical activation was higher in PwMS in left occipital cortex and right temporal cortex (HbO:t=2.14, p=0.03; HBr:t=-2.22, p=0.02) during ST_R, and in left frontal cortex (HbO:t=2.47, p=0.015) during ST_I.

Conclusion: In our preliminary results PwMS showed greater balance impairment during EC without any difference in cortical activity compared to HS. Conversely, greater balance impairments and higher cortical activity were found when performing dual task conditions compared to HS. Further analysis should be conducted with a larger sample size to confirm these results.

Disclosure
All the authors have nothing to disclose

P396
Optimizing sensorimotor function and physical activity for people with multiple sclerosis – a test-retest pilot feasibility study

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Introduction: People with multiple sclerosis (PwMS) often have lower levels of physical activity than recommended and many are unemployed or work part time even when disability is mild. Function, physical activity and employment are not systematically integrated in the follow-up of PwMS and interventions addressing these issues are needed.
Objectives: To investigate the feasibility and preliminary effects of a new multidiciplinary intervention (CoreDISTparticipation) for PwMS delivered across health care levels targeting promotion of balance, walking, physical activity and employment.
Methods: A baseline-, 6- and 11 weeks post-test-design, including 15 PwMS, EDSS 0-4.5, who recived CoreDISTparticipation including: a) MS-outpatient clinic; MS-nurse digital work-focused session and physiotherapist (PT) exploring possibilities for change in balance b) Municipality; a digital meeting with the patient, employer, MS-nurse and PT addressing employment and physical activity, 4 weeks indoor + 4 weeks outdoor training 2 day/week for 60 min. Structured interviews where additionally undertaken to capture PwMS, PT and employers experiences.
Primary outcome: MS work difficulties questionnaire (MSWDQ-23). Secondary outcomes: 6 Minute walktest (6MWT), Mini-Balance Evaluation Systems Test (MiniBESTest), Trunk Impairment Scale modified Norwegian Version (TIS-modNV), MS Walking Scale-12 (MSWS-12), MS Impact Scale-29 Norwegian version (MSIS-29), European Quality of Life 5-Dimension-3 Level (EQ-5D-3L), ActiGraph wGT3x-BT monitors, AccuGait Optimized force platform. Descriptive statistics and paired sample t-test were used for the analysis.
Results: MSWDQ-23, 5.33 points (p=0.091) demonstrated no significant within-group effects. 6MWT 46.41 meters (p=0.001), Mini-BESTest 1.69 points (p=<0.001), TIS-NV 1.77 points (p=0.012), MSIS-29 6.70 points (p=0.023), EQ-5D-3L 0.09 points (p=0.022) demonstrated significant within-group improvements at week 11. Thirteen participants completed the study with no reports of adverse events. Indoor training had higher attendance (77.5%) than outdoor training (>80%). The digital meetings were reported as moderately useful.
Conclusions: CoreDISTparticipation is feasible, provided preliminary effects on trunk control, balance and health related quality of life and showed a tendency for change regarding barriers for work. Slight improvements will be made to the intervention regarding group training frequency and digital meetings. Randomized controlled trials are warranted.

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P397
Predictive ability of the original and short form of the activities-specific balance confidence scale and its individual items for falls in people with multiple sclerosis

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Introduction: Balance confidence is an essential component of fall risk assessment in persons with multiple sclerosis (pwMS).
Objectives: The aims of this study were to 1) investigate the ability of the 16-item Activities-specific Balance Confidence scale (ABC-16), 6-item Activities-specific Balance Confidence scale (ABC-6), and each item of the ABC-16 for predicting falls and 2) determine cutoff scores of these scales in pwMS.
Methods: Balance confidence assessed using the ABC-16 and ABC-6. Fall history has been recorded. Descriptive outcome measures including walking, balance, and cognition were performed. Logistic regression and receiver operating characteristic analyses estimated the sensitivities and specificities of the ABC-16 and ABC-6 have been performed.
Results: One hundred fifty-six participants [fallers/non-fallers: 60 (38.5%) / 96 (61.5%)] were enrolled. Both the ABC-16 (AUC:0.85) and ABC-6 (AUC:0.84) had the predictive ability for falls. Each item of the ABC-16 scale was a significant predictor of falls [odds ratio (OR) range:1.38 to 1.89]. Items 8 and 10 had the highest odds ratio (OR:1.85; 95%CI:1.47–2.33, OR:1.89; 95%CI:1.49–2.40; respectively). We found cutoff scores of ⩽70 of 100 (sensitivity:71.67, specificity:86.46) and ⩽65/100 (sensitivity:76.67, specificity:79.17) in prediction of falls for the ABC-16 and ABC-6, respectively.
Conclusion: Both original and short forms of the ABC scale are an efficient tool for discriminating fallers and non-fallers in pwMS. Although all items can predict falls, outdoor walking activities predict falls better than other items. Researchers and clinicians can use these findings to specify fall risk in pwMS.

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RIMS - (Tele)Rehabilitation (physical, neuropsychological and psycho-social approaches)

P398

Telehealth use during the COVID-19 pandemic, analysis from the australian multiple sclerosis longitudinal survey

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Objective: During the COVID-19 pandemic, people living with multiple sclerosis (MS) experienced reduced access to in-person care. There is a need to understand the impact of increased use of telehealth services for MS healthcare.
Aim: This cross-sectional study, in a large Australian sample, investigated use of, and consumer-suggested improvements to, MS care via telehealth.
Methods: Participants of the Australian MS Longitudinal Study completed the survey in October-December 2020. The survey was created with input from persons with MS. We measured use of telehealth for MS care during the pandemic and participants' opinion on needs for future telehealth-related care. We gathered and analysed responses with respect to age, sex, disability level, disease type, education level and geographical rurality.
Results: The survey was completed by 1,485 participants. Of the 70% who used telehealth healthcare services, 79% rated their experience with *existing* healthcare providers as good or very good, with 4.4% rating their experience as poor or very poor. Experience with *new* healthcare providers was still rated well, with 74% rating it as good or very good and 7.5% as poor or very poor. Experiences with telehealth through *existing* providers was largely rated as similar to in-person consultations (76%), with 5.2% rating it as better and 19% as worse. To improve the experience, 60% suggested guidance on preparing and getting the most out of telehealth. Other suggestions included the use of digital self-monitor tools such as Apps and wearables (26%), access to local clinics with online facilities (22%), and access to better telehealth home facilities such as a better internet connection (20%).
Conclusions: Seventy percent of people with MS used telehealth during the COVID-pandemic. Whilst most people with MS had a positive experience, improved guidance on using telehealth, additional use of digital self-monitoring tools, and locally accessible telehealth clinics might improve telehealth experiences.

Disclosure
The authors declare no conflict of interest

P399

Under and Over: Findings from a remote upper limb rehabilitation study in people with MS

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Introduction: Remote assessments and interventions are gaining prominence in clinical settings. However, little is known about the efficacy of home-based, upper limb rehabilitation for people with advanced MS (PwMS) as this group is underrepresented in research.
Objective: Evaluate the efficacy of repeated use of the Under and Over (U&O) tool alongside patient experiences.
Methods: The U&O study is a waitlist controlled, remote upper limb rehabilitation study for PwMS with an Expanded Disability Status Scale (EDSS)>6.0. Participants were randomised into three groups with different 12-week rehabilitation programmes: (1) U&O tool 5 times a week for 30 mins, following specific patterns; (2) U&O tool 5 times a week for an unspecified time, choosing any pattern; (3) cardboard 9 Hole Peg Test (c9HPT) 5 times a week. Participants were asked to complete questionnaires about their experience at the end of the study. Outcome data were analysed using linear regression controlling for age, gender and EDSS. Descriptive statistics were used for other analyses.
Results: 105 PwMS (mean age 54 years (SD 9); 77 women; median EDSS 6.5), participated. At 3 months, participants randomised to c9HPT 5 times a week showed a significant improvement in times compared to those using the U&O tool ($p<0.001$). There was no effect of age, gender, or EDSS. At 6 months, there was no significant difference in c9HPT times between groups. 40 PwMS responded to the questionnaire. 89% had a positive experience of participating in the study and 61% managed to stay motivated.7%felt face to face would have been preferable. Videos, visually tracking progress, daily reminders and peer support were suggestions to improve motivation within future remote studies.
Conclusion: There is a significant learning effect of the c9HPT. Although accessible and engaging, there are clear suggestions as to how to maintain and improve motivation throughout remote studies.

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P400

The effects of online exercise training on physical activity and functionality in patients with pediatric-onset multiple sclerosis

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Introduction: Patients with POMS have a variety of symptoms as patients with MS such as low levels of physical activity, fatigue, balance and walking problems. The efficacy of exercise in adult MS is known, but there is no evidence in patients with POMS.
Objectives & Aims: To examine the effects of online exercise training on physical activity and functionality in patients with POMS.
Methods: 21 individuals were included and randomly divided into online exercise training group (n=11) and control group (n=10). Godin leisure-time exercise questionnaire (GLTEQ) and pedometer were used to assess physical activity level. Timed up and go test (TUG) and 6-minute walk test (6MWT) were used for functionality evaluation. The online exercise training group performed aerobic, strengthening and balance exercises 2 days/8 weeks under the supervision of a physiotherapist. Each online exercise session lasted approximately 60 minutes and was conducted synchronously via Zoom. The control group was placed on a waiting list.
Results: The 6MWT (p=0.005), TUG (p=0.005) and number of steps (p=0.009) results in the online exercise training group showed statistically significant improvement after treatment, while in the control group a significant change was observed only in the TUG (p=0.017). Changes in number of steps (p=0.004), GLTEQ-MVPA (p=0,048), 6MWT (p=0.000) and TUG (p=0.013) were found to be superior in online exercise training group compared with control group. All patients completed 16 online exercise training session with excellent adherence and no adverse events were observed.
Conclusions: The online exercise training has positive effects on physical activity and functionality in POMS patients. We think that participation to rehabilitation programs will provide significant benefits on the patients symptoms. Also, online exercise training can be used as an effective method in patients who have difficulty in coming to the rehabilitation unit due to pandemic, school hours, time constraints and transportation difficulties.
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Disclosure
Authors have nothing to disclose.

Poster Session 2

Clinical aspects of MS - Diagnosis and differential diagnosis

P401

Neurological features of CTLA4 insufficiency: a nationwide study of a poorly understood neuroinflammatory genetic disorder

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Introduction: Cytotoxic T-lymphocyte antigen-4 (CTLA4) is a major negative regulator of T-cell immune response. It has been shown CTLA4 or LRBA genes mutations can lead to CTLA4 insufficiency, characterized by a wide range of clinical manifestations including autoimmune diseases, infections, and lymphoproliferation. Among these manifestations, neurologic involvement has been mentioned, in up to 29% of patients, but not described in a comprehensive manner.

Objectives and aims: To perform a clinical, radiological and biological description of a French nationwide cohort of patients with CTLA4 insufficiency.
Methods: We retrospectively identified all patients genetically diagnosed with CTLA4 or LRBA mutation in the French Reference Centre for Primary Immunodeficiencies (CEREDIH) registry and collected demographic data, medical history, clinical signs and symptoms, laboratory features, CNS imaging, medication type and effects.
Results: 13 patients (5 male and 8 female) with CTLA4 haploinsuficiency and neurological involvement were selected.Twelve patients carried a CTLA4 mutation, and 1 patient a LRBA mutation. Their median ageat thefirstautoimmunemanifestationwas6 [3-15] years. All but one patients had at least one systemic (autoimmune, infectious or lymphoproliferative) manifestation. Lymphopenia (77%) and hypogammaglobulinemia (69%) with systematic hypoIgA were commonly found. Eleven patients (85%) presented neurologic symptoms. They almost systematicaly occurred after systemic manifestations (median time of 8.5 [4.5-10.5] years. Most patients suffered from multiple symptoms including headaches (54%), epilepsy (38%) and focal deficit (91%). MRI evidenced different type of lesions including 1) large (>2cm) lesions (57%), 2) cerebellar lesions (42%) and 3) transverse myelitis (21%). Moreover, small nodular lesions were seen in 63% of the patients: they had a Multiple Sclerosis-like (MS-like) pattern in 42%.
All the patients had a history a recurrent disease with a very limited efficacy of different immunomodulatory and immunosuppressive drugs but the infusion of CTLA4-Ig fusion protein resulted in a stabilization of the disease in all but one patients.
Conclusion: Our study allows a better characterization of the neuroinflammatory disease and MRI pattern of lesions associated with CTLA4 insufficiency. It appears as a potential mimicker of acquired central nervous system neuroinflammatory disorder and should be considered in their differential diagnosis.

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P402
Is the clinical onset of demyelinating CNS disease after COVID-19 vaccination a *denovo* disease or the clinical manifestation of a preexisting condition?

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Introduction: Within the last year, cases with multiple sclerosis (MS) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) associated with SARS-CoV-2-vaccination have been published worldwide. It remains unclear, whether the clinical onset in these patients is either causal and *denovo* or, alternatively, the initial manifestation of a preexisting demyelinating disease and thus a coincidence in time.
Objectives: We therefore compared clinical, laboratory and neuroimaging data of MS patients with clinical onset after SARS-CoV-2-vaccination ($MS^{postvacc}$) with a MS cohort without association to the vaccination ($MS^{reference}$), respectively, with a single case of MOGAD following SARS-CoV-2-vaccination ($MOGAD^{postvacc}$).
Aims: To determine whether there is evidence of a preexisting, chronic inflammatory disease at clinical onset in $MS^{postvacc}$ and $MOGAD^{postvacc}$ patients.
Methods: We included patients with clinical manifestation of MS or MOGAD ⩽30 days following SARS-CoV-2-vaccination and analysed clinical, cerebrospinal fluid (CSF), magnetic resonance imaging (MRI) and optical coherence tomography (OCT) data. The $MS^{postvacc}$ characteristics were compared to an age- and gender-matched MS cohort recruited at our neuroimmunological outpatient clinic.
Results: In 5 patients (3 female) the initial diagnosis of MS was made in association to SARS-CoV-2-vaccination (4 after BNT162b2 vaccine; mean clinical onset after 8 days). CSF-specific oligoclonal bands and indications of a preexisting inflammatory process were detectable on MRI and OCT in all $MS^{postvacc}$ patients. Their analysed parameters (clinical, CSF, MRI, OCT) were assimilable to those of the $MS^{reference}$ cohort.
One woman with onset of MOGAD after ChAdOx1 nCoV-19 vaccination was identified. Here, CSF analysis revealed an acute inflammatory profile (106 cells per μl; no CSF-specific OCB). After treatment with high-dose corticosteroids, the initial cerebral and cerebellar lesions resolved on follow-up MRI.
Conclusion: Since we found CSF-specific oligoclonal bands, chronic inflammatory lesions on MRI and retinal neuroaxonal damage on OCT a *denovo* disease seems unlikely for the $MS^{postvacc}$ cohort. Our data point to the hypothesis that the $MS^{postvacc}$ patients described had a subclinical disease that first manifested coincidentally with the SARS-CoV-2-vaccination. However, this cannot be assumed for the $MOGAD^{postvacc}$ patient.

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P403
Patterns of disease exacerbation and outcomes in neurosarcoidosis

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Introduction: The factors that influence long-term outcomes in patients with Neurosarcoidosis (NS) are not very well understood, with series suggesting that monophasic profiles have more favorable outcomes.
Objective: To characterize the pattern of disease activity, factors associated with exacerbation, and outcomes among patients with NS.
Methods: In this retrospective study, a cohort of 260 patients followed at the Johns Hopkins Neuroimmunology Clinic between January 2000 and December 2021, fulfilled criteria for probable or definite NS. The pattern of disease activity, exacerbation, and functional outcomes were established for patients with at least 18 months of follow-up. Patients with a single NS-related clinical event were defined as monophasic, whereas patients with multiple NS-related clinical events (exacerbations) were classified as recurrent. The modified Rankin scale (mRs) was calculated for each patient at the time of last visit.
Results: One-hundred and thirty patients had a clinical follow-up for at least 18 months(mean 69.9, range 18-250 months). A monophasic temporal profile was observed in 85 subjects(65.4%), while 45 subjects (34.6%) exhibited a recurrent pattern of exacerbations. There was no significant difference in follow-up period between the groups (p=0.556). The cumulative incidence of exacerbations at one year was 10.8%,at two years 22.4% (95% CI 11.4%-36.7%) and at 7 years, 33.8%. A total of 119 exacerbations were documented, most of them associated with steroid taper (n=57, 47.8%) and treatment discontinuation (n=34, 28.5%). No clear cause of exacerbation was noted in 28 subjects (23.5%). Clinical characteristics associated with a recurrent pattern were: multifocal involvement ($p<0.001$) and an encephalitic phenotype (p=0.03). The median mRs was lower in the monophasic group (1.88) when compared to the recurrent group (2.7) (p=0.002). First-line therapy with corticosteroids was initiated in all patients and most also received a second-line therapy medication (n=101, 77.7 %). Most of the patients were on treatment (n=113, 86.9%) and remained ambulatory (n=117, 90%) at the time of the last clinic follow.
Conclusions: In patients with NS higher disability scores were associated with recurrent disease, an encephalitic phenotype, and disease multifocality. Steroid tapering or treatment discontinuation were frequent contributors to recurrent disease, although a quarter of the subjects exhibited exacerbations without clear precipitants.

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P404
COVID-19 associated myelitis: early insights from a multi-center study

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Introduction: Neurologic complications of Coronavirus Infectious Disease 2019 (COVID-19) are well recognized and may affect both the central and peripheral nervous system.Cases of acute myelitis in close temporal relationship withCOVID-19 are increasingly reported in the literature but may underly a reporting bias.
Aim: This study aimed to provide insights into acute myelitis associated with COVID-19 by analyzing cases treated at four tertiary care neurology centers.
Patients and Methods: The retrospective observational study was conducted at the University Hospital Centre Zagreb in Croatia, University Medical Centre Ljubljana in Slovenia, University Clinical Centre of Serbia in Serbia, and Landesklinikum Mistelbach-Gänserndorf in Austria.We searched foracute myelitis cases that occurred during or after COVID-19. Demographic data, clinical course, magnetic resonance imaging (MRI) findings, cerebrospinal fluid (CSF) analysis, treatment, and outcome were analyzed.
Results: We identified ten patients (70% male). The mean age was 49.2 years (standard deviation 17.9). In five patients COVID-19 presented with upper respiratory symptoms. Five patients suffered from COVID-19 pneumonia, but none required mechanical ventilation. Neurological disturbances caused by acute myelitis occurred after a median of 13 days (range 5 to 76 days following the onset of systemic or respiratory COVID-19 symptoms. Spinal cord lesions were identified in eight patients on MRI. CSF examination was performed in eight patients and oligoclonal bands were detected in one patient. Anti-myelin oligodendrocyte glycoprotein

(MOG) antibodies were present in one patient. Eight patients were treated with corticosteroids, and three of them received intravenous immunoglobulins. One patient received mycophenolate mofetil. The outcome was good, with partial or complete recovery in nine patients and only one patient experiencing no significant improvement.

Conclusion: Our study raises awareness for this potential neurological complication of COVID-19. While the time lag of COVID-19 and clinical signs of myelitis point at either post- or parainfectious mechanisms, causality needs to be corroborated. Moreover, further studies need to define the diagnostic approach and clarify the optimal standards of care.

Disclosure

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JD:serves on scientific advisory boards for Bayer, Biogen, Medis, Merck, Novartis, Roche, Sanofi-Genzyme, Janssen and Teva and have received speaker bureaus for Biogen, Bayer, Merck, Roche, Sanofi-Genzyme, Janssen, Medis, Hemofarm, Medtronic, Zentiva, and Teva.

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Clinical aspects of MS - NMOSD

P405

Predictors of early serologic diagnosis of aquaporin-4 IgG positive NMOSD

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Introduction: Early serologic diagnosis and appropriate therapy are imperative for improving long-term outcomes in aquaporin-4 (AQP4) IgG positive neuromyelitis optica spectrum disorder (NMOSD).

Objective: To determine predictors of early serologic diagnosis of AQP4-IgG positive NMOSD.

Methods: In CANOPTICS, a multi-centre, Canadian longitudinal cohort study of NMOSD, we evaluated time (in months) from the first clinical attack to the first positive AQP4-IgG serology. Early serologic diagnosis was defined as an AQP4-IgG positive test obtained in the same month or month following the first demyelinating attack. We used a multivariable logistic regression model to evaluate possible predictors of early diagnosis including age, sex, ethnicity, first attack type (optic neuritis (ON), myelitis, or brain), and historical epoch (before 2010, 2010-2015, 2016- 2021).

Results: We identified 91 patients with AQP4-IgG positive NMOSD. Eighty-eight (96.7%) had a known time of serologic diagnosis, 34 (37.4%) of whom had early serologic diagnosis. Among the 55 patients who had a delayed serologic diagnosis, median (Q1-Q3) duration of delay was 21 (7-101) months. First attack of myelitis compared to optic neuritis predicted early diagnosis (odds ratio [OR]: 4.9, 95% CI: 1.4-17.1). Asian, African/Caribbean, and other non-White patients (compared to White patients) and serologic diagnosis in more recent years (from 2010 onwards compared to before 2010) were associated with higher odds of an early diagnosis, although these results did not meet statistical significance.

Conclusion: Despite advances in diagnostic assays and therapies, more than 60% of patients with NMOSD, and in particular patients with a first attack of optic neuritis, experienced delays to AQP4-IgG serologic diagnosis in this Canadian cohort. Clinicians should be alert to atypical cases of optic neuritis and consider early AQP4-IgG testing to avoid diagnostic delays.

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P406

Is C5a a marker of inflammatory activity during clinical remission in patients with neuromyelitis optica spectrum disorders AQP4+

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Introduction: Neuromyelitis Optica Spectrum Disorders (NMOSD) is an antibody-mediated disorder of the Central Nervous System where a leading role of the complement system has been demonstrated.
Objective: To measure the levels of complement factors C3, C4 and C5a in serum and plasma of clinically stable patients with AQP4-IgG+ NMOSD.
Subjects/Methods: Twelve patients with NMOSD AQP4+ according to 2015 criteria from a General Hospital in Buenos Aires, Argentina, were included in the study, and 19 age- and sex-matched healthy volunteers as a control group (HC). AQP4 antibodies were measured in serum by CBA analysis. Fresh blood samples were centrifuged to obtain serum and plasma. C3, C4, and AQP4 antibodies were measured in the serum, whereas C5a was measured in the plasma, which was obtained using Futhan (BD FUT-175®, BD Biosciences, San Jose, CA, USA).
Results: The complement factors, C3, C4, and C5a were measured in all samples. The mean concentration of C3 was 130.7 mg/dl (SD 16.1 mg/dl), and the mean concentration of C4 was 21.6 mg/dl (SD 4.8 mg/dl); both values were within the normal reference range (C3: 84–193 mg/dl; C4: 20–40 mg/dl) and were not significantly different ($p>0.05$) from the mean levels in healthy controls (C3: 116.9 mg/dl; C4: 21.9 mg/dl). When analyzing the mean plasma level of C5a, we found a statistically significant difference ($p=0.0444$) between the mean concentration of C5a in NMOSD patients (43.1 ng/ml; SD 48.7 ng/ml) and the HC group (17.7 ng/ml; SD 16.7 ng/ ml).
Conclusions: In this study, we demonstrated a significant higher amount of C5a in the bloodstream of AQP4-IgG+ NMOSD patients, when comparing to normal controls. This could suggest activation of the complement system during remission disease.

Disclosure
Nothing to disclose.

P407

Cancer prevalence in a neuromyelitis optica spectrum disorder cohort

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Background: The contribution of cancer to disease pathogenesis in Neuromyelitis optica spectrum disorder (NMOSD) is unclear and AQP4 antibodies are generally considered lower-risk antibodies in the context of Paraneoplastic Neurologic Syndromes.
Objective: To investigate the co-existence of neoplasms in NMOSD and assess AQP4 immunoreactivity in available tumor specimens.
Methods: We exploredNMOSD AQP4+ patients followed at the Johns Hopkins Neuromyelitis Optica Clinic from 2010 to 2021 and determined the co-existence of NMOSD and cancer diagnosis. We assessed the presence of AQP4 immunoreactivity in tumor biopsy specimens.
Results: Of 143 AQP4+ NMOSD patients, 17 (11.8%) had a diagnosis of cancer with 19 different types of cancer found. Median ages of NMOSD disease onset and cancer diagnosis were 52.8 (IQR 46.5 – 59.1) and 54.5 (IQR 48.5 – 61.2) years, respectively. Cancer diagnosis preceded or followed NMOSD onset[ess1][MR2](median 0.6, range -19.1 – 43.7 years).The most common neoplasm was breast cancer (n=7; 41.1%) followed by melanoma (n=3; 17.6%), neuroendocrine tumor (n=3; 17.6%) thyroid carcinoma (n=2; 11.7%) and others that include one case each of appendiceal cancer, lymphoma, cervical cancer and chronic lymphocytic leukemia. Clinical phenotypes mainly included recurrent myelitis (n=11; 64.7%), optic neuritis (n=2; 11.7%) or both (n=3; 17.6%).In 9 cases (6.2%) the tumor was identified within +/-2 years of NMOSD symptom onset, which was used as a marker of possible paraneoplastic NMOSD. In this subgroup, most patients were above age 50 years (n = 7; 77.7%) at NMOSD disease onset.Tumor specimens were available for 3 NMOSD cases (2 neuroendocrine tumors, 1 breast tumor) and 2 controls (pituitary adenomas from non-NMOSD patients). Immunohistochemistry was performed and AQP4 immunoreactivity was found in tumor cells of the 2 neuroendocrine NMOSD cases. The breast tumor was negative for AQP4 staining. The control group included 2 pituitary adenomas, both of which did not display AQP4 immunoreactivity.
Conclusions: Cancer diagnosis preceded or emerged after the onset of NMOSD in more than 10% of our NMOSD cohort. A small proportion of patients, developed cancer within 2 years of NMOSD onset, with most cases occurring after the sixth decade of life. The presence of AQP4 immunoreactivity in neuroendocrine tumors may support a paraneoplastic pathogenesis but the antigenic role of other common malignancies is less clear and may be coincidental.

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Baseline characteristics of initial patients in the CorEvitas SPHERES registry for NMOSD

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Introduction: Novel therapies have recently been approved to treat anti-aquaporin-4–immunoglobulin G seropositive (AQP4-IgG+) neuromyelitis optica spectrum disorders (NMOSD). Thus, systematic evidence is needed to explore patterns of care, clinical impact and patient-reported outcomes (PROs) in real-world settings. CorEvitas launched the SPHERES (Synergy of Prospective Health & Experimental Research for Emerging Solutions) Registry in June 2021, with the goal of enroling 800 patients via 35 academic institutions and private practices across North America.

Aim: To describe characteristics of the initial patient cohort enroled in the SPHERES Registry as of April 2022.

Methods: SPHERES eligibility criteria are diagnosis of NMOSD at enrolment according to the 2015 International Panel for Neuromyelitis Optica Diagnosis consensus diagnostic criteria and age ⩾18 years. Sociodemographic, comorbidities, NMOSD disease activity, treatment characteristics and PROs at time of enrolment were summarised using mean and SD for continuous measures and frequency and percentage for categorical measures.

Results: Forty-four patients were enroled at the time of this analysis. Mean (SD) age was 51.3 (13.4) years, 80% were female, and 73% were White, 21% Black, 7% other and 9% were Hispanic. The majority (59%) were AQP4-IgG+, and 23% were anti-myelin oligodendrocyte glycoprotein immunoglobulin G seropositive (MOG-IgG+). Mean time from symptom onset to enrolment was 9.9 years and 12% were newly diagnosed (within 1 year). Most patients (51%) had ⩾3 relapses before enrolment; most common manifestations of previous relapses involved optic neuritis (72%), acute transverse myelitis (61%) or acute brainstem syndrome (7%). The mean Expanded Disability Status Scale (EDSS) score was 3.2 (1.7), Montreal Cognitive Assessment (MoCA) 25.0 (3.8) and MoCA Blind 18.2 (3.1). PROs were Modified Fatigue Impact Scale 34.6 (21.4), EuroQol visual analogue scale 71.4 (23.6) and Visual Function Questionnaire-Utility Index 0.8 (0.1). At enrolment, 23% of patients reported current use of biologics approved for NMOSD and 36% of patients reported current use of off-label biologics.

Conclusion: SPHERES is actively following patients with NMOSD who exhibit distinct serotypes, clinical courses and treatment regimens. As the registry expands to more sites and enrolment is increased, in-depth analyses of this real-world data is anticipated to significantly advance our knowledge regarding the disease and its therapies.

Disclosure

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Alex Exuzides is an employee of Genentech, Inc. and shareholder of F. Hoffmann-La-Roche Ltd. **Shervin Gholizadeh** is an employee of Genentech. **Paris Sidiropoulos** is an employee of F. Hoffmann-La-Roche Ltd. **Nicole Middaugh**is an employee of CorEvitas, LLC. **Margaux M Crabtree** is an employee of CorEvitas, LLC. **Angel Cronin** is an employee of CorEvitas, LLC. **Dimitrios A. Pappas** is an employee of, has ownership interest in, and stock options in CorEvitas; is an Officer or Board Member of the Corrona Research Foundation; participates in Speakers Bureau for Sanofi and Novartis; is a paid Instructor for Novartis; and consultant for Roche and Sanofi. **Jacinta Behne**is an employee of the Guthy-Jackson Charitable Foundation. **Jeffrey L. Bennett** reports payment for consultation from MedImmune/Viela Bio/Horizon Therapeutics; personal fees from AbbVie, Chugai, Clene Nanomedicine, Genentech, Genzyme, Mitsubishi-Tanabe, Reistone Bio, and Roche; grants and consulting fees from Alexion; grants from Novartis, Mallinckrodt, and the National Institutes of Health; and has a patent for Aquaporumab issued. **Terrence F. Blaschke** is an advisor to the Guthy-Jackson Charitable Foundation. **Lawrence J. Cook** has nothing to disclose. **Michael Levy** has received consulting fees from Alexion, Viela Bio, Genentech/Roche, UCB Pharmaceuticals, Mitsubishi

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Clinical outcomes and prognostic factors in patients with optic neuritis related to NMOSD and MOGAD from Latin America in distinct ethnic groups

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Background: Although pathologically distinct from each other, neuromyelitis optica spectrum disorders (NMOSD) associated to aquaporin 4-antibody (AQP4-Ab) and myelin oligodendrocyte glycoprotein antibody (MOG-Ab)-associated disease (MOGAD) can present with optic neuritis (ON) relapses and have overlapping paraclinical and radiological features. These conditions may have different outcomes and prognoses. We aimed to investigate clinical outcomes and prognostic characteristics of NMOSD and MOGAD patients with ON as first attack from Latin America in distinct ethnic groups.

Methods: We conducted a retrospective observational multicenter study in patients from Argentina (n = 61), Chile (n = 18), Ecuador (n = 27), Brazil (n = 30), Venezuela (n = 10) and Mexico (n = 49) with ON-related MOGAD or NMOSD. Predictors of disability outcomes at last follow-up, namely visual disability (Visual Functional System Score ⩾4), motor disability (permanent inability to walk further than 100 m unaided) and wheelchair dependence based on EDSS score were evaluated.

Results: After a mean disease duration of 42.7 (±40.2) months in NMOSD and 19.7 (±23.6) in MOGAD, 55% and 21% ($p>0.001$) experienced permanent severe visual disability (visual acuity from 20/100 to 20/200), 22% and 6% (p=0.01) permanent motor disability and 11% and 0% (p=0.04) had become wheelchair dependent, respectively. Age at disease onset (OR=1,03 CI95%1.00-1.06, p=0.03) was a predictor of permanent motor disability and ON associated to myelitis at disease onset was predictor of visual disability (OR=0,42, CI95%0.16-1.08, p=0.007), permanent motor disability (OR=2,66, CI95%1.02-6.94, p=0,046) and wheelchair dependency (OR=5,75, CI95%1.82-17.89, P=0.003) in NMOSD patients. No differences were found when evaluating distinct ethnic groups (Mixed vs. Caucasian vs. Afro-descendant)

Conclusions: NMOSD was associated with poorer clinical outcomes than MOGAD. Age and ON plus myelitis at disease onset were predictors of permanent visual and motor disability and wheelchair dependency in NMOSD patients.

Disclosure

None of the authors has any potential financial conflict of interest relating to this poster.

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Population-based mortality data of the Danish nationwide AQP4 antibody-seropositive NMOSD cohort

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a severe relapsing inflammatory disease of the CNS and may result in increased mortality and life expectancy loss compared to the general population.

Objectives/Aims: We aimed to evaluate the mortality of AQP4 antibody-seropositive (Ab+) NMOSD patients in the Danish nationwide population-based cohort compared to the general population and to provide information about the cause of death.

Methods: We identified 66 AQP4-Ab+ patients fulfilling the 2015 IPND criteria among the 9932 patients tested for AQP4-Ab from the availability of the analysis in 2007 to Jan. 2021. We obtained medical data from all laboratories performing AQP4-Ab test in Denmark and hospital records, and from Statistics Denmark regarding the general population. We calculated the disease-specific mortality and the excess mortality ratio as the observed number of deaths divided by the expected number derived from sex-specific, age-specific and calendar year-specific general population mortality. In the comparison of deceased cases with the alive cases, chi-squared, Mann Whitney and t-test were applied.

Results: In total, 15 out of 66 patients died during follow-up until 01 Jan. 2021. The disease-specific mortality was 0.0204 (95%CI:0.014-0,0337) per 100.000 person-year, and case fatality rate was 22.7%. Based on the matched (sex, age, calendar-year) population mortality, the expected number of deaths was 1.57, giving a standardized mortality ratio of 9.55 (95% CI:4.72-14.38). The median age at disease onset was 55 (IQR:47-62) and the median age at death was 62 (IQR:57-69). Fourteen out of 15 deaths were related to NMOSD due to severe relapse, infection, or the combination of these. Comparing the deceased subgroups with patients still alive, we found significant differences in the number of initially misdiagnosed patients, median number of severe relapses and relapses with poor recovery, as well as the mean EDSS during the follow-up. The two subgroups were similar concerning the median age at disease onset, median length of follow-up, type of first relapse, median number of relapses, and percentage of other autoimmune comorbidities.

Conclusions: We found significantly increased, about 9.5-times higher mortality in patients with NMOSD than in the general Danish population. Our data highlight the importance of prompt diagnosis, prevention of severe relapses, and immediate relapse treatment to achieve a decrease in NMOSD mortality.

Disclosure

Viktoria Papp: has served in scientific advisory board for Roche, Merck and Alexion.

Finn Sellebjerg: has served on scientific advisory boards for, served as consultant for, received support for congress participation or received speaker honoraria from Alexion, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche and Sanofi Genzyme. His laboratory has received research support from Biogen, Merck, Novartis, Roche and Sanofi Genzyme.

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Magnus Christian Lydolph: nothing to disclose.

Anne Christine Nilsson: nothing to disclose.

Melinda Magyari*: has served in scientific advisory board for Sanofi, Novartis, Merck, and has received honoraria for lecturing from Biogen, Merck, Novartis, Roche, Genzyme, Bristol Myers Squibb.

Zsolt Illes*: has served in scientific advisory board for Sanofi, Novartis, Merck, Roche, Biogen, has received honoraria for lecturing from Biogen, Merck, Novartis, Roche, Sanofi, Bristol Myers Squibb, and has been member of Clinical Endpoint Committee of phase 3 trials.

***equal contribution**

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Inebilizumab reduces attack risk independent of low affinity igG Fc region receptor III-a gene polymorphisms in neuromyelitis optica spectrum disorder

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Introduction: Inebilizumab, a humanized, afucosylated IgG1 monoclonal antibody that targets CD19 for efficient B-cell depletion, is approved to treat aquaporin 4 (AQP4) immunoglobulin G positive (IgG+) neuromyelitis optica spectrum disorder (NMOSD). Afucosylated monoclonal antibodies are engineered to enhance affinity for the Fc receptor III-A (FCGR3A) receptors and maximize antibody-dependent cellular cytotoxicity. The F allele of the F176V polymorphism (rs396991) of FCGR3A is associated with decreased IgG binding affinity and reduced efficacy of rituximab in NMOSD. We previously reported that, during the first 6 months of inebilizumab treatment, F/F homozygotes allele had modestly slower kinetics of B cell depletion but no difference in risk of attack. Here we report data for the duration of the N-MOmentum trial.

Aims: To characterize the relationship between the rs396991 polymorphism and the treatment response in N-MOmentum trial participants.

Methods: N-MOmentum (NCT02200770) was a double-blind, phase 2/3 trial of inebilizumab in adults with NMOSD, with a 28-week randomized controlled period (RCP); (inebilizumab 300 mg or placebo on days 1 and 15) and an optional open-label period (OLP) of ⩾2 years. A total of 142 participants (inebilizumab, n=104; placebo, n=38) consented for genotyping via TaqMan qPCR assay.

Results: V-allele carriers (V-allele genotype [V/V or V/F], n=74) and F/F–allele homozygotes (n=68) did not demonstrate a significant difference in baseline demographics or disease duration. Depletion of $CD20^+$ B-cells was similar in V allele vs F/F allele participants (0.6 (0.1–3.2) vs 1.3 (0.5–4.2) cells/μL at end of RCP) and was sustained in both groups throughout the duration of the study. We did not find any difference in risk of relapse (OR 0.94 (0.39, 2.24)) or Expanded Disability Status Scale worsening (OR: 1.55 (0.54, 4.70)) in V vs F/F allele participants. Annualized attack rates (Standard Error of the Mean [SEM]) for patients on inebilizumab treatment were V/V 0.00 (0.00), V/F 0.10 (0.04), and F/F 0.06 (0.03).

Conclusions: Inebilizumab treated participants in the N-MOmentum trial did not demonstrate differences in clinical outcomes between those with F and V allele genotypes.

Disclosure

O. Aktas has received speaker honoraria and travel reimbursement from Alexion, Bayer HealthCare, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, Teva, and Viela Bio.

J.L. Bennett has received personal fees from Viela Bio, Mitsubishi Tanabe, Reistone Biopharma, AbbVie, Clene Neuromedicine Alexion, Biogene, Genentech, Inc., and F. Hoffmann-La Roche Ltd and grants from Mallinckrodt, Novartis, Alexion, and the National Institutes of Health. In addition, Dr Bennett has a patent 'Compositions and methods for the treatment of neuromyelitis optica' issued.

B.G. Weinshenker received payments for serving as chair of attack adjudication committees for clinical trials in NMOSD for Alexion, Horizon Therapeutics and MedImmune; has consulted with Chugai, Genentech, Mitsubishi Tanabe Pharma, Roche Pharmaceuticals and UCB Biosciences regarding clinical trial design; and has a patent for NMO-IgG for diagnosis of neuromyelitis optica, with royalties paid by Hospices Civils de Lyon, MVZ Labor PD Dr. Volkmann und Kollegen GbR, Oxford University and RSR.

F. Paul has received research support, speaker honoraria and travel reimbursement from Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, and Teva; is supported by the German Research Council (DFG Exc 257) and the German Competence Network for Multiple Sclerosis; has received travel reimbursement from the Guthy-Jackson Charitable Foundation; and serves on the steering committee of the OCTIMS study, sponsored by Novartis.

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H.-P. Hartung has received fees for consulting, speaking and serving on steering committees from Bayer HealthCare, Biogen Idec, Celgene Receptos, CSL Behring, GeNeuro, Genzyme, Horizon Therapeutics (formerly Viela Bio), MedDay, MedImmune, Merck Serono, Novartis, Roche, Sanofi, and TG Therapeutics with approval by the Rector of Heinrich-Heine-University Düsseldorf.

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Understanding treatment decisions in neuromyelitis optica spectrum disorder: a global clinical record review with patient interviews

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a rare relapsing disorder of the central nervous system. Relapses can result in permanent neurological disability, and relapse prevention is the main therapeutic aim in NMOSD. Off-label immunosuppressants (ISTs) have typically been the mainstay of treatment. However, three approved biologics now exist for aquaporin-4-immunoglobulin-G-seropositive (AQP4-IgG+) NMOSD. The availability of additional treatment options has increased the complexity of decisions around treatment initiation/switch.

Objectives: We sought insights into global NMOSD treatment practices, to develop a clearer understanding of patient's characteristics and other drivers of treatment choice.

Methods: Neurologists from US, Germany, Italy, Brazil, South Korea, and China completed an online survey, contributing clinical records for adults with AQP4-IgG+ NMOSD, which included patient demographics, diagnosis, maintenance treatment history, relapse occurrence, and severity. Interviewed patients receiving NMOSD maintenance therapy provided information about their diagnosis, treatment, perceptions about relapse severity or disease stability, and treatment switches.

Results: 389 neurologists submitted clinical records for 1,185 patients with AQP4-IgG+ NMOSD (Jul–Aug 2020); 33 patients with NMOSD were interviewed (Oct–Nov 2020). Approximately 25% (228/910) of patients from the clinical record review (CRR) were initially misdiagnosed; 24% (8/33) of patients interviewed reported formal misdiagnosis. Misdiagnosis was associated with treatment delay and more relapses compared with correct diagnosis (mean 3.3 vs 2.8). Maintenance therapy was not initiated within 2 months for 47% (221/472) of patients from the CRR and 24% (8/33) of interviewed patients.

Oral corticosteroids/ISTs were typically the first maintenance treatment initiated, except for the US, where monoclonal antibodies were equally likely to be prescribed. Relapse severity influenced the decision to initiate/change therapy and use monoclonal antibodies. 76% (25/33) of interviewed patients did not recall having a choice of treatment and many did not know the rationale for treatment choice.

Conclusions: Misdiagnosis of NMOSD appears common and is associated with a delay in initiating maintenance therapy, with decisions influenced by relapse severity. Further studies assessing relapse severity in treatment initiation/switch are required to revise NMOSD treatment recommendations.

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M. Ringelstein received speaker honoraria from Novartis, Bayer Vital GmbH, Roche, Alexion, and Ipsen and travel reimbursement from Bayer Schering, Biogen Idec, Merz, Genzyme, Teva, Roche, and Merck, none related to this study.

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Longitudinally extensive transverse myelitis in neuromyelitis optica and beyond: an observational study of the etiologic spectrum and distinguishing factors

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Introduction: Neuromyelitis optica spectrum disorders (NMOSD) constitute a well-recognized etiology for longitudinally extensive transverse myelitis (LETM). However, the etiologic spectrum of LETM is wider.

Objectives: To characterize our experience with LETM in a tertiary centre, describe the etiologic spectrum and compare the main clinical, radiological, serologic and cerebrospinal fluid features between NMOSD and non-NMOSD related LETM.

Methods: We performed an observational retrospective cross-sectional study of adults with radiologically identified LETM at our center in a twelve year period. We collected demographic, clinical, radiological and other paraclinical variables. Etiologies were reviewed according to current diagnostic criteria. NMOSD and non-NMOSD related LETM were compared using the Fisher exact test for categorical and Mann-Whitney U test for continuous variables.

Results: Forty-one LETM were identified. The main etiologic group was NMOSD: 12 patients (29.3%) followed by ischemia with six (14.6%) multiple sclerosis (MS) with four (9.8%) and arteriovenous fistula with three (7.3%). Other less frequent etiologies, with two cases each, included: parainfectious, paraneoplastic, infectious, metabolic, radiation and idiopathic LETM. There were also single cases of acute demyelinating encephalomyelitis, anti-GAD associated myelitis, Erdheim-Chester disease, and CNS vasculitis.

Compared to non-NMOSD, NMOSD patients were significantly more likely to be female (p = p.006) and to develop quadriparesis (p.003) and a cervical sensory level (p=0.04). Spinal cord involvement in magnetic resonance imaging (MRI) displayed preference for cervical regions in NMOSD (p= 0.001) and for thoracic segments in non-NMOSD LETM (p=0.002). In brain MRI, only

NMOSD typical lesions were statistically significative for NMOSD group but excluding optic nerve involvement.
Conclusions: LETM exhibit great clinical diversity. As reported elsewhere, NMOSD was the main etiology in our series. While non-specific, LETM presenting in females including cervical involvement in MRI could increase the chance for a NMOSD diagnosis, while cases in males with thoracic segment involvement could be more linked to non-NMSOD etiologies like ischemia or arteriovenous fistula. Despite being a red flag for MS diagnosis, LETM can be a presenting form and in our experience with less severe and asymmetric symptoms when compared to NMOSD.

Disclosure
Name: nothing to disclose

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Determinants of visual impairment in aquaporin-4 antibody associated neuromyelitis optica spectrum disorders compared to MOG-antibody associated disorders and multiple sclerosis

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Introduction: Neuroaxonal visual pathway damage leads to more severe visual impairment in neuromyelitis optica spectrum disorders (NMOSD) than in myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD), despite similar neuroaxonal damage. People with NMOSD feature specific changes in the fovea, an area rich in aquaporin-4 (AQP4)-expressing Müller cells.
Objectives: To investigate the role of Müller cell damage for visual impairment in NMOSD.
Aims: To evaluate the influence of foveal shape changes as a marker of Müller cell damage on structure-function correlations in NMOSD compared to MOGAD and multiple sclerosis.
Methods: We included people with AQP4-Immunoglobulin G (AQP4-IgG) positive NMOSD (n=28),MOGAD (n=14) and relapsing remitting multiple sclerosis (MS, n=14). All subjects underwent examination with retinal optical coherence tomography, best corrected high and low contrast visual acuity, and visual fields.
Results: High contrast visual acuity in NMOSD (0.08±0.43 logMAR) was worse than in MOGAD (-0.11±0.13 logMAR; p=0.03), despite similar peripaillary retinal nerve fiber layer and ganglion cell-inner plexiform layer thinning. Foveal inner rim volume was lower in NMOSD (0.09±0.02 mm^3) than in both MOGAD (0.10±0.02 mm^3; p=0.008) and MS (0.11±0.02 mm^3; p<0.001). All patient groups showed a relevant association between visual function and retinal layers only below a cutoff point of ~60 µm. Below the cutoff, loss of HCVA per µm of retinal layer was stronger in NMOSD compared with MOGAD. Foveal inner rim volume was associated with visual field mean deviation, low and - in trend - high contrast visual acuity of NMOSD eyes. There was no such association in MOGAD eyes.
Conclusions: Foveal shape changes as a possible proxy of Müller cell dysfunction might contribute to worse visual outcome in NMOSD.

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AUB is cofounder and holds shares of medical technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patents and patent applications describing methods for retinal image analyses, motor function analysis, multiple sclerosis serum biomarkers and myelination therapies utilizing N-glycosylation modification. He is cofounder, member of the board and currently elected Secretary/Treasurer of IMSVISUAL.

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Spatial association between gene expression and brain damage in neuromyelitis optica spectrum disorders

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Background: Antibodies in autoimmune disorders of the central nervous system (CNS) target antigens with different expression across CNS regions. A former study suggested that typical brain lesions in aquaporin-4 positive Neuromyelitis Optica Spectrum Disorders (AQP4+NMOSD) occur at areas with high AQP4 expression. However, this represents a partial view of both brain damage and NMOSD pathogenesis, since the former also includes atrophy and microstructural abnormalities, and the latter involves other elements of the immune system such as complement and granulocytes.
Objectives: To investigate the spatial association between brain damage and gene expression in NMOSD.
Methods: 3.0 Tbrain magnetic resonance imaging (MRI) scans were acquired from 80 AQP4+NMOSD and 94 controls. In patients, brain damage was assessed through (i)T2-hyperintense lesion probability map, (ii) white (WM) and grey matter (GM) atrophy at voxel-based morphometry on 3D T1-weighted sequences, (iii) WM microstructural abnormalities at tract-based spatial statistics on diffusion-tensor imaging. The spatial association between the previous maps and gene expression according to the Allen Human Brain Atlas was obtained with the MENGA platform. The Open Target Platform was consulted to find a list of 414 genes associated with NMOSD. We performed a functional-enrichment analysis to investigate the overrepresented biological processes involving the genes significantly associated with the different types of brain damage.
Results: T2-hyperintense lesions were mainly located in the periventricular WM; GM atrophy was observed in the visual, prefrontal cortex, and insula, WM atrophy selectively involved the optic tracts; patients also had a widespread increase of WM mean diffusivity and no fractional anisotropy abnormalities.
Among significant genes, the expression of AQP4 and C5 associated with all types of brain damage, IL6 family signal transducer associated with brain atrophy only, and CD59 was protective.
Interferon-gamma, interleukin-4 and -13 signalling and activation of C3/C5 were associated with both lesions and microstructural abnormalities. A number of pathways, sometimes not specific for NMOSD pathogenesis, were associated with brain atrophy.
Conclusions: Brain lesions and WM microstructural abnormalities are associated with biological processes specific of AQP4+NMOSD, including complement activation and eosinophils/neutrophils recruitment. More complex mechanisms contribute to atrophy.

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Leigh disease; brainstem and spinal myelitis with a diagnosis of mitochondrial DNA mutations, mimicking mimicking neuromyelitis optica spectrum disorder (NMOSD**)**

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Introduction: Mitochondrial diseases are a large heterogenetic group of illnesses that largely involves neurological systems. Arriving to a definitive diagnosis of mitochondrial diseases could be long-winded and complicated with a wide range of differential diagnoses.
Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of a central nervous system (CNS) with immune-mediated demyelination, predominantly targeting the optic nerves and the spinal cord. We report 2 patients with a brainstem syndrome who had a confirmed diagnosis of Leigh syndrome.
Aims: We described a clinical journey of children who presented with rapid neurological deterioration at tertiary paediatric centres with Leigh disease, mimicking signs and symptoms of NMOSD.

Methods: Parental consents were gained and patient's medical records were reviewed.
Result: Case 1: a previously healthy 15 months old girl presented with 5 days history of fever and progressive neurological concerns such as central hypoxia, nystagmus, and ataxia on examination. She had fluctuating lactate levels with negative investigation for infection and autoimmune diseases. Magnetic resonance imaging (MRI) has shown bilateral multiple signal changes in T2 weighted imaging in the brain stem and longitudinally extensive transverse myelitis. DNA study confirmed a mitochondrial DNA m.8344A>G mutation, leading to a diagnosis of Leigh syndrome. She died within 1 month of her presenting illness with a worsening respiratory failure.
Case 2: a previously healthy 5 years old girl presented with reduced visual acuity and increasingly poor coordination. She had concerning neurological signs such as blurry vision, ptosis, nystagmus and poorly coordinated gait. She had extensive investigations to rule out infective and autoimmune causes. MRI has shown bilateral optic atrophy with T2 signal abnormalities in the brain stem. She received immunomodulation therapies including intravenous methylprednisolone, oral prednisolone and plasma exchange. DNA study has confirmed a mutation in the m.13094T>C within the MT-ND5 mitochondrial DNA gene, confirming Leigh Syndrome.
Conclusion: This report highlights the importance of considering a broad range of differential diagnoses at presentation and raise awareness in rare mitochondrial diseases such Leigh disease that can mimic NMSOD. Early diagnosis can lead to avoidance of potentially harmful and unnecessary immunosuppression therapy and early introduction to symptom care.

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Nothing to disclose

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Characterisation of disease severity and stability in neuromyelitis optica spectrum disorder: a global clinical record review with patient interviews

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a rare and debilitating autoimmune disease of the central nervous system that predominantly affects the optic nerve and spinal cord. NMOSD is characterised by unpredictable relapses that are associated with permanent neurological damage and disability. The severity of each relapse may vary, and recovery is usually incomplete, meaning that neurological damage and disability accumulates with each relapse. Therefore, relapse prevention and management of acute attacks are therapeutic priorities in NMOSD.
Objectives: This study aimed to provide global insights into current clinical practice and management of patients with aquaporin-4-immunoglobulin G-seropositive NMOSD (AQP4-IgG+ NMOSD), to include how assessments of disease (e.g., classification of relapse severity and disease stability) are made in clinical practice worldwide, as well as patient perceptions of these measures.
Methods: Neurologists from 6 countries (US, Germany, Italy, Brazil, South Korea, and China) participated in a 30–60-minute online survey and submitted 2–4 clinical records for adults with AQP4-IgG+ NMOSD, which included patient demographics, diagnosis, maintenance treatment history, relapse occurrence, and severity. Separately, patients with NMOSD receiving maintenance therapy were interviewed over the telephone about their treatment journey as well as perceptions of relapse severity and disease stability, and their potential influence on treatment decisions.
Results: Clinical records for 1,185 patients with AQP4-IgG+ NMOSD were provided by 389 neurologists (July–August 2020); 33 patients were interviewed (October–November 2020). There was no clear consensus on how relapse severity was defined in clinical practice, with geographical variations in relapse classification also found. Neurologists tended to rely on clinical assessments when determining severity, viewing each relapse in isolation, while patients had a more subjective view based on the changes in their daily lives and comparisons to prior relapses. Similarly, there was a disconnect in definition of disease stability: the complete absence of relapses was more important for patients than for neurologists.
Conclusions: A clear consensus on how to assess relapse severity and disease stability is needed to ensure that patients receive appropriate and timely treatment. In the future, clinical measures should be combined with patient-focused assessments.

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Activity impairment and support needs in neuromyelitis optica spectrum disorder: a patient's perspective

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a rare, complement-mediated autoimmune disease that damages the optic nerves and spinal cord. NMOSD is characterised by unpredictable attacks that cause symptoms such as visual impairment, paralysis, sensory loss, spasms, and pain. To date, there has been a lack of information on how NMOSD symptoms impair patients' daily lives and the support these patients require to cope with NMOSD.
Objective: To understand the patient perspective of NMOSD disease burden, caregiver support, and lifestyle adaptations required of patients with NMOSD.
Methods: Adults (aged ⩾ 18 years) with NMOSD who received an immunosuppressant therapy or an approved treatment for NMOSD were recruited for the study. Patients were interviewed via telephone/teleconference by trained personnel who moderated the discussion using a semistructured interview guide. ATLAS.ti was used to organize the qualitative data transcripts, which were coded to identify narrative themes of living with NMOSD.
Results: A total of 34 patients with NMOSD were interviewed (mean age: 48.4 years; female: 82.4%). Almost two-thirds (65%) of patients reported stable activity impairment following their last attack, with physical function and impact on work as the most common. Many patients reported feeling uncomfortable engaging in daily activities (21%–60%) and with social/leisure involvement (26%–53%), and some patients felt uncomfortable performing family responsibilities (5%–7%). Forty-one percent of patients had to stop working or reduce work hours after their NMOSD diagnosis; only 26.9% felt comfortable returning to work after their last attack. Notably, over one third of patients (35.3%) reported no longer being able to earn an income due to disability. In addition, almost all patients indicated relying on caregiver support (82.4%), with 56.5% needing daily support, most often with activities, transportation/driving, and mobility assistance.
Conclusions: This study demonstrated that many patients with NMOSD experience persistent and stable impairment following an attack, which affects multiple aspects of their lives, including ability to work and daily activities. Furthermore, reliance on caregiver support was almost always required among patients with NMOSD we interviewed. These findings highlight the need to prevent attacks to avoid the accumulation of symptoms that often lead to long-term disability.

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Safety and efficacy of Inebilizumab in AQP4+ NMOSD participants with history of immunosuppression treatment prior to N-MOmentum study

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Introduction: Inebilizumab, an anti-CD19 B cell-depleting antibody, is approved for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults seropositive for aquaporin-4 antibody ($AQP4^+$). Immunosuppressants were prohibited during the N-MOmentum pivotal trial, although many participants had a history of immunosuppressant therapy before enrolment.
Aims: To evaluate long-term outcomes of inebilizumab treatment in $AQP4^+$ NMOSD participants from the N-MOmentum trial with a history of immunosuppressant therapy as compared to those without.

Methods: N-Momentum (NCT02200770) was a 28-week randomized phase 2/3 trial of inebilizumab vs placebo, with an optional Open-Label Extension (OLE) (>2 years). Immunosuppressant medication for the prevention or treatment of NMOSD relapses was allowed prior to dosing on Day 1. In this post hoc analysis, AQP4$^+$ participants who received inebilizumab (through the OLE) were grouped by no history of immunosuppression therapy beyond treatment of acute NMOSD attacks (naïve), or prior azathioprine (AZA) and/or mycophenolate mofetil (MMF) therapy. Outcomes compared for these two groups included annualized relapse and hospitalization rates, as well as safety assessments.
Results: Among participants who received inebilizumab during the study, 94 received prior AZA/MMF and 103 were immunosuppressant naïve. The total patient-years of inebilizumab treatment in the prior AZA/MMF group was 300.35 and for immunosuppressant naïve participants, 335.7. The annualized relapse rate (95% confidence interval [CI]) for participants with prior AZA/MMF was 0.11 (0.07, 0.17), compared to 0.08 (0.05, 0.14) for naïve. The annualized NMOSD-related inpatient hospitalization rate (annualized rate [95% CI]) for prior AZA/MMF was 0.15 (0.08, 0.27), and 0.12 (0.06, 0.22) for naïve. The percentage of participants with ⩾1 study drug-related treatment-emergent adverse event (TEAE) was 30.9% (29/94) in prior AZA/MMF and 47.6% (49/103) of naïve; 4.3% (4) of prior AZA/MMF and 5.8% (6) of immunosuppressant-naïve reported ⩾1 study drug-related serious adverse event. Most adverse events were infection-related for both groups; (72.3% (68/94) for prior AZA/MMF and 77.7% (80/94) for naïve).
Conclusions: This post hoc analysis evaluating long-term outcomes of inebilizumab in AQP4$^+$ NMOSD participants treated with prior AZA/MMF therapy demonstrated a similar efficacy and safety profile as participants without prior immunosuppressant therapy.

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Clinical and radiologic characteristics of seropositive neuromyelitis optica spectrum disorder in a Turkish cohort

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease that presents with recurrent optic neuritis and transverse myelitis in most patients. Because of the high rate of relapse-related disability, preventing therapies are important for the management of the patients. However, we still have limited information on the frequency and timing of the clinical attacks.
Objectives: To determine the clinical, demographic, and imaging characteristics of a Turkish cohort with aquaporin-4-antibody positive (AQP4-IgG+) NMOSD from a single center.
Aims: With this cohort, we aimed to determine the cluster period of the clinical attacks and more frequently affected segments in transverse myelitis (TM) attacks of the NMOSD patients.
Methods: 35 patients followed between January-1985 and December-2021 with a diagnosis of AQP4-IgG+ NMOSD were included in the study.Inclusion criteria were determined as: i) NMOSD diagnosis according to the International Consensus Diagnostic Criteria ii) AQP4-IgG positive serology at least once by Euroimmune transfected cells assay (EU90). Information about demographic, clinical, and radiological features were obtained retrospectively from the files.
Results: The female-to-male ratio was 16.5: 1. The mean age of disease onset was 26,16±10,96 years for patients with optic neuritis onset (n:12), and 43.17±11,95 for the subgroup that started with transverse myelitis (TM) (n:16), confirming a significant difference in age at onset according to the first attack type ($p < 0.001$). Half of the total attacks occurred within the first year of disease onset (98/196). 24% of the total attacks occurred ten years after the diagnosis of the disease. C5 (26.2%) and C6 (27.9%) vertebra levels were found to be the most frequently involved cervical region in the TM attacks. T2, T4, T5 (26.9%), and T3 (28.8%) vertebral levels were found to be the most frequently involved thoracic regions in the TM attacks.
Conclusions: Turkish AQP4-IgG+NMOSD patients with ON-onset have an earlier age of onset compared to the ones with TM-onset. Half of the total attacks occur within the first year of

disease onset. It was observed that the other quarter of the total attacks occurred after the tenth year of the disease onset. The involvement rate of the T2-5 segment in the TM attacks was found to be significantly higher than the other thoracic segments.

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Clinical aspects of MS - MOGAD

P421
Pregnancy and post-partum in patients with myelin-oligodendrocyte glycoprotein antibody-associated disease

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Background: Myelin-oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) frequently initiates during childbearing years. Nevertheless, data on pregnancy and post-partum relapse risk in patients with MOGAD are very limited.
Objectives: This study investigated the impact of pregnancy and post-partum on MOGAD activity.
Methods: Retrospective analysis of clinical and demographic data from a multicenter French cohort of adult patients with MOGAD. All adult female patients who had a pregnancy after disease onset or in the year before disease onset were included. The annualized relapse rate was evaluated in patients who had a pregnancy after disease onset, to evaluate the impact of pregnancy and post-partum on MOGAD course.
Results: Twenty-five informative pregnancies after disease onset were identified. No relapse was recorded during these pregnancies, and only three relapses occurred during the first 3 months post-partum. The annualized relapse rate decreased from 0.67 (95% confidence interval : 0.40 – 1.10) during the pre-pregnancy period to zero during pregnancy and 0.21 during the first year post-partum. Over 144 female patients in their childbearing age were recorded in the database, 18 (12.5%) reported the first symptoms of the disease during pregnancy or in the 12 months post-partum.
Discussion: Our study suggests a marked reduction of MOGAD relapse rate during pregnancy and the post-partum period. Prospective studies on the role of pregnancy and delivery in MOGAD course are needed.

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P422
Quantitative MRI measures of MOGAD compared to MS, NMOSD and healthy controls

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Introduction: Myelin oligodendrocyte glycoprotein immunoglobulin G associated disorder (MOGAD), multiple sclerosis (MS), and neuromyelitis optica spectrum disorder (NMOSD) are distinct inflammatory demyelinating disorders. MS is associated with whole brain and grey matter atrophy.
Objectives: To determine whether whole brain and regional volume loss in MOGAD is different from MS and NMOSD.
Aims: To compare volumetric magnetic resonance imaging (MRI) measures in MOGAD, MS, NMOSD, and healthy controls (HC).
Methods: MOGAD patients ages 18-55 with standardized volumetric MRI scans were identified from the Cleveland Clinic Mellen Center registry and matched by age, sex and disease duration to MS patients. Two non-matched cohorts were evaluated; aquaporin-4-IgG positive NMOSD, HC.

3T MRIs were analyzed using an in-house automated algorithmto calculate whole brain (WBF), gray matter (GMF), white matter (WMF), caudate (CF) and thalamic fraction (TF); T2 lesion volume (T2LV) (ml); upper cervical cord area (UCCA) (C1-C2); and corpus callosum area (CCA) (mm^2). MRI parameters were compared by disease categories using linear regression adjusted for age, sex, and disease duration.

Results: To date, 98 patients were included: MOGAD (n=19), NMOSD (n=22), MS (n=57), HC (n=34). Median ages (years) were MOGAD 31 [IQR 37-49], MS 34 [IQR 30-48], NMOSD 38, [IQR 25-52], and HC 42 [37-48]. Median disease durations (years) were MOGAD 1.23 [IQR 0.59-3.14], MS 1.36 [IQR 0.99-3.27], and NMOSD 8.83, [IQR 2.41-11.83].

MOGAD first attacks included optic neuritis 8, [45%] (6 bilateral), myelitis 7, [30%], myelitis with brain/brainstem lesions 3, [15%], multifocal brain lesions 1, [5%], and brainstem 1, [5%]. Five patients had a relapsing course (myelitis 3, brainstem 1, optic neuritis 1). The median MOG-IgG titer was 1:100 [range 1:20-1:1000].

MOGAD compared to MS had lower T2LV (-5.79, p=0.015), greater TF (0.0005, p=0.036), greater CF (0.0003, p=0.02). After adjustment for T2LV, TF and CF were not significantly different between MOGAD and MS. There were no other significant differences between MOGAD compared to MS for UCCA, CCA, WBF and WMF. There were no inter-group differences between MOGAD, NMOSD and HC.

Conclusions: MOGAD patients have fewer focal white matter lesions than MS patients and this is associated with volume preservation in the thalamus and caudate.

Disclosure

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P423

Patterns of visual pathway neurodegeneration and demyelination in MOG-antibody associated disease, multiple sclerosis and neuromyelitis optica spectrum disorders

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are recognized as distinct disease entities with different etiologies. An absent visual evoked potentials (VEP) signal has been suggested as a feature of NMOSD due to predominant neuroaxonal damage of the visual pathway while prolonged VEP latency has been suggested as a feature of relapsing-remitting multiple sclerosis (RRMS) due to predominant demyelination.

Objective: To identify disease specific patterns of neurodegeneration and demyelination of the afferent visual system in these entities.

Aims: To compare VEP and OCT measures of these entities in eyes with history of ON.

Methods: Patients with MOGAD, RRMS or aquaporin-4 immunoglobulin G seropositive NMOSD (AQP4-IgG+) and healthy controls (HC) underwent OCT and VEP. Eyes with ocular comorbidities and/or blind eyes (defined as >1.0 logMAR) were excluded. Z-scores of VEP P100 latency and peripapillary retinal nerve fiber layer (pRNFL) were calculated using the mean and standard deviation (SD) from HC. Differences in OCT-VEP correlations were compared with linear mixed models with pRNFL-z as dependent variable and VEP-z as independent variable.

Results: 14 patients with MOGAD (age (mean ± SD) 48.3±12.7 years, 8 female, 19 ON eyes), 83 with RRMS (39.2±10.6 years, 29 female, 78 ON eyes), 27 with AQP4-IgG+ (53.19 ± 12.24 years, 2 female, 19 ON eyes), and 64 HC (34.0±12.3 years, 17 female) were included. pRNFL in ON eyes was 58.9±18.6 μm in MOGAD, 78.59±14.28 μm in RRMS and 72.3±20.0 μm in NMOSD. VEP latency in ON eyes was prolonged/absent in 7(36.8%)/6 (31.6%) in MOGAD, 37(57.8%)/8(12.5%) in RRMS and 8(42.1%)/4 (21.1%) in NMOSD, respectively. In eyes with recordable P100, the latency was 117.73±10.64ms in MOGAD, 123.40±14.86ms in RRMS and 117.46±12.74ms in NMOSD. The effect size for the influence of VEP-z on pRNFL- z was similar in the three entities (MOGAD: B=-0.342, RRMS: B=-0.237, NMOSD: B=-0.307).

Conclusions: While the extent of neuroaxonal damage and demyelination differs between MOGAD, NMOSD and RRMS, our results indicate that both are associated with each other in a similar fashion. These results do not support a disease-specific predominant demyelination or neurodegeneration. Our analysis is limited by a small MOGAD and NMOSD sample size and potential bias by excluding blind eyes towards more benign ON, thus challenging the use of VEP in a real-world approach.

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Alexander Ulrich Brandt is is cofounder and holds shares of medical technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patents and patent applications describing methods for retinal image analyses, motor function analysis, multiple sclerosis serum biomarkers and myelination therapies utilizing N-glycosylation modification. He is cofounder, member of the board and currently elected Secretary/Treasurer of IMSVISUAL.
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P424
Seasonal distribution of relapses in MOG antibody associated disease (MOGAD)

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Introduction: The influence of environmental factors on central nervous system demyelinating conditions have been recently studied. In MOG antibody associated disease (MOGAD), a seasonal distribution of relapses is not yet well-defined.
Objectives:: To investigate the presence of seasonal distribution of MOGAD relapses.
Methods: Prospective data from consented MOGAD patients within the Oxford National NMO Highly Specialised Service were analysed until April 2022. Demographic and clinical characteristics, including relapse date and phenotype, were recorded. All relapses with month-defined dates were used to calculate observed monthly frequencies. Expected frequencies were calculated assuming an uniform distribution throughout the year, adjusting for month's length and patient numbers under follow up. Any deviation from a uniform distribution was analysed, and seasonal peaks were assessed using Friedman's, Edward's, Ratchet circular scan and Hewitt's rank-sum tests.
Results: Three-hundred-four MOGAD patients were included, 190 (62.5%) females, mean age at onset 31 years (SD 16.9), median disease duration 3.0 (IQR 5.0) years, 77 (25.3%) with paediatric age onset. No significant seasonal pattern was identified when analysing all relapses (n=691), or onset relapses (n=286). Regarding age of disease onset, no seasonal pattern was found in onset under 18 (n=483) or over 18 years old (n=208). Regarding phenotype, no seasonal pattern was found in optic neuritis (n=483), transverse myelitis (n=180) or brain and brainstem relapses (n=125). Analysing all the relapses from the start of the COVID-19 pandemic (March 2020 – February 2022, n=112), a seasonal peak was identified from March to May (V(N)=0.132, $p<0.05$).
Conclusions: No seasonal pattern of relapses in MOGAD was noted until the COVID-19 pandemic started in the UK. Seasonal infection peaks during winter and subsequent lockdowns could have influenced MOGAD relapse rates in the past two years.

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P425

Exploring the patient pathway from first symptoms to diagnosis: results from an international survey of patients with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

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Introduction: Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is a rare, autoimmune, demyelinating central nervous system disorder characterised by inflammatory attacks of optic neuritis, transverse myelitis and/or encephalomyelitis/encephalitis. Earlier diagnosis and treatment may reduce disability and improve long-term quality of life by avoiding recurrent attacks.
Objective: Explore the experience of patients with MOGAD from first symptoms to diagnosis via an online survey.
Methods: The survey included 23 multiple-choice and free-text questions for patients and caregivers with MOGAD, covering disease history and healthcare interactions up to diagnosis. The survey was distributed by The MOG Project, a patient advocacy group, via their online survey tool to their patient network, with responses collected between 18 January and 1 March 2022. Survey respondents were informed that data were being collected for publication. Survey responses were anonymous and identifying free-text information was removed before analysis.
Results: There were 204 respondents from 21 countries; 68% (n=138) were from the United States, and 15% (n=31) were from Europe. The MOGAD-related health problem that typically led to patients seeking medical advice was blurred vision/loss of vision (57%, n=117). The most frequent medical specialities seen at symptom onset were emergency care (39%, n=79), primary care (26%, n=53) and ophthalmologists (15%, n=31), whereas the diagnosis was rendered by general neurologists (40%, n=82) and neuroimmunologists (30%, n=61). The median number of physicians seen before MOGAD diagnosis was four (IQR 3–6); 24% of patients (n=48) saw five or more physicians before diagnosis. For 39% (n=80) of respondents the elapsed time from symptom onset to diagnosis was ⩾6 months; for 18% (n=36) it was ⩾5 years. Reasons for delay included misdiagnosis, physician misunderstanding/lack of knowledge, long periods without symptoms, and lack of access to MOG antibody testing.
Conclusions: Many patients experienced diagnostic delays and misdiagnoses, with nearly 20% stating they were not diagnosed for 5 years or more after first symptom onset. The relatively recent classification of MOGAD as a separate disease is also likely a factor for those with longer disease durations; however, both patient and physician-based education and awareness must be improved to reduce diagnostic delays and, potentially, disability. Funded by UCB Pharma.

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P426

A retrospective investigation of MOG-IgG titers in relapse and disability prediction in adult and pediatric myelin oligodendrocyte glycoprotein antibody-associated disease patients

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Background: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an inflammatory-demyelinating disease of the central nervous system.[1]Relapses can result in accrual of neurological disability and have been reported in 27-80% of patients.[2,3]No randomized controlled trials of pharmacologic

therapies have been conducted; treatment has been based on observational studies. Persistence of MOG-IgG is associated with relapse,[4]but there is limited data on MOG-IgG titer and disease course. The identification of prognostic serological biomarkers has potential therapeutic implications.

Methods: We conducted a multi-center retrospective chart review of pediatric and adult-onset MOGAD. Differences in baseline characteristics were assessed using unpaired t-test, chi-square, and fisher's exact test. MOG-IgG was modeled as both a continuous and categorical variable (1:20-1:40 low, 1:80-1:100 medium, >1:100 high). Time to relapse was analyzed using Kaplan Meier and stratified by MOG-IgG titer. Linear regression evaluated MOG-IgG index titer as a predictor of index event severity (measured by Expanded Disability Status Scale (EDSS)) and event recovery (change in EDSS).

Results: Out of 77 participants (n=37 pediatric, n=40 adult), the mean onset age was 9.8 and 36.6 years in pediatric and adults, respectively, with mean disease duration 3.8 years. Optic neuritis was the most common presenting phenotype (bilateral 32.5%, unilateral 23.4%) followed by myelitis (15.6%). Among children and adults, relapses occurred in 32.4% and 40.0%, respectively (p=0.30), while mean time to relapse was 374 (+610 SD) and 864 (+1623 SD) days, respectively (p=0.33). Index MOG-IgG titer was not associated with relapse in whole group or sub-group analyses. MOG-IgG titer did not predict event severity (whole group p=0.06, age-adjusted p=0.11). There was a significant positive association between MOG-IgG titer and event recovery in whole group and age-adjusted analyses (p=0.0027 and p=0.001, respectively).

Conclusions: Index MOG-IgG titer was not associated with either relapse or clinical event severity but was positively associated with degree of event recovery. Patients with higher titers may have more severe disease at onset resulting in greater change in EDSS; however, sample sizes may lead to imprecise estimates. Further, prospective, investigation will elucidate the relationship between MOG-IgG titer and clinical outcomes.

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P427

Impaired brain growth in myelin oligodendrocyte glycoprotein antibody - associated acute disseminated encephalomyelitis

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Introduction: Acute disseminated encephalomyelitis (ADEM) is the most common phenotype in pediatric myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease. A previous study demonstrated impaired brain growth in ADEM. However, the effect of MOG antibodies on brain growth remains unknown.

Objectives: Here, we performed brain volume analyses in MOG-positive and MOG-negative ADEM at onset and over time.

Aims: To assess brain growth in ADEM patients with and without MOG antibodies.

Methods: We included a total of 62 MRI scans from 24 ADEM patients (54.2% female; median age 5 years), of which 16 (66.7%) were MOG-positive. Patients were compared to healthy controls from the NIH pediatric MRI data repository and a matched local cohort. Mixed-effect models were applied to assess group differences and other relevant factors, including relapses.

Results: At baseline and before any steroid treatment, ADEM patients, irrespective of MOG-antibody status, showed reduced brain volume compared to matched controls (median[IQR] 1741.9cm^3 [1645.1, 1805.2] vs. 1810.4cm^3 [1786.5, 1836.2]). Longitudinal analysis revealed reduced brain growth for both MOG-positive and -negative ADEM patients. However, MOG-negative patients showed a stronger reduction (-138.3cm^3 [95%CI -193.6; -82.9] than MOG-positive patients (-50.0cm^3 [-126.5, -5.2]), independent of age, sex, and treatment. Relapsing patients (all MOG-positive) showed additional brain volume loss (-15.8cm^3 [-68.9; 37.3]).

Conclusions: ADEM patients exhibit brain volume loss and failure of age-expected brain growth. Importantly, MOG-negative

status was associated with a more pronounced brain volume loss compared to MOG-positive patients.

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P428
MOGAD with concurrent malignancy

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Introduction: Myelin oligodendrocyte glycoprotein IgG associated disease (MOGAD) has been proposed as a distinct inflammatory demyelinating disease of the central nervous system. Several studies have revealed that a link between a broad spectrum autoimmune diseases, chronic inflammatory disease, and cancer. Neuromyelitis optica spectrum disorder (NMOSD) can occur in a paraneoplastic context, and cancer was frequently reported in large NMOSD cohorts.
Objectives and Aims: The aim of this study is to assess the prevalence of malignant tumor in MOG-EM and NMOSD with aquaporin-4-IgG (NMOSD-AQP4) populations. We also discuss cases of MOG-EM presented with concurrent primary malignant tumor.
Methods: A total of 63 patients with MOG-EM and 183 patients with NMOSD-AQP4 were included from 6 tertiary referral hospitals in South Korea, from August 2012 to February 2019. Concurrent cancer was defined as the cancer identified within 12 months of the diagnosis of CNS demyelinating disease. Subgroup analysis was done among elderly population aged 50 years or over.
Results: The prevalence rate of cancer was not different between MOG-EM and NMOSD-AQP4 (11.3% vs. 7.1%, p = 0.293). However, the prevalence rate of concurrent cancer was significantly higher in patients with MOG-EM compared to NMOSD-AQP4 (6.5% vs. 0.5%, p = 0.015). Furthermore, in elderly population, the prevalence rate of cancer was higher in MOG-EM compared to NMOSD-AQP4 significantly (28.6% vs. 8.2%, p = 0.018)
Conclusions: Concurrent cancer could be frequently diagnosed in patients with MOG-EM compared to NMOSD-AQP4. Further prospective large cohort study will be needed in this field.

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P429
Clinical profile of MOGAD patients binding to the P42S MOG variant

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Introduction: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an inflammatory disorder characterized by attacks of immune-mediated demyelination, targeting the optic nerves, brain, and spinal cord, and frequently affecting children. The risk of relapse is considered lower than 50%, and most patients experience a good outcome. However, there is a proportion of patients that experience a severe course or devastating relapses. Until now, no clear markers of poor outcome and/or relapse risk have been identified.
In humans, several isoforms of MOG protein exist where the extracellular part is highly conserved. Autoantibodies (Abs) do not react to those variants similarly, yet all Abs react to native full-length MOG (alpha-1). The importance of several extracellular epitopes in binding has been studied. Proline at position 42 (P42) is a highly conserved rigid epitope in human MOG, which plays an important role in Ab binding. However, not all Abs need P42 for binding, as previous studies showed that several MOG-IgG positive samples were able to bind to the mutated proline to serine 42 (P42S) native form. Interestingly, P42S binding was recently associated with a specific clinical profile in a MOGAD cohort.
Aim: The aim of our study was: i) to identify the ratio of MOG-IgG positive patients that can bind MOG P42S variant; and ii)

whether binding to MOG P42S is associated with specific clinical symptoms and disease course.
Methods: This French cohort (n=147) study included 39 children and 108 adults, who tested seropositive for MOG-IgG after a first demyelinating episode, between December 2015 and February 2021. Live cell-based assay using native full-length form and P42S variant (gift from Dr. A. Saiz, Spain) as substrates were used separately with a 1:640 sample dilution.
Results: 58 (39.5%) of the 147 serum tested positive for autoantibodies against native full-length MOG were also able to bind MOG P42S variant. Among the whole cohort, 32/71 women (45.1%) and 26/76 men (34.2%) bound to this variant. As of age, 17/39 children (43.6%) and 41/108 adults (38%) bound to P42S. MOG P42S binding was associated with acute disseminated encephalomyelitis presentation (12/15 patients). Interestingly, P42S binding was related to a lower risk of relapse.
Conclusion: The binding capacity to MOG P42S variant may be clinically useful as a predictive marker of relapse and disability, after the first episode of MOGAD.

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P430
Cognitive impairment in MOGAD is associated with a history of ADEM-like episodes and cortical atrophy

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Objective: To identify prevalence and clinical risk factors for cognitive impairment (CI) in adult patients with myelin oligodendrocyte glycoprotein-IgG associated disease (MOGAD).

Methods: Patients were examined in relapse-free remission by certified neuropsychologists using a standardised test battery including tests for attention, mental flexibility, visual and verbal memory. Patients were considered cognitively impaired if their performance was $<$7th percentile in $\geqslant$2 tests representing different cognitive functions. Clinical data explored as potential risk factors for CI included age, disease duration, number and type of relapses, disability (Expanded Disability Status Scale (EDSS)), fatigue and depression. 3 Tesla T1-weighted magnetic resonance images were processed with FreeSurfer for grey and white matter volume estimation.
Results: 33 MOGAD patients were included (33.6$\pm$13.3 y.o., 20 female). Median disease duration was 18 months with a median of two relapses, median EDSS was 1.0. 20 patients had experienced optic neuritis, 17 myelitis and 8 Acute Disseminated Encephalomyelitis (ADEM) or ADEM-like episodes in their history. 7 of 33 patients (21.2%) demonstrated significant cognitive impairment. Most prevalent were deficits in mental flexibility (16.7%), alertness (phasic alertness 14.4%, tonic alertness 11.1%) and verbal working memory (9.4%). Regression analysis revealed history of ADEM/ADEM-like episodes as the only potential factor associated with cognitive impairment (ExpB 7.333 95%CI 1.168-46.052, p=0.034). Neither depression, fatigue, disease duration nor disability were risk factors. Patients with CI had significantly reduced total grey matter volume (U=12, z=-2.460, p=0.014) and cortex volume (U=9, z=-2.683, p=0.007) compared to cognitively unimpaired MOGAD patients.
Conclusions: Despite a low overall disability measured by EDSS, a substantial part of MOGAD patients suffers from CI. We identified a history of ADEM/ADEM-like episodes as only clinical risk factor. CI was specifically associated with reduction of cortical grey but not white matter volume. Further studies are needed to identify underlying microstructural post-ADEM changes associated with CI in MOGAD.

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Clinical aspects of MS - Neuropsychology

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Predictors of suicidal ideation in people with multiple sclerosis

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Introduction: Rates of suicide in people with multiple sclerosis (MS) are twice those in the general population. Suicidal intent (SI) is also common.
Aims: In this study, we explored predictors of both general SI as well as active SI in a sample of people with MS (n=72).
Methods: Participants completed the Beck Suicide Scale (BSS), Hospital Anxiety and Depression Scale (HADS), and the Minimal Assessment of Cognitive Function in MS (MACFIMS) in addition to the Iowa Gambling Task (IGT), a marker of impulsivity. Clinical and demographic data (including employment status) were also collected. Participants with SI (BSS $>$ 0; n= 28) and a subset with active SI (score $>$0 on questions 4 and/or 5 on the BSS, n=8) were compared to those without SI (n=44).
Results: There were no significant correlations between scores on the MACFIMS measures and BSS in our sample. Participants with SI were more depressed ($t(70)$=-4.273, p= $<$.001) and anxious ($t(70)$=-3.934, p= $<$.001) than those without SI. Logistic regression using HADS scores as predictive variables modelled SI versus no SI data well ($X^2(2)$=20.816, $p<.001$) with HADS scores for depression (B=.207, p=.017) and anxiety (B=0.176, p=0.033) emerging as independent predictors of SI. Participants with active SI were more depressed ($t(50)$=-2.886, p=.006), anxious($t(50)$=-2.377, p=.021) and were more likely to have scores on the lowest quartile of the IGT ($r(50)$=-.279, p= 0.045) and be unemployed ($r(50)$=.355, p= .010) than those who were not suicidal. Logistic regression using HADS scores, employment status and IGT quartile score as predictive variables modelled active versus no SI data well ($X^2(4)$=15.394,p=0.004) though no independent predictors reached significance.
Conclusions: These findings compliment earlier studies and suggest patients with depression and anxiety are at increased risk of suicidal ideation and those additionally unemployed with elevated impulsivity are more likely to develop active SI.

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Cognitive profile of persons with newly diagnosed multiple sclerosis

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Introduction: Cognitive impairment is observed in at least half of the people with multiple sclerosis (pwMS). Cognitive deficits can begin to appear even in the early stages of multiple sclerosis. The most affected cognitive functions are the speed of information processing, attention, and memory in pwMS.
Cbjectives: The first aim was to assess and compare the cognitive functions between pwMS who had a new diagnosis and age-education level and gender-matched healthy controls (HC). The second aim was to demonstrate the rate of cognitive impairment in newly diagnosed pwMS.
Methods: Five hundred and seventy-two pwMS who had new diagnoses (402 female; mean age=33.51$\pm$10.65) and 81 HC (58 female; mean age=35.41$\pm$11.52) were enrolled in the study. The clinic and demographic characteristics of the participants were

recorded. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery which included the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-II (CVLT-II), and the Brief Visuospatial Memory Test-Revised (BVMT-R) were used to assess cognition. Average scores of the BICAMS battery subtest were calculated in healthy controls. The patients who have at least one subtest under -1.5 SD in these scores were identified as cognitively impaired.

Results: There were significant differences between pwMS (50.53±12.22; 24.89±6.48) and HC (54.48±11.82; 27.29±5.50) in terms of mean CVLT-II and BVMT-R scores ($p<0.05$). SDMT scores were less in pwMS than HC, but it was not statistically significant (pwMS=48.13±13.59, HC=50.60±12.90; $p>0.05$). According to the calculated cut-off score, 162 (28.3%) pwMS newly diagnosed have cognitive involvement.

Conclusions: This study suggests that pwMS with newly diagnosed patients have lower cognitive function performance than HC. There are so many factors that may affect the cognitive impairment in MS, such as duration of diagnosis, age of onset, psychological well-being, number and severity of relapses, etc. Cognitive functions are affected depending on how these factors impact the pwMS at the beginning of the disease. For this reason, it is essential to start diagnosis and treatment faster to preserve cognitive functions in pwMS. Follow-up studies are planned in THOSE newly diagnosed pwMS with to clarify their cognitive impairments.

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The impact of biological sex and cognitive reserve on cognition in multiple sclerosis

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Introduction: Biological sex and cognitive reserve (CR) have shown to have an impact on cognitive performance in people with Multiple Sclerosis (pwMS) (Santangelo et al., 2019; Donaldson et al., 2019; Altieri et al., 2021). To date, no studies focused on the interaction effect between biological sex and CR on cognitive status in pwMS by employing a specific CR scale assessing the engagement on multiple cognitively stimulating activities.

Aim: The aim of the study was to assess, in pwMS, the possible presence of a combined effect of CR and biological sex on performance on several cognitive domains.

Materials and methods: 196 people with RRMS (117 women) were consecutively recruited at the MS Center of the I Division of Neurology at University of Campania. They underwent a neurological examination and the Expanded Disability Status Scale was calculated to evaluate the degree of physical disability. Moreover, each participant was administered: i) the Stroop test to assess performance on inhibitory control, and ii) the Italian version of the Brief Repeatable Battery of Neuropsychological Tests to evaluate levels of verbal and spatial memory (Selective Reminding Test [SRT-LTS, SRT-CLTR, SRT-D] and Spatial Recall Test [SPART, SPART-D]), processing speed/attention (Symbol Digit Modalities Test [SDMT], Paced Auditory Serial Addition Test [PASAT]), and verbal fluency (Word List Generation [WLG]). Levels of CR were assessed with the Cognitive Reserve Scale (I-CRS; Altieri et al., 2018). T-test for independent samples was calculated to evaluate possible differences between clinical and socio-demographic variables among sexes; a MANOVA served to evaluate the effects of CR and sex, and their possible interaction effect on cognitive performance. Bonferroni correction was applied.

Results: Men and women with MS did not differ for clinical and socio-demographic variables. The MANOVA revealed a significant main effect of CR on SRT-LTS ($p=.010$), SRT-CLTR ($p<.001$) and WLG ($p=.042$) scores (high CR>low CR), and a significant main effect of biological sex on PASAT 3" ($p=.025$), PASAT 2" ($p= .005$) (men>women), and on WLG ($p=.004$) scores (women>men). The interaction effect between sex and CR was not significant.

Discussion: The results revealed that the possible impact of CR on cognitive performance did not depend on being a man or a woman with MS. Both sexes may equally benefit from specific tailored psychosocial neuropsychological rehabilitation programs to increase CR and cognitive performance.

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Functional and structural MRI changes associated with cognitive worsening in multiple sclerosis: a 3-year longitudinal study

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Introduction: Heterogeneous pathological processes may contribute to cognitive impairmentin multiple sclerosis (MS); however, the association between brain structural and functional MRI changes and cognitive worsening in MS still need to be fully explored.
Aim: To apply a multiparametric MRI approach to identify the mechanisms associated to cognitive worsening in MS patients.
Methods: Brain dual-echo, 3D T1-weighted, diffusion-weighted imaging, and resting state (RS) functional MRI scans were acquired at baseline and after a median follow up of 3.4 years in 35 MS patients and 22 healthy controls (HC). Associations between cognitive worsening at Rao's battery and global and regional voxel-wise longitudinal changes in white matter (WM) microstructural damage, gray matter (GM) atrophy and RS functional connectivity (FC) were explored using tract-based spatial statistic (TBSS), tensor-based morphometry (TBM) and independent component analysis (ICA).
Results: Fifteen (43%) MS patients were cognitively impaired at baseline and 10 (29%) showed cognitive deterioration at follow-up. At baseline, compared to HC, MS patients showed widespread WM damage and GM atrophy, and decreased RS FC in some clusters of executive control (ECN) and working memory networks (WMN). At follow-up, annualized volume loss of caudate nucleus was significantly higher in MS patients with vs those without cognitive deterioration (-1.2% vs -0.2%, $p<0.05$), whereas no significant between-group differences in regional WM microstructural changes or GM atrophy were found. Compared to cognitively-stable MS patients, those with cognitive deterioration showed decreased RS FC in the right hippocampus of right WMN and in right insula of default mode network. In the opposite comparison, an increased RS FC in the left insula of the ECN was found.
Conclusions: While cognitively-stable MS patients showed increased RS FC in the left insula, possibly reflecting a compensatory mechanism, cognitive deterioration at medium-term in MS patients was associated with decreased RS FC in several functional brain networks, with a more limited GM atrophy progression. Our study, suggests that, in MS patients already characterized by substantial structural damage, cognitive deterioration might be secondary to functional network collapse.

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Time-varying functional connectivity of the hippocampus is associated with cognitive performance in multiple sclerosis patients

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Introduction: The hippocampus has a key role in cognition and mood regulation. In multiple sclerosis (MS), cognitive impairment is related to hippocampal damage. Hippocampal time-varying (TV) functional connectivity (FC) in MS is yet to be completely investigated.
Objectives: To explore hippocampal static FC (sFC) and TVFC in patients with MS, and assess their association with cognitive performances.
Methods: 3D T1-weighted and resting state (RS) functional MRI scans were acquired at 3.0 T from 108 right-handed MS patients and 63 right-handed healthy controls (HC). Subjects underwent a neuropsychological evaluation comprising the Brief Repeatable Battery of Neuropsychological Tests. Sliding-window correlation analysis using the left (L) and right (R) hippocampus as seed regions assessed TVFC, which was quantified by the standard deviation of connectivity across windows. Mean connectivity indicated sFC.
Results: Compared to HC, MS patients had decreased sFC between the L hippocampus and temporo-parietal regions, and increased sFC between L and R hippocampus and thalamus, precuneus and superior frontal regions. TVFC was decreased in MS patients *vs* HC between L hippocampus and temporo-parietal regions. Conversely, TVFC was increased in MS patients*vs* HC between L and R hippocampus and L pre- and postcentral gyri, cuneus, orbitofrontal cortex and inferior temporal gyrus (ITG). In MS patients, better global cognition correlated with higher TVFC between L hippocampus and L pre- and postcentral gyri (r=range 0.21-0.28; p=range 0.04-0.006). Better verbal memory correlated with higher TVFC between L hippocampus and L precentral gyrus (r=0.21, p=0.03), and better visuospatial memory correlated with higher TVFC between L and R hippocampus and L cuneus, pre- and postcentral gyri and ITG (r=range 0.19-0.23, p=range 0.02-0.04). Better information processing speed correlated with higher TVFC between L hippocampus and L postcentral gyrus (r=0.21, p=0.03) and with higher sFC between R hippocampus and L superior frontal cortex (r=0.21, p=0.03). Finally, better attention scores

correlated with higher TVFC between L hippocampus and L temporal cortex (r=0.24, p=0.01) and with higher sFC between R hippocampus and L superior frontal cortex (r=0.20, p=0.05).
Conclusions: Increased hippocampal TVFC and sFC contributed to explain better cognitive performances in MS. A peculiar association between higher hippocampal TVFC and better memory scores was detected.

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Probing mental fatigue in multiple sclerosis: brain activation patterns during cognitive tasks and their relationship with state and trait fatigue

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Introduction: Mental fatigue is an extreme feeling of tiredness present in several neurological disorders, including multiple sclerosis. People with multiple sclerosis (PwMS) typically report high levels of mental fatigue (both trait and state fatigue) especially when exposed to challenging cognitive tasks.
Objectives/Aims: We investigated differences in brain activation patterns among PwMS and healthy controls while performing single and dual cognitive tasks, and their relationships with subjective measures of mental fatigue.
Methods: We recruited PwMS (n = 15) and matched controls (n = 12) who had normal cognition. They underwent functional Near Infrared Spectroscopy (fNIRS) during the single (serial subtraction by 7's), and dual tasks (serial subtraction by 7's alternating with letters). Trait fatigue was measured using the Fatigue Scale for Motor and Cognitive Functions, and state fatigue was measured pre- and post-fNIRS using a visual analogue scale. Relative concentration of oxy- hemoglobin (HbO) was calculated for each channel, and peak concentrations were averaged for the dorsolateral prefrontal cortex and the frontopolar area of both hemispheres. Relationships between fatigue and HbO concentrations were assessed using correlation analysis.
Results: PwMS presented with significantly higher levels of trait fatigue compared to healthy controls ($p = 0.007$). There was a significant increase in state fatigue in people with MS after the experiment ($p = 0.004$), but not in controls. Visual inspection revealed an overall incoherence in activation patterns in MS compared to controls. Preliminary analysis suggests that there were no significant differences in HbO peak concentrations between the groups. Data analysis is ongoing.
Conclusions: Despite having no impairments in cognition, patterns of brain activity during cognitive tasks suggest low synchronization in PwMS compared to controls. PwMS experienced greater fatigue during the single and dual cognitive tasks. Further results will be presented.

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Prediction of cognitive impairment in multiple sclerosis: 10- and 16-year follow-up studies

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Introduction: The early predictors of cognitive impairment in patients with multiple sclerosis (MS) are lacking.
Objectives: To identify early predictors of cognitive impairment in MS patients after long-term follow-up.
Methods: The SET study included patients after the first demyelinating event suggesting MS fulfilling McDonald 2005 criteria. The ASA study included clinically active relapsing remitting MS patients. The mean duration of the disease at baseline was 2.7 ± 0.8 months in the SET and 5.5 ± 5.1 years in the ASA cohort. Together, 161 (89%) out of the original 181 patients from the ASA and 184 (84%) out of 220 patients from the SET study underwent cognitive follow-up assessment in 2017/2018. Binomial logistic regression models adjusted for age, sex, follow-up duration, education and depressive symptomatology were used to identify baseline clinical and MRI parameters predicting the presence of cognitive impairment (at least 1 neuropsychological test [Brief International Cognitive Assessment for MS; BICAMS] below -1.5 SD of the normative population; with a 95% confidence interval taken into

an account) at follow-up after 15.3 (range: 13.7-19.1; ASA study) or 10.1 years (range: 8.1-12.4; SET study).
Results: Together, 5 (2.7%) of the SET study and 25 (16%) of the ASA study patients had cognitive impairment at follow-up. Considering low number of SET study patients with cognitive dysfunction, we assessed only predictors in the ASA cohort. In the ASA study, we identified the following independent baseline predictors of future cognitive impairment: T2 lesion volume (log[x+1] transformed; odds ratio [OR]=3.5 [2.0-6.7], $p<0.001$), absolute change in T2 lesion volume during the first year (OR=2.74 [1.6-5.2], $p<0.001$), normalized lateral ventricles volume (OR=1.0 [1.0-1.0], p=0.004), normalized cortical volume (OR=1.0 [1.0-1.0], p=0.018), and normalized gray matter volume (OR=1.0 [1.0-1.0], p=0.016).
Conclusions: Larger lesion burden and its change in the first year, together with global and regional brain atrophy are associated with higher risk of cognitive impairment after long-term follow-up. The high volume of T2 lesion was the strongest predictor of future cognitive impairment. The evaluation of volumetric MRI measures could improve the identification of patients who could benefit from more frequent cognitive monitoring to detect cognitive deterioration as soon as possible.

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The relationship between cognitive impairment and stigma in people with multiple sclerosis

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Introduction: Cognitive impairment (CI), which is reported at high rates in people with multiple sclerosis (MS, pwMS), also negatively affects daily life activities. Stigma, which includes cognitive, emotional, and behavioral dimensions, is also seen in people with chronic diseases such as MS.
Aims: The aim of the study is to examine the relationship between the presence of CI and stigma in pwMS.
Methods: Sixty-nine pwMS who were followed by the outpatient MS Clinic of Dokuz Eylul University Hospital were included in the study. Demographic and clinical characteristics such as the Expanded Disability Status Scale (EDSS) and education level were recorded. The stigma levels of the participants were evaluated with the Quality of Life in Neurological Diseases (NeuroQoL) -Stigma Scale. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery was used to assess cognitive function. CI was accepted in patients who were matched with the healthy group in terms of age, education, and gender and was below -1.5 standard deviations of the mean of the healthy group.
Results: CI was detected in 15 (22.9%) participants. There was a significant difference between pwMS with CI and without CI in terms of EDSS (1.97 ± 1.92 vs. 0.84 ± 1.32), age (43.20 ± 12.29 vs. 30.57 ± 8.44), and disease duration (10.25 ± 9.25 vs. 6.21 ± 6.20), ($p< 0.05$). When these variables were taken as a covariate, there was no difference in stigma scores between the two groups ($p> 0.05$).
Conclusions: The results of this study show that stigma in pwMS is not affected by the presence of CI. The low rate of pwMS with CI may be one of the limitations of our study. Studies with larger sample sizes are needed.

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P439

The seasonal fluctuation of fatigue in multiple sclerosis

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Introduction: Fatigue is a common symptom in patients with multiple sclerosis. Several studies suggest that outdoor temperature can impact fatigue severity, but a systematic investigation of seasonal fluctuations is missing.
Methods: Fatigue was assessed with the Fatigue Scale for Motor and Cognitive Functions (FSMC) in a temperate climatic zone with an average outdoor temperature of 8.8°C. This study included 258 patients with multiple sclerosis from 572 visits temporally distributed over the year. The data were adjusted for age, sex, cognition, depression, disease severity, and follow-up time. Linear regression models were performed to determine whether the temporal course of fatigue was time-independent, linearly time dependent, or non-linearly time dependent.
Results: Fatigue was lowest during January (mean FSMC: 49.84) and highest during August (mean FSMC: 53.88). The regression analysis showed the best fit with a model that included months + months², which was a non-linear time dependency. Mean FSMC per month correlated significantly with the average monthly temperature ($\rho=0.972$;$p<0.001$).
Conclusion: In multiple sclerosis, fatigue showed a natural temporal fluctuation. Fatigue was higher during summer compared to winter, with a significant relationship of fatigue with outdoor temperature. This finding should be carefully taken into account when clinically monitoring patients over time to not interpret higher or lower scores independent of seasonal aspects.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

P440
Factors influencing fatigue in persons with multiple sclerosis: contribution of psychological and magnetic resonance imaging assessment

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Introduction: Although motor and cognitive fatigue frequently co-occur in people with multiple sclerosis (pwMS), confounding variables likely differ underlining the necessity of a multidimensional assessment. Besides demographics, clinical and psychological variables, MS-related structural damge has been associated with fatigue. Therefore, a multifactorial approach might be best suited to identify relevant predictors of fatigue.
Objectives: The aim of this study was to investigate predictors of total, motor, and cognitive fatigue in pwMS.
Methods: 136 pwMS (63% female; age=39±10 years; disease duration=10±7 years) and 49 healthy controls (HC) (69% female; age=33±10 years) underwent clinical, neuropsychological, and magnetic resonance imaging (MRI) assessment. Fatigue was assessed with the "Fatigue Scale for Motor and Cognitive Function", comprising a total, motor and cognitive fatigue score. Global and subcortical brain volumes, lesion volume and pattern, as well as white matter integrity (WMI) of the motor and associative cortico-striatal-thalamo-cortical (CSTC) loops were analysed.
Results: At least mild fatigue was present in 54% of pwMS and 22% of HC. 20% of pwMS showed distinct cognitive or motor fatigue. Severity of total fatigue (adjusted (adj.) $R^2=0.53$) was predicted by female sex ($R^2=0.04$, ß=0.17, p=0.024), education ($R^2=0.04$, ß=-0.14, p=0.022), physical impairment ($R^2=0.16$, ß=0.25, $p<0.001$), depression ($R^2=0.25$, ß=0.38, $p<0.001$), self-efficacy ($R^2=0.02$, ß=-0.18, p=0.014) and WMI of thalamic tracts in the motor CSTC loop ($R^2=0.02$, ß=-0.16, p=0.009). Cognitive fatigue (adj. $R^2=0.45$) was predicted by depression ($R^2=0.38$, ß=0.30, p=0.003), self-efficacy ($R^2=0.02$, ß=-0.21, p=0.008), and WMI of thalamic tracts in the associative loop ($R^2=0.02$, ß=-0.14, p=0.041). Motor fatigue (adj. $R^2=0.54$) was predicted by education ($R^2=0.06$, ß=-0.16, p=0.009), physical impairment ($R^2=0.31$, ß=0.33, $p<0.001$), depression ($R^2=0.16$, ß=0.44, $p<0.001$), and self-efficacy ($R^2=0.01$, ß=-0.15, p=0.036). Total (adj. $R^2=0.45$, $p<0.001$), cognitive (adj. $R^2=0.46$, $p<0.001$) and motor (adj. $R^2=0.41$, $p<0.001$) fatigue in HC was predicted solely by demographics and psychological variables.

Conclusions: Our results indicate that independent from demographics and clinical data, depression and self-efficacy strongly contribute to prediction of fatigue, providing targets for treatment approaches. Furthermore, incremental variance was explained by thalamic WMI underlying total and cognitive fatigue.

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P441
Hippocampal microstructural integrity and speed of information processing in multiple sclerosis

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Introduction: The contribution of hippocampal atrophy to cognitive impairment has been widely described in multiple sclerosis (MS). However, less is known about measures of microstructural damage, which could provide further insights on mechanisms of cognitive dysfunction.
Objectives: We investigated the association between hippocampal microstructural integrity and information processing speed deficit (IPS) in MS.
Methods: Fifty healthy controls (HC) and 117 MS patients underwent 3.0T MRI. Global and subregional hippocampal volumes were assessed with the cross-sectional pipeline of the Freesurfer 6.0. Measures of microstructural integrity were obtained using diffusion tensor imaging (i.e., fractional anisotropy [FA], mean diffusivity [MD]) and neurite orientation dispersion and density imaging (NODDI, i.e., neurite density index, orientation dispersion index [ODI]). Symbol Digit Modalities Test (SDMT) was administered to assess IPS, and z-scores were calculated according to normative data. Age- and sex-adjusted linear models were used for between-group comparisons, while hierarchical linear regression analysis was run to identify predictors of SDMT z-scores among clinical and MRI variables in MS patients.
Results: Compared to HC, MS patients showed an average volume reduction in the fimbria ($p<0.01$).The hippocampus of MS patients was characterized by reduced FA and increased MD and ODI compared to HC ($p<0.01$). Older age ($\Delta R^2=0.19$; $p<0.001$), higher T2-lesion volume ($\Delta R^2=0.06$; $p<0.01$) and higher MD of the fimbria ($\Delta R^2=0.05$; $p=0.01$) were selected as significant predictors of slower IPS measured with SDMT (Adjusted-$R^2=0.27$).
Conclusion: The integrity of the fimbria appears to be a critical anatomical correlate of information processing speed performance in MS.

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Clinical aspects of MS - Paediatric MS

P442
Seizure as a presenting symptom in children with neuroinflammatory disorders

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Introduction: Seizures are not common as a presenting symptom of neuroinflammatory disorders in children.
Methods: A retrospective observational study of seizure manifestations in children diagnosed with neuroinflammatory disorders was conducted at a tertiary paediatric center (Dana-Dwek Children's Hospital, Tel-Aviv) between 2016 and 2021.
Results: Fifty-three children (25 males and 28 females) with pediatric neuroinflammatory disorders under 18 years of age at diagnosis were included. The median (IQR) age of first event in the study group was 11 (4.4-13.1) years. The most common disorder was myelin oligodendrocyte glycoprotein antibody-associated demyelination (MOGAD) (n=14, 26.4%) followed by multiple sclerosis (MS) (n=10, 18.8%), seronegative-acute disseminated encephalomyelitis (ADEM) (n=8, 15.1%), autoimmune encephalitis (n=5, 9.4%), autoimmune cerebellitis (n=4, 7.5%), AQP4-Ab neuromyelitis optica spectrum disorder (AQP4-Ab- NMOSD) ((n=3, 5. 6%), transverse myelitis (n=3, 5.6%),radiological isolated syndrome

(RIS) (n=2, 3.7%), opsoclonus-myoclonus syndrome (OMS) (n=2, 3.7%), clinically isolated syndrome (CIS) (n=1, 1.8%) and optic neuritis (n=1, 1.8%).
Thirteen children presented with seizures (24.5%); 4 autoimmune encephalitis (2 with anti-NMDA-R encephalitis), 6 ADEM (of those 3 MOGAD), 1 RIS, 1 MS and 1 autoimmune cerebellitis. There was no difference in the proportion of patients with seizures in those with predominantly white matter disease (8/42) compared to those with predominantly grey matter disease (5/11) (p=0.11, Fischer's exact).
Focal-onset seizures were seen in 12 patients (92%) and no patients had status epilepticus. Seizures resolved after the acute phase of the disease in all patients apart from one child with ADEM. No children required anti-epileptic medications at 1 year post-presentation.
Conclusion: Seizures can be seen in both grey and white matter disorders and may result from cortical lesions in addition to surrounding cytotoxic oedema playing an epileptogenic role. Prognosis from an epilepsy perspective in these conditions is overall favorable.

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nothing to disclose

P443
Stable incidence and sex-ratio in the paediatric onset multiple sclerosis population for over a decade in Ontario, Canada (2003-2019)

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Introduction: Few population-based studies have estimated the incidence of paediatric-onset MS (PoMS).
Objectives: To estimate the incidence of PoMS in Ontario, Canada's most populous province.
Methods: We used population-based linked health administrative data from Ontario, capturing nearly 40% of Canada's population. To identify individuals with PoMS, we applied a validated case definition requiring at least 3 hospital or physician claims (International Classification of Diseases (ICD) 9/10 diagnostic codes 340/G35). The index date was the first demyelinating or MS specific claim recorded at age ⩽18 years, with no such claims during the preceding five years to ensure identified cases were incident. We estimated the crude and age-standardized annual incidence rates of PoMS, and 95% confidence intervals between 2003 and 2019. We also report the sex- and age- (<12, 12-15, 16-18 years) stratified annual incidence rates, and compared rates between groups using incidence rate ratios. Temporal changes in the annual crude incidence, and the incidence sex and age ratios for PoMS were assessed using negative binomial regression models.
Results: A total of 672 incident PoMS cases were identified from 2003 to 2019. Females accounted for 66% of cases, and the mean (standard deviation) age at the index date was 15.0 (3.9) years. The crude and age-standardized annual incidence of PoMS was largely stable, albeit with some expected fluctuations, averaging a crude and age-standardized incidence of 0.98 (95%CI: 0.91-1.06) and 0.98 (95%CI: 0.84-1.12) per 100,000 population, respectively. The incidence female:male ratio was also stable over the study period, with an average of 2.0:1. The annual incidence rates were greater in the 12-15 and 16-18 age groups relative to the <12 age group (average age ratios of 4.5:1 and 14.5:1, respectively), and no temporal trends were found for the age ratios.
Conclusions: Canada's most populous province (Ontario) has one of the highest rates of PoMS globally. Over a sixteen-year period, the incidence, sex ratio and age ratios remained relatively stable.

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P444
Ocrelizumab dose selection for treatment of relapsing-remitting multiple sclerosis in children and adolescents: Preliminary pharmacokinetic, safety and efficacy results from the OPERETTA 1 study

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Background: Paediatric multiple sclerosis (MS) is a highly active disease with frequent relapses and rapid accrual of MRI lesions occurring early in the disease course. Current treatment strategies are largely based on those used in adults and are still limited by the lack of regulatory approval for paediatric MS. Ocrelizumab (OCR) may improve outcomes, treatment adherence and offer a new treatment option for patients with paediatric MS.
Aims: To select the OCR dosing regimen in patients (pts) with paediatric relapsing-remitting MS (RRMS), with a comparable pharmacokinetic/pharmacodynamic (PK/PD) and safety profile as observed in adult pts treated at the approved intravenous dose of 600 mg, through analysis of PK, PD and safety data.
Methods: Pts aged ⩾10 to <18 years with RRMS were enrolled in OPERETTA 1 (NCT04075266). This 4-year study evaluates safety, tolerability, PK and PD of OCR in two cohorts, Cohort 1 (body weight ⩾25 kg to <40 kg; OCR 300 mg) and Cohort 2 (body weight ⩾40 kg; OCR 600 mg), during a 24-week (24W) dose exploration period (DEP) followed by an optional OCR extension with OCR given at 24W intervals. Exploratory endpoints include protocol-defined relapses and MRI activity (new T1 gadolinium-enhancing [T1-Gd] lesions at W12 and new/enlarging T2 [N/E T2] lesions at W12, W24, W48, W72 and W96, thereafter at 48-week intervals).
Results: As of April 2022, 21 pts were enrolled (Cohort 1: N=4; Cohort 2: N=17). Within Cohort 2 (⩾40 kg; N=17), all pts completed the 24W-DEP and showed a similar safety profile to adult pts. A clinical cut-off date of Jan 2022 was applied to the analyses. Infusion-related reactions were reported in 11 pts (Grade 1: n=5; Grade 2: n=5; Grade 3: n=1), mostly observed at the first dose (10 pts, 91%). Serious adverse events were reported in three pts, with no new safety signals, or treatment discontinuations. Since OCR treatment start, no pts experienced clinical relapses. No new T1-Gd lesions were reported at W12; N/E T2 lesions were observed in 11 pts at W12 and three pts at W24, with none reported in pts that completed W48 to W96. The observed OCR PK and PD profile in patients ⩾50 kg was within the same range as in adult pts with MS.
Conclusions: In paediatric pts ⩾50 kg, 600 mg OCR showed a comparable PK/PD and safety profile to adult pts; this dose was selected for further investigation in the Phase III OPERETTA 2 study for this population. Enrolment of pts <50 kg to confirm the dose in this weight range is ongoing.

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P445
Natalizumab rapidly and strongly suppresses inflammatory disease activity in pediatric-onset multiple sclerosis

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Introduction: Pediatric-onset multiple sclerosis (POMS) is characterized by an aggressive course and early development of physical and cognitive disability.

Objectives: To evaluate the efficacy of natalizumab (NTZ) in POMS on clinical, radiological, and cognitive outcomes.
Methods: All POMS starting NTZ between and June 2015 and October 2021 were enrolled in this single-centre, prospective study. Patient were evaluated every 6 months both clinically and radiologically and followed up for 31.0±17.6 months (6-71 months). No radiological (i.e., no evidence of new/enlarging white matter lesions nor gadolinium-enhancing lesion) or clinical (i.e., no evidence of clinical relapse or EDSS worsening) evidence of disease activity (rNEDA and cNEDA respectively) were evaluated at 12 and 24 months. In addition, survival analysis for overall NEDA condition (i.e., radiological and clinical) was also analyzed. As control, an EDSS-, disease duration, and gender-matched cohort of adult-onset MS starting natalizumab during the same period was enrolled.
Results: Thirty-seven POMS were enrolled in our study. None of POMS and 2 adult-onset patients experience a clinical relapse (p=0.5) during the first 2 years of treatment. 29 POMS (78.4%) and 33 (76.7%, p=0.80) adult-onset MS fulfilled the rNEDA condition at 12 months, while between 12 and 24 months, 1 out of 26 POMS (3.8%) and 13 (30.2%) experienced a radiological disease reactivation (p=0.001). After 24 months of NTZ therapy, 80.8% of POMS and 60.5% of adult-onset MS fulfilled the NEDA condition (p=0.054). After month 24, no POMS experience any radiological disease reactivation. Median EDSS value was 1.0 at month 12 and 24, and it did not change significantly during the follow-up (p=0. 86). Indeed, only 2 patients had 0.5 increase confirmed after 6 months. NEDA condition was not associated to any clinical or demographic baseline variable. However, survival analysis revealed a trend for the risk of NEDA based on naïve- or switching- baseline status (Log rank p-value: 0.19).
Conclusions: NTZ is a highly effective treatment for POMS. While in adult-onset MS disease reactivation may occur during the first year of NTZ therapy, in POMS the effect of NTZ is rapid and stable. Our data further support the use of NTZ as first treatment choice in POMS.

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Clinical aspects of MS - Progressive MS

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Progression independent of relapse activity is the main determinant of disability accumulation in relapsing-onset multiple sclerosis patients

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Introduction: Disability worsening in multiple sclerosis (MS) may derive from relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA).
Objectives: We assessed whether RAW and PIRA events can coexist in a single patient in case of multiple confirmed disability accumulation (CDA) events.
Methods: Relapsing-onset MS patients with follow-up >/= 5 years (*n*=16,130) were extracted from the Italian MS Registry. CDA was defined by an increase in Expanded Disability Status Scale (EDSS) score confirmed at 6 months, and classified per temporal association with relapses. Predictors of PIRA and RAW were assessed using logistic multivariable regression analyses.

Results: Over a follow-up of 11.8 + 5.4 years, a total of 16,731 CDA events occurred in 8,998 (55.8%) patients. Overall, PIRA (n=12,175) accounted for 72.3% of CDA events. Focusing on 4,217 patients with at least 2 CDA events, only 279 (6.6%) had exclusively RAWs, whereas 2,100 (49.8%) had exclusively PIRAs. In the remaining 1,838 (43.6%) patients RAW and PIRA were variably interwoven over time. PIRA accounted for 67.2% of first CDA (2,100 out of 4,217), 77.1% of 2nd-4th CDAs (5,507 out of 7,151) and 86.9% of CDAs from 5th onwards (506 out of 582). Having exclusively RAW events was associated with female sex (OR=1.5; 95%CI 1.1-2.0; p=0.010), younger baseline age (OR=1.5; 95%CI 1.1-2.0; p<0.001), lower baseline EDSS (OR=0.97; 95%CI 0.96-0.99; p<0.001), shorter follow-up duration (OR=0.88; 95%CI 0.86-0.91; p<0.001) and higher number of relapses over-time (OR=1.20; 95%CI 1.17-1.24; p<0.001).

Conclusions: In a real-world relapsing-onset MS cohort, PIRA was the main determinant of disability accumulation. RAW events were relatively more represented in younger, less disabled, female patients and in early CDA events. The analysis on multiple RAW-PIRA events and the risk of conversion to secondary progressive MS is ongoing.

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Determine whether relapse associated worsening can be separated from PIRA using the MSIS-29 PRO in the UKMSR

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Introduction: Among multiple sclerosis (MS) patients, the contribution of progression independent of relapsing activity (PIRA) to disability accumulation remains to be fully established. The UK MS register (UKMSR) collects patient reported outcomes (PRO) and has developed a time-to-event outcome 'streaks' adapted for the MSIS-29 that mirrors the EDSS. Here we develop the concept of PIRA using the UKMSR registry data.
Objectives/Aims: We aim at determining whether relapse associated worsening can be separated from PIRA using the MSIS-29 PRO in the UKMSR.
Methods: Using the UKMSR, we extracted 'streak' data generated based on a set of criteria; A. minimum (30 days) and B. maximum (270 days) length between assessments with C. $\geqslant$3 assessments required. To generate a time-to-event outcome a 10-point change of a normalized MSIS-29 (0-100) defined a clinically relevant worsening of disease. PIRA 'streaks' were generated by removing any assessment occurring within 6 months from any relapse.
Results: 3652 subjects streaks were initially generated. After applying PIRA rules, we identified 218 subjects who reported relapse associated worsening (RAW), as well as 414 subjects, whose initial streak was of different length to their PIRA streaks (relapse associated shortening – RAS). In the remaining population with equal length streaks and PIRA streaks, 434 experienced a relapse (no relapse impact – NRI). Therefore, a final group of 2586 subjects had equal length streaks and PIRA streaks and had no relapse during the data collection period (PIRA). In the RAW, RAS and NRI groups, 89-92% patients had relapsing remitting (RR)MS course with a mean age ranging from 51-56 years, whereas the PIRA group had 66% RRMS with an older mean age 58.4 years. Those with RAW and NRI had a higher rate of worsening than the PIRA group ($p<0.0001$).
Conclusions: In the UKMSR, relapses impact on rates of disability progression, which can be quantified using the MSIS-29. Such impact can be separated from the progressive accumulation of disability as measured through PIRA.

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Amasia study: real-world data on MS therapy optimization with siponimod

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Background: Progressive motor dysfunction and cognitive decline are typical hallmarks of secondary progressive multiple sclerosis (SPMS). Siponimod, a selective sphingosine-1-phosphate receptor modulator, is specifically approved for the treatment of active SPMS in the EU. The non-interventional AMASIA study will provide real-world evidence on the long-term effectiveness and safety of siponimod as well as its impact on quality of life.
Methods: A large cohort of Siponimod treated active SPMS patients are followed over 3 years. Every 6 months, disability progression and cognitive changes are evaluated by the expanded disability status scale (EDSS) and the symbol digit modalities test (SDMT). Questionnaires from the perspective of patients, physicians, and relatives on disability progression, cognitive worsening and quality of life are documented.
Results: In this recent interim analysis we present results of therapy effectiveness and treatment satisfaction of approximately 570 siponimod patients observed in real-world in the AMASIA study 12 months after siponimod treatment initiation. The patients will be analyzed in subgroups based on their last pre-treatment regimen before starting siponimod, focussing on interferons, glatiramer acetate and oral baseline/platform disease modifying therapies (DMTs) (teriflunomid, dimethylfumarate). Previous results indicate that EDSS remains stable with siponimod therapy regardless of the previous therapy regimen. Treatment satisfaction is increased in patients that switched from interferons to siponimod.
Conclusions: AMASIA provides valuable insights into the effectiveness, tolerability, safety, and treatment satisfaction of active SPMS patients on siponimod in a real-life setting after having switched from first-line injectable and oral MS therapies.

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Identification of novel CSF measures of disease activity and chronic progressive biology in MS: results of the Ocrelizumab Biomarker Outcome Evaluation Study (OBOE): a randomised, open-label clinical trial

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Introduction: Cerebrospinal fluid (CSF) measures assessed before and after ocrelizumab (OCR) treatment may help identify novel markers of progressive disease biology and further elucidate mechanisms of anti-CD20 therapy in multiple sclerosis (MS).
Aims: To identify CSF biological measures of chronic progressive biology and assess the impact of OCR on measures of disease activity and progressive biology in persons with relapsing MS (pwRMS) or primary progressive MS (pwPPMS).
Methods: The OBOE (Ocrelizumab Biomarker Outcome Evaluation; NCT02688985) study is a prospective, multiarm, multicentre, open-label, randomised clinical trial assessing CSF biomarkers over 52 wks of treatment. In total, 100 pwRMS were randomised to arms with baseline (BL) and either 12-, 24- or 52-wk lumbar punctures (LPs) or assigned to a 12-wk interval, noninterventional control arm before initiating OCR; 31 pwPPMS were assigned to an arm with BL and 52-wk LPs. All patients received OCR 600 mg IV every 24 wks. CSF markers (neurofilament light [NfL] and heavy [NfH] chain, glial fibrillary acidic protein [GFAP]), brain MRI measures (T2 lesion volume [T2LV], brain and thalamic volume [THV], slowly evolving lesions [SELs]) and clinical outcome measures (including Expanded Disability Status Scale [EDSS]) were assessed.
Results: CSF GFAP and NfH correlated with MS disease severity (higher EDSS, higher T2LV, lower THV) and measures of chronic progressive biology (higher SEL count, lower T1 intensity within SELs), while lymphocyte activity/trafficking measures (sCD27, sBCMA, sTACI, CXCL10, CXCL13) correlated with relapsing biology (gadolinium [Gd+] lesion count) in the combined cohort (all $P<.05$). CSF NfL was associated with elements of both relapsing (Gd+ lesion count) and progressive biology (SEL count) (all $P<.001$). OCR reduced CSF measures of lymphocyte activation/trafficking (CD19+ B and CD3+ T cells, sCD27, sBCMA, sTACI, CXCL10, CXCL13), neuroaxonal injury (NfL, NfH) and some markers of glial activity (sTREM2, YKL-40), collectively reflecting both relapsing and chronic progressive biology, in pwRMS and/or pwPPMS (all $P<.05$).
Conclusions: This study identified CSF GFAP and NfH as novel putative biomarkers of MS progressive biology independent of acute relapse biology. These results also point to the broader impact of ocrelizumab on central nervous system–compartmentalised inflammation and neuronal and glial networks, in addition to its impact on peripheral B cells, in MS pathophysiology.

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P450

The late onset of emotional distress in people with progressive multiple sclerosis during the COVID-19 pandemic: longitudinal findings from the CogEx study

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Background: An earlier follow-up study from the CogEx rehabilitation trial showed little change in symptoms of depression, anxiety and psychological distress during the first COVID-19 lockdown compared to pre-pandemic measurements.
Objective: Here we provide a second follow-up set of behavioral data on the CogEx sample.
Method: Data were obtained from the CogEx study, a randomized controlled trial of exercise and cognitive rehabilitation in people with progressive MS involving 11 centres in North America and Europe. Participants completed the same COVID Impact Survey and self-report measures of depression, anxiety and MS symptoms that had been obtained during the first pandemic lockdown period.
Results: The average time between measurements was 11.4 (SD=5.56) months. Sample size declined from 131 to 72 largely because pandemic restrictions prevented data collection from sites in Denmark and England. There were no significant differences in age, sex, EDSS, disease course and duration between those who participated in the current follow-up study (n=74) and the group that could not (n=57). One participant caught Covid in the time between assessments. Participants now took a more negative view of their mental/psychological wellbeing (p=.0001), physical wellbeing (p=.0009) and disease course (p=.005) compared to their last assessment. Depression scores increased on the HADS-depression scale ($p = .01$) and now exceeded the clinically significant threshold of $\geqslant 8.0$ for the first time. Anxiety scores on the HADS remained unchanged. Poorer mental wellbeing was predicted by HADS depression scores (p=.012) and a secondary-progressive disease course (p=.0004).
Conclusions and Relevance: A longer follow-up period revealed the later onset of clinically significant depressive symptoms on the HADS and a decline in self-perceptions of mental and physical wellbeing associated with the COVID-19 pandemic.

Disclosure

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Anthony Feinstein is on Advisory Boards for Akili Interactive and Roche, and reports grants from the MS Society of Canada, book royalties from Johns Hopkins University Press, Cambridge University Press, Amadeus Press and Glitterati Editions, and speaker's honoraria from Novartis, Biogen, Roche and Sanofi-Genzyme.

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Amber Salter is a statistical editor for Circulation: Cardiovascular Imaging.

P451

Neuregulin-1 treatment facilitates neurogenesis and cognitive recovery in chronic cuprizone mouse model of multiple sclerosis

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Cognitive impairments such as memory loss, learning, depression and anxiety are common symptoms in progressive multiple sclerosis (MS). Degree of cognitive dysfunction in MS correlates with the extent of neurodegeneration and hippocampal atrophy. Continuous adult neurogenesis by neural precursor cells (NPCs) supports learning and memory, and its decline in progressive neurodegeneration underlies MS associated cognitive deficits. Thus, development of targeted treatments aimed at enhancing neuroprotection and NPC neurogenesis is a critical step towards promoting cognitive recovery in progressive MS. We previously demonstrated that Neuregulin-1 (Nrg-1), an important factor for development, maintenance and physiology of NPCs, neurons and oligodendrocytes, diminishes in demyelinating lesions of MS brain and MS mouse models. Restoration of Nrg-1 bioavailability by peptide treatment was able to promote oligodendrogenesis and remyelination in acute demyelinating lesions in mice. To date the impact of Nrg-1 on brain neurogenesis and cognitive behavior in chronic demyelinating conditions is unexplored. Here, we have performed *in vivo* and *in vitro* studies using a cuprizone-induced demyelination mouse model of progressive MS and relevant *in vitro* platforms to evaluate whether Nrg-1 treatment can attenuate neurodegeneration and promote hippocampal neurogenesis and cognitive recovery. We induced demyelination in Nestin-Cre reporter mouse that allows tracking NPCs and their progenies. In chronically demyelinated cuprizone mice, we found evidence of hippocampal atrophy that was associated with a significant increase in the expression of neurodegenerative markers and a concomitant decline in spatial and long-term memory assessed by Y-mase and novel object recognition tests. *In vitro* neurosphere assay on NPCs isolated from hippocampus of chronic cuprizone mice confirmed smaller number of NPCs and their reduced neurogenic capacity. We delivered Nrg-1 subcutaneously to the mice that received 10 weeks of cuprizone diet. Our tissue analysis after 4 weeks of daily Nrg-1 treatment showed a significant increase in proliferation and neurogenesis of hippocampal NPCs and attenuation of neurodegeneration. These findings identify, for the first time, the potential of Nrg-1 treatment in enhancing neurogenesis in progressive demyelinating conditions and its promise as a therapeutic strategy to promote cognitive recovery associated with progressive MS.

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P452

Analysis of long-term disability trajectories in patients with primary progressive multiple sclerosis

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Background: Several primary progressive multiple sclerosis (PPMS) natural history studies have emonstrated a large degree of heterogeneity in time from disease onset to high levels of disability.

Objective: We aimed to investigate the heterogeneity of long-term disability accumulation in a cohort of PPMS patients and to determine if there are differences between the trajectories of PPMS adjusting for sex.

Methods: All PPMS patients enrolled in RelevarEM registry who had $\geqslant 2$ Expanded Disability Status Scale (EDSS) score, were included in the analysis. A linear mixed model was used to model longitudinal EDSS scores. The best model (lower values better fit) was selected according to both Akaike Information Criterion and Bayesian Information Criterion fit indices and also to parsimony and clinical interpretability of the data. The same indices were used to determine which time function (linear, quadratic, square root, logarithm) best fit the EDSS trajectories over time. Fractional polynomials were used to obtain the best longitudinal fit of the dependent variable (EDSS). The root mean square errors were also calculated.

Results: A total of 125 patients with longitudinal data were included (median observations/patients was 3 (2-5). Mean age at onset of PPMS was 41 years ($\pm$ 11), and mean PPMS duration was 11 years $\pm$ 5.9. The male/female ratio was 1.4. Baseline EDSS was 2.97 ($\pm$1.16) in women and 3.11 ($\pm$1.20) in men, ($p = 0.50$); last EDSS was 5.66 ($\pm$1.56) in women and 6.06 ($\pm$1.56) in men ($p = 0.155$). The mean follow-up time was 10 years ($\pm$5.11) in women and 12.8 ($\pm$6.49) in men ($p < 0.001$). We found high heterogeneity between individuals (intraclass coefficient 43%), suggesting the usual clinical and radiologic variables are not enough to explain the variability in disability accumulation trajectories. We did not observe differences in disability trajectories stratified by sex, adjusted for potential confounders.

Conclusion: A high heterogeneity was found in the trajectory between individuals regarding disability accumulation. We have not found differences stratified by sex. As previously reported, there is a high variability between individuals that cannot be explained by the prognostic markers that we currently have.

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P453

Prevalence of motor and cognitive fatigability in progressive multiple sclerosis and related factors

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Introduction: A progressive MS (PMS) type is a negative prognostic factor for clinical outcomes. The majority of people with PMS present motor (e.g. walking) and cognitive impairments while also reporting fatigue. Objectively, fatigue can be measured by the capacity to sustain a motor or cognitive task which is termed fatigability. Currently, the prevalence of fatigability in PMS is unknown, as well as potential explanatory factors.

Objectives: To investigate the prevalence of walking and cognitive fatigability in PMS and to explore potential explanatory factors in a large sample of PMS patients with cognitive impairments.

Methods: this study analysed baseline data from the CogEx trial, including 298 PMS patients collected across 11 sites in Europe and North America. Inclusion criteria: diagnosis of PMS, 25-65 years old, Expanded Disability Status Scale$<$7, 1.28 SD or more below normative data for the symbol digit modality test (SDMT). Measures, cognitive: Brief International Cognitive Assessment in MS; physical: cardiorespiratory fitness, 6-minute walk test (6MWT) and physical activity (MVPA); Patient reported outcomes (PRO's): hospital anxiety depression scale (HADS), modified fatigue impact scale (MFIS), MS impact scale (MSIS-29), MS walk scale (MSWS-12). For walking fatigability (WF) the distance walk index (DWI$\leqslant$-10%) comparing distance at last and first minute during the 6MWT was used. Cognitive fatigability (CF), $\geqslant$10% decline in the SDMT (last 30sec compared to the first 30sec).

Results: Of 298 participants (83 PPMS, 215 SPMS), 153 (51%) presented WF (DWI=-28.9$\pm$22.1%) and 196 (66%) presented CF (-29.7$\pm$15%). Clinical outcomes were different between patients with *vs* without WF (EDSS=6.0 *vs* 5.0; disease duration=15.7 *vs* 12.9; SPMS, n=124 *vs* 91; use of assistive device, n=115*vs* 72). Patients with WF, presented higher scores of MSIS-29 physical, MFIS total and physical, and MSWS-12, and reduced 6MWT distance, cardiorespiratory fitness and physical activity. Patients with CF showed lower MSIS-29 physical and MFIS psychosocial than non-CF group. Cognitive functions were not different across motor or cognitive fatigability groups.

Conclusions: Half of the cognitively impaired PMS population presented WF which was related to overall higher disability, physical functions and fatigue. Two thirds of PMS showed CF which was not related to overall disability, physical and cognitive functions.

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Gary Cutter is a member of Data and Safety Monitoring Boards for Astra-Zeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Horizon Pharmaceuticals, Hisun

Pharmaceuticals, Mapi Pharmaceuticals LTD, Merck, Merck/Pfizer, Opko Biologics, OncoImmune, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Teva pharmaceuticals, VielaBio Inc, Vivus, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee). He is on Consulting or Advisory Boards for Biodelivery Sciences International, Biogen, Click Therapeutics, Genzyme, Genentech, GW Pharmaceuticals, Klein-Buendel Incorporated, Medimmune, Medday, Neurogenesis LTD, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion/Cerexis Pharmaceuticals, Roche, TG Therapeutics. Dr. Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. a private consulting company located in Birmingham AL.
Amber Salter is a statistical editor for Circulation: Cardiovascular Imaging.
Deborah Severijns no conflict of interest
Peter Feys is editorial board member of NNR, MSJ and Frontiers in Rehabilitation Sciences, provides consultancy to NeuroCompass and was board of advisory board meetings for BIOGEN.

Clinical aspects of MS - Natural course

P454
Characterization of the familial multiple sclerosis population in Israel

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Background: While most Multiple Sclerosis (MS) cases are sporadic (SMS), MS may cluster in families, a phenomenon known as familial MS (FMS), possibly due to aggregation of genetic, epigenetic and environmental factors. To date, no study, to the best of our knowledge, has characterised FMS in the Israeli population. Our hypothesis was that demographic and clinical features may differ between FMS and SMS.
Methods: In a retrospective study of 102 patients with FMS and 516 patients with SMS attending our clinic, ethnicity and gender distribution was compared. In a sub-cohort of 76 FMS and 76 SMS patients, matched for age, gender, ethnicity and disease course, clinical aspects were compared.
Results: In the total cohort, females comprised 75% of FMS and 67% of SMS patients. There was a significant difference in ethnic distribution between FMS and SMS; 54.9%, 21.6%, 15.7%, 6.9%, 1% and 73.8%, 16.1%, 5.2%, 2.3%, 2.1% for Jews, Muslims, Christian Arabs, Druze and others, respectively (p=0.00041). In the matched cohort, age at disease onset or diagnosis, frequency of positive oligoclonal bands (OCB) and comorbidity of other autoimmune diseases was comparable, with Hypothyroidism as most frequent comorbidity occurring in 7.9% of FMS and 10.5% of SMS. Most frequent symptom at disease onset was sensory disturbances in both groups, but significantly more in FMS (53% vs. 36%, p=0.024). Relapse rates throughout 15 years were comparable. 33% and 26% of FMS and SMS patients, respectively, had a progressive disease course (relapsing-progressive or secondary-progressive). MS Severity Score was higher in FMS (3.73 vs. 2.98, p=0.033), and Expanded Disability Status Scale tended to be significantly higher throughout 15 years following diagnosis, compared to SMS.
Conclusions: The proportion of Arab ethnicities among FMS is higher compared to among SMS, especially that of Christian Arabs, which is also higher compared to their frequency in northern Israel, where the clinic resides, and beyond our previous observation in the general MS population in Israel.
In comparison to SMS patients, disease progression and disability accumulation are faster in patients
with FMS.

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P455
Clinical and radiological concordance in sibling pairs with multiple sclerosis

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Introduction: Familial forms of Multiple Sclerosis (MS) represent 12.6% of all cases. However, little is known about intrafamilial concordance in both clinical and radiological phenotypes. To this day, most studies on this subject are limited to demographic data or general disability scores such as EDSS.
Objective: The goal of this study is to identify clinical and radiological correlations between siblings with MS.
Aim: To improve the understanding of familial forms of MS and to guide familial counseling for co-affected siblings.
Methods: 31 pairs of siblings in which both individuals have MS have been included. Each patient (n=62) received a comprehensive neuropsychological evaluation, clinical examination, and medical history assessment. Furthermore, a volumetric 3T MRI analysis was performed to quantify key volumes: whole grey matter, cortical grey matter, thalamic volume, and white matter T2-lesions. The identification of correlations between siblings is based on discordance ratio (r = pairwise mean absolute

difference/population mean absolute difference, concordant pair if r<1). Statistical significance of intra-pair concordance (r<1) was estimated using a Monte-Carlo simulation and clinical and radiological variables were adjusted for disease duration using linear regression models.

Results: A similar age of onset was found in sibling pairs (r=0.8; p=0.02). Adjusted for disease duration, cognitive functions were also concordant (r=0.77, p=0.01), including attention and working memory (digit span: r=0.68, p=0.001) mental flexibility and inhibitory processes (Stroop interference: r=0.75, p=0.007). Conversely, no significant intrafamilial concordance was found on motor scores or cerebellar dysfunction. Finally, volumetric magnetic resonance imaging showed a correlation within siblings on both thalamic (r=0.75, p=0.007) and whole grey matter atrophy (r=0.83, p=0.04) but not on white matter T2-lesion volume nor distribution.

Conclusions: Our results showed a selective intra-pair concordance in siblings with MS on cognitive functions as well as on thalamic and whole grey matter atrophy, consistent with recent results showing an association of polygenic risk scores with thalamic atrophy in a large database of patients with MS. The results presented here will help improve family counseling, especially with regard to prognostic aspects. Furthermore, they will help better the understanding of the role of genetics in the phenotypical expression of the disease

Disclosure

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Deciphering multiple sclerosis disability progression in the elderly: a multicenter cohort study

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Introduction: Little is known about Multiple Sclerosis (MS) in the elderly.

Objectives: Primary objective: to describe the dynamics of disability progression rates in MS patients between 65 and 75 years old (EDSS ⩾ 4.0, EDSS ⩾ 6.0, EDSS ⩾ 7.0 milestones). Secondary objectives: to describe secondary progression rates, relapses and other clinical, MRI and therapeutic data.

Methods: Patients between 75 and 77 years old with MS onset before age 65 followed in 3 main large OFSEP database centers (Bordeaux, Rennes and Lyon) were identified. Patients were contacted again to collect retrospectively clinical, MRI and therapeutic data (OLDMUS study, ClinicalTrials.gov Identifier: NCT03854123). Dynamics of disability progression rates (irreversible EDSS milestones) according to time were evaluated using unidimensional penalized parametric hazard models. Baseline was defined as the 65th birthday of each patient.

Results: 256/592 MS with available EDSS data from age 65 to 75 in the databases were included (65% female; mean EDSS 5.4 +/- 1.79 at age 65). There was no significant difference between the two populations (included / not included lacking EDSS data from age 65 to 75) in terms of demographic and clinical characteristics before the age of 65.

From age 65 to age 75, the cumulative probability of event (EDSS ⩾ 4.0; EDSS ⩾ 6.0; EDSS ⩾ 7.0) was 54.5% (35.6-75.6); 52.1% (39.8-65.7) and 44.0% (35.1-54.1).The event rates of disability progression (EDSS ⩾ 4.0; EDSS ⩾ 6.0) decreased from 65 years to 75 years. The yearly probability of EDSS ⩾ 4.0 (respectively EDSS ⩾ 6.0) was around 21.1% (8.7%) at baseline and was 1.8% (6.2%) at 75 years-old.

There was an almost linear decrease in secondary progression (SP) transition rates between 65 and 75 years of age, from a yearly probability of reaching a SPMS phenotype of 6.8% at baseline to 3.9% at 75 years.

From age 65 to age 70, the risk of relapse was similar (around 3.0% per year) and then decreased to 1.6% (0%-4.0%) at age 75.

Over the period 65 - 70 years, 13 patients with gadolinium (gd) enhancement were identified among the 75 patients who had an injected MRI (17.3%) whereas there were 5/57 (8.8%) over the period 70-75 years.

Conclusions: MS may switch off in the very-old patients, especially after the age of 70, with a decrease in disability progression, a decrease in the achievement of a secondary progression, very few relapses and uncommon MRI activity.

Disclosure

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Impact of COVID 19 vaccination or infection on disease activity in radiologically isolated syndrome cohort: the VaxiRIS study

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Introduction: Nowadays, mandatory vaccination in patients with multiple sclerosis (MS) is widely recommended. Regarding COVID19, the absence of specific warnings led to the proposal of vaccination in patients with inflammatory diseases of the central nervous system. However global vaccination hesitancy remains and potential effect of COVID19 vaccination on disease activity needs to be assessed.

Objectives: We aimed to evaluate if COVID19 vaccination or infection increased the risk of clinical conversion to multiple sclerosis or evidence of disease activity (EDA) in a cohort of RIS subjects.

Methods: This multicentric observational study is based on the RISC cohort. Data regarding COVID19 infection and vaccination has been collected between January 2020 and December 2021. We compared the occurrence of clinical conversion to MS and EDA in patients according to their vaccination status. The same analysis was conducted by comparing patients according to their history of COVID19 infection.

Results: 217 subjects with known vaccination status were included (Mean age: 44yrs, F/M sex ratio 2.7). 80% of subjects had a complete vaccination and 20% were incompletely or not vaccinated. Both groups did not differ regarding the main demographical data and known risk factors of conversion to MS. No difference was found concerning clinical conversion to MS in the vaccinated versus unvaccinated group (2.4% versus 2.5%, $p = 0.9747$). We did not observe any statistical difference regarding the rate of EDA in both groups.

20% of subjects had a history of COVID-19 infection. The rate of clinical conversion to MS in the infected compared to the non-infected group did not show any difference

The global conversion rate to MS in the whole RISC cohort in 2021 was 2.64%, which is comparable with the observed rates during the four previous years (5.75%, 2.55%, 4.79%, and 4.85% per year respectively).

Conclusions: Our study suggests that COVID19 vaccination does not increase the risk of clinical conversion to MS in RIS subjects and supports that immunization can be safely proposed for these patients.

Disclosure

Authors have nothing to disclose

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Self-reported disabilities and health-related quality of life in persons with multiple sclerosis in the Netherlands: 10-year prospective web-based study in a population-based real-life cohort

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Introduction: Long-term data on patient-reported disabilities and health-related quality of life (HRQoL) in multiple sclerosis (MS) and clinically isolated syndrome (CIS) are crucial to quantify the

risk of reaching major disability levels. As yet, this information is lacking for patients in the Netherlands.
Objectives: To study in Dutch MS and CIS patients self-reported disabilities and HRQoL.
Methods: A prospective web-based study with direct-to-patient recruitment. https://trialsearch.who.int/Trial2.aspx?TrialID=NL9520. Participants completed the Multiple Sclerosis Impact Profile (MSIP) and Multiple Sclerosis Quality of Life-54 item (MSQoL-54) questionnaires at 6-months intervals. Data at 5, 8 and 10 years follow up were analyzed using paired t-test and Wilcoxon signed ranks test with two-sided p<.001 to correct for multiple testing.
Results: ***Patients.***341 patients from all over the Netherlands enrolled themselves, 88% between May 2011 and September 2012. Seventy percent completed baseline and at least one follow-up MSIP (n=272) and MSQoL-54 (n=267) assessment. *Demographics* (n=272): female 201 (74%); mean (standard deviation, SD) age 45 (11) yrs. *Disease characteristics*: relapsing-remitting MS 177 (63.4%); secondary progressive 35 (12,5%); primary progressive 32 (11,5%); disease course unknown 28 (10.0); CIS 7 (2.5%). Disease duration: <5 yrs. 72 (26,5%); 5-15 yrs. 108 (39,7%); >15 yrs. 92 (33.8%). Expanded Disability Status Scale score (n=197): 0.0-4.0 116 (58.9%); 4.5-6.5 70 (35.5%); >6.5 11(5.6%). MSIP and MSQoL-54 data at 5, 8 and 10 yrs. were obtained from 135, 94 and 64, and 131, 91 and 61 patients with similar demographic and disease characteristics. ***MSIP*** mean (SD) scores at baseline: Muscle and Movement Functions 3.68 (SD 2.46), Excretion and Reproductive Functions 2.72 (2.17), Basic Movement Activities 3.17 (3.01, Activities of Daily Living 5.81 (5.23), Participation in Life Situations 3.62 (3.80), Environmental Factors 5.34 (3.89), Mental Functions 2.46 (1.73), Fatigue 1.84 (0.98),Pain 0.78 (0.85), Speech 0.35 (0.52), Vision 0.71 (0.85). At 5, 8 and 10 years the Environmental Factors score was substantially lower (-31%, -0.42 SD baseline; -40%, -0.55 SD baseline; -38%, -0.51 SD baseline) (p<0.001) than at baseline indicating a clinically relevant increase in support from environmental factors. Ad hoc analyses showed that the improvement occurred in the first two study years (period 2011-2014) and that it was caused by two items: increased support from professional help and from social security facilities; support from next to kin and healthcare facilities had not changed. Other MSIP scores showed no consistent changes. ***MSQoL-54*** mean (SD) Physical and Mental Composite scores at baseline: 56.38 (16.56) and 70.15 (18.11), resp. No significant changes in Physical or Mental scores at 5, 8 or 10 yrs.
Conclusions: Our data suggest stable self-reported disabilities and HRQoL in Dutch MS patients in the period 2012-2022. Unexpectedly, in the period 2011-2014 patients reported a substantial improvement of support from professional help and social security facilities, possibly related to an increase in nursing care and implementation of legislation.

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Peter Jongen is founding director of MS4 Research Institute.

Clinical aspects of MS - Epidemiology

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Relapse associated worsening and progression independent of relapse according to age in multiple sclerosis

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Background: Confirmed disability accrual (CDA) in Multiple Sclerosis (MS) results from worsening associated to relapse (RAW) and progression independent of relapse activity (PIRA). Age is a key determinant of disability accrual.
Objectives: To estimate age at and time to first CDA, RAW and PIRA events and the age-related EDSS longitudinal trajectories.
Methods: MS patients with ⩾5-year follow-up and ⩾1 visit every 6 months were selected from the Italian MS Registry. Time (years) from the date of the first visit and the date of birth to the first CDA, RAW and PIRA events were evaluated by using multivariable Cox models. Disability trajectories were evaluated by applying a longitudinal model for repeated measures (LMMRM) in 3 subgroups of patients stratified according to age at onset: ⩽18 years–pediatric onset (POMS), 19-49 years–adult onset, >49 years–late onset (LOMS).
Results: 3777 MS patients were included (median [IQR] age: 31.40 [24.7-39.4]). A first CDA event occurred in 1037 patients (27.5%). PIRA accounted for the 81.2% (n=842) of CDA events. Median ages at and median time to the first CDA, PIRA and RAW events were (33.9 [27.3-42.6], 2.0 [1.3-3.0]), (34.5 [27.6-43.2], 2.1 [1.3-3.1]) and (32.5 [24.9-40.4], 1.6 [1.0-2.7]), respectively. The cumulative incidence of CDA, PIRA and RAW increased with age, being 0%, 0% and 0% at 10 years; 1.7%, 1.3% and 0.5% at 20 years; 10.8%, 9.0% and 3.5% at 30 years; 25.3%, 21.6% and 7.8%

at 40 years; 44.1%, 39.1% and 14.4% at 50 years; 64.9%, 60.8% and 24.1% at 60 years; 81.3%, 78.7% and 27.7% at 70 years. LOMS patients (n=227) presented a 39% increased risk of reaching a first CDA event (p=0.05) and a 51% increased risk of reaching a PIRA event (p=0.03) in comparison to POMS (n=268); the risk of reaching a RAW event did not differ between the 3 groups. The LMMRM showed that the slope of disability trajectories significantly diverged between POMS and LOMS from the beginning of the follow-up (Year 1: delta-EDSS 0.3 (0.1-0.5), $p<0.001$) and reached the value of 0.6 (0.4-0.8, $p<0.0001$) at year 5.
Conclusions: Our results confirm that PIRA is the major determinant of CDA in MS across all age groups. The incidence of both PIRA and RAW events increases with age, which becomes much more evident between 20-30 years. POMS show a slower disability accumulation in comparison to older patients likely due to higher compensation mechanisms and better treatment response which decline with age.

Disclosure
All the authors report no competing interest related to this specific project. The authors report no conflicts of interest with respect to the contents of the current study, but
note that the patients in the study were treated with a number of disease modifying drugs and that authors report have received advisory board membership, speakers honoraria, travel support, research grants, consulting fees, or clinical trial support from the manufacturers of those drugs, including Actelion, Allergan, Almirall, Bayer Schering, Biogen, Celgene, Excemed, Genzyme, Forward Pharma, Ipsen, Medday, Merck, Merz, Mylan, Novartis, Sanofi, Roche, Teva, and their local affiliates.

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Central demyelination due to biologic agents in rheumatic diseases

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Introduction: Biologic agents are frequently used in rheumatic diseases such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), and rheumatoid arthritis (RA). Nowadays, central nervous system (CNS) demyelinating disease especially in patients who receive anti-TNF therapy is a topic of concern.
Objectives: To evaluate the annual incidence rate and clinical characteristics of CNS demyelinating disease in patients who receive biologic agents.
Methods: Patients who received biologic agents due to rheumatic diseases between January 2000 and September 2021 were identified in a retrospective manner and data of the patients who developed CNS demyelinating disease were recorded.
Results: 4838 out of 5926 patients -who attended regular follow-up visits- were included in the study. CNS demyelinating disease was observed in 7 patients during 19391 patient-years. 4 of 7 were diagnosed with multiple sclerosis (MS). Among the patients who developed CNS demyelination, the mean age was 44.28 ± 7.06SD, and the female to male ratio was 1,3:1. The mean age at rheumatic disease diagnosis was 35.14 ± 6.36SD and the mean age at neurological symptom onset was 40.85 ± 5.89SD. 71,4% (n: 5) of the patients had AS, 14,3% (n: 1) had PsA and 14,3% (n: 1) had RA. CNS demyelinating disease developed under adalimumab in 57%, infliximab in 29%, and secukinumab in 14% of patients. 6 out of 7 were under anti-TNF therapy. The mean duration was 13 months under causative drugs.
Conclusion: Annual incidence rate of CNS demyelinating disease was 36.1/100000 (95% CI: 16-71). The incidence rate of MS was calculated as 20.6/100000 (95% CI: 8-54) under anti-TNF therapy in our cohort, whereas it was reported as 3.4/100000 (95% CI: 1,8-6,3) in the Turkish population in 2021 ($p<0,05$). Therefore, clinicians must be aware of neurological signs and symptoms in patients who receive biologic agents.

Disclosure
Doruk Arslan has nothing to disclose. Basak Sayinalp-Arslan has nothing to disclose. Dr. Ozen has nothing to disclose. Dr. Bilgin has nothing to disclose. Dr. Ertenli has nothing to disclose. Dr. Kiraz has nothing to disclose. Dr. Kalyoncu has nothing to disclose. Dr. Karabudak has nothing to disclose. Asli Tuncer has nothing to disclose.

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Patterns of age and sex distribution by a population-based incidence and prevalence study of multiple sclerosis in the province of Palermo

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Introduction: Recent descriptive epidemiological studies indicate increasing rates of Multiple Sclerosis (MS), partly explained by changes in diagnostic criteria. It has been reported indeed an increasing age at onset of the disease despite a shorter time interval between onset and diagnosis.
Objective/Aims: To investigate by a large population-based study in the Province of Palermo, incidence and prevalence rates and their sex and age at onset distribution.
Methods:[A1] In the present study, the incidence and prevalence of MS in the Province of Palermo were investigated up to June 30th, 2018 (prevalence day) in a population of 1,252,588 inhabitants. Incidence rates were calculated for the period 2000-2018 (person/years). We obtained clinical and demographical data for each patient using a multi-source approach. Patients living and present in the study area who satisfied current validated criteria were included. Crude and age and sex-specific onset adjusted

prevalence and incidence rates (95% confidence intervals) were compared to those of previous studies. Sex and age at onset curves were also calculated.

Results: Crude onset adjusted prevalence was 169,9/ 100,000 inhabitants (95% CI 161,7-177,1), it was 114.5 men and 221.8 in women (W:M ratio 1.94), with a peak of nearly 300/100,000 in the age classes between 35 and 45 years of age. Mean annual incidence[A2] rates were 6.3/100.000 inhabitants (95% CI 6.0-6.7) for the whole population, with a peak of 13.8/100,000 in the age class between 25 and 29 years of age. Incidence was 4.1/100,000 in men (95% CI 3.7-4.5) and 8.5/100,000 (95% CI 8.0-9.1) in women (sex ratio 2.09). Progressive disease onset was observed in 9.7% of incident cases with no clear differences within sexes. The peak of age at onset of incident cases was observed in the age classes between 25-29 and 30-40 years of age[A3]. As expected, the trend to a higher age at onset was more pronounced in prevalent cases where it was observed between 40 and 49 years of age, despite the shortening of the time interval between onset and diagnosis in the last five years of observation compared to the previous.[A4]

Conclusion: This large population-based study performed in Sicily[A5] confirms an increasing trend of incidence and prevalence of MS with rates considerably higher compared to all previous studies and among the highest in the Mediterranean area except for Sardinia. This study also confirms a trend through a higher age at disease onset.

Disclosure

The authors report nothing to disclose with respect to the present study.

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Examination of racial disparities in multiple sclerosis clinical care

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Introduction: Non-Hispanic blacks (NHBs) with multiple sclerosis (MS) experience substantially worse neurologic outcomes than non-Hispanic whites (NHWs). Existing data reveal disparities in which NHBs experience lower quality of care, poorer patient-provider communication, and different care recommendations. This is particularly detrimental because lower quality care and inadequate communication impede patient engagement in decision-making, adherence to recommendations, and satisfaction with care, thereby leading to poorer health outcomes.

Objectives: In this study, we seek to examine disparities in the quality of care of NHBs and NHWs with MS.

Aims: We aim to quantify disparities in the quality of health care and examine differences in patient adherence to recommended plan of MS care in NHBs and NHWs with MS.

Methods: We examined patient charts across sites at the Johns Hopkins MS Precision Medicine Center of Excellence and the John L. Trotter MS Center at Washington University in St. Louis to assess for racial disparities in MS care. Provider documentation in patient medical records were reviewed. Differences in the level of care of initial visits, patient adherence to recommended follow-up visit frequency, and adherence to disease and medication safety monitoring plans of NHBs and NHWs evaluated between 2013-2021 were assessed.

Results: The charts of 26 NHBs (92% female, age M±SD=49.0+11.2 years) and 25 NHWs (72% female, age M±SD=56.6+11.6 years) were assessed. There were no significant differences between NHBs (16/26) and NHWs (16/25) who received the highest Level of Care, with negligible effects (Cohen's d = .050). Of those recommended to have monitoring, 95% (19/20) of NHBs and 100% (18/18) of NHWs completed monitoring as recommended within 1 year of the index visit. Of those with documented follow up, 72.7% (16/22) NHBs attended the next recommended visit as compared to 90.5% (19/21) of NHWs. The mean time between the index visit and follow up visit was shorter for NHBs (M±SD=258.9±141.7 days) when compared to NHWs (M±SD=303.2±182.9 days), with small effects (Cohen's d = .271; 95% CI: -0.28-0.82).

Conclusions: In this biracial cohort of patients, the data suggest that health disparities may not arise at initial care visits, but over time. Factors such as access to care, and follow-up may impact outcomes more profoundly. Nonetheless, this work will provide a basis for further longitudinal analyses to determine if disparities arise over time.

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P463

Risk of stroke in multiple sclerosis and neuromyelitis optic spectrum disorder: a nationwide cohort study in South Korea

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Background: People with multiple sclerosis (MS) are more likely to develop stroke than those without. However, little is known about the association between neuromyelitis optica spectrum disorder (NMOSD) and the risk of stroke.

Objectives: We aimed to estimate the risk of stroke in patients with MS and NMOSD in South Korea.

Methods: Data from the Korean National Health Insurance between January 2010 to December 2017 were analyzed. A total of 1,541/1,687 adult patients with MS/NMOSD, who were free of stroke were included. Matched controls were selected based on age, sex, and the presence of hypertension, diabetes mellitus, and dyslipidemia.
Results: The risk of developing stroke was 2.78 times higher (adjusted hazard ratio [aHR], 95% CI = 1.91–4.05) in patients with MS compared with controls matched by age, sex, hypertension, diabetes mellitus, and dyslipidemia. The risk of stroke in NMOSD was also higher than that in matched controls (aHR = 1.69, 95% CI = 1.10–2.61) and not statistically different from that of MS (p = 0.216). The patients with MS had a higher risk for either of ischemic or hemorrhagic stroke (HR = 2.63 and 2.93, respectively), whereas those with NMOSD had a higher risk for ischemic stroke (HR = 1.60) only with marginal statistical significance.
Conclusions: The risk of stroke is increased in patients with MS and NMOSD and seemed comparable between the two conditions. This is the first study that estimates the risk of stroke in patients with MS and NMOSD within the same population.

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P464
Rising prevalence of multiple sclerosis in Israel

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Introduction: Increase in multiple sclerosis (MS) prevalence is a worldwide trend, which can be attributed in part to increased survival of both people with MS (pwMS) and the wider general population and also to improvements in the diagnosis and reporting of MS. In Israel there is currently no registry of pwMS. Clalit Health Services (CHS) is Israel's largest health care organization, providing universally funded health care for about half of the Israeli population.
Aim: To develop an optimal algorithm to identify pwMS using CHS database and to validate it against a gold-standard diagnosis by expert neurologists.
Methods: People with a possible diagnosis of MS were identified in CHS database according to the following criteria: ICD code 340 (MS) in any diagnosis field (community, hospital and established diagnoses) or at least a single dispense of an MS specific disease modifying treatment (DMT).The electronic medical records (EMRs) of a random sample of 25% of this population (sample size=1387; population size=5447), stratified by age and sex were examined to determine positive predictive value (PPV) of various case ascertainment definitions. Another age- and sex-stratified random sample of about 15% of confirmed pwMS under our care (sample size=221; population size=1296) were searched in the CHS database to determine database sensitivity (Sn). Finally, an age- and gender- stratified random sample of 40% of people without MS, who were referred for evaluation with suspected MS (sample size=204, population size=459) were searched in CHS database to evaluate database specificity (Sp).
Results: The best case definitions to retrieve pwMS in CHS database were: a) at least one dispense of a DMT (PPV=95%, Sn=87%, Sp=97%) and b) ICD code 340 as an established diagnosis or at least one dispense of a DMT (PPV=87%, Sn=92%, Sp=90%). Using the last definition there were 2263, 2643 and 3831 pwMS in the database by the end of 2010, 2013 and 2020, respectively. These numbers translate into prevalence of 57, 63 and 82 per 100,000 population by the end of 2010, 2013 and 2020, respectively.
Conclusion: Prevalence of MS in Israel is rising, in line with the global worldwide trend. The case ascertainment definitions that were validated herein will enable to harness CHS database for future population based studies of MS in Israel.

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P465
Ensemble genetic machine learning identifies multiple sclerosis genetic loci associated with future worsening of disability

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Introduction: Limited studies have been conducted to identify and validate multiple sclerosis (MS) genetic loci associated with disability progression.
Objectives: To predict future worsening of disability in MS using robust and clinically applicable ensemble genetic machine learning models.
Aims: To identify MS genetic loci associated with worsening of disability over time, and to develop and validate ensemble genetic machine learning model(s) to identify people with MS (PwMS) at risk of future worsening.
Methods: We examined associations of*208*previously established MS genetic loci with the risk of worsening of disability using penalised Cox models. Using the identified loci, we learned multivariable mixed-effects machine learning ensembles, and developed robust genetic decision rules for predicting worsening events using a training cohort of PwMS (N=202), and validated the obtained predictions in an external cohort (N=67).
Results: We found 7 genetic loci (*rs7731626: HR=0.92, P=2.4x10^{-5};rs12211604: HR =1.16, P=3.2x10^{-7}*; *rs55858457: HR=0.93, P=3.7x10^{-7}*; *rs10271373: HR=0.90, P=1.1x10^{-7}*; *rs11256593: HR=1.13, P=5.1x10^{-57}*; *rs12588969: HR=1.10, P=2.1x10^{-10}*; *rs1465697: HR=1.09, P=1.7x10^{-128}*) associated with worsening of disability; most of which were located near or tagged to*13*genomic regions enriched in peptide hormones and steroids biosynthesis pathways by positional and expression quantitative trait loci (*eQTL)*mapping. The derived ensembles provided a set of genetic decision rules that can be translated to provide additional prognostic values to existing clinical predictions, with the additional benefit of incorporating relevant genetic information into clinical decision making for PwMS.
Conclusions: The present study extends our knowledge of MS progression genetics and provides the basis of predicting future disability progression for PwMS.

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P466
Influence of socio-economic status on excess mortality of multiple sclerosis

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Introduction: Low socio-economic status (SES) has been linked to higher mortality in multiple sclerosis (MS) patients. The difficulty lays in determining whether differences in mortality between lower and higher SES are due to MS-specific mortality or due to differences in other-cause mortality. It is crucial to use methods that allow an estimation of the influence of SES on MS-specific

mortality to avoid revealing differences due to SES in all-cause mortality, with a preference for excess hazard models to avoid using sometimes unreliable death certificate information.
Objective/aims: To examine excess mortality according to SES in order to measure the influence of socio-economic deprivation on MS-related mortality.
Methods: A retrospective observational cohort design was used, with recruitment from 18 French MS expert centres participating in the Observatoire Français de la Sclérose en Plaques.All patients living in metropolitan France with a definite or probable diagnosis of MS according to either Poser or McDonald criteria and an onset of disease between Jan-1960 and Dec-2015 were included. SES was measured by an ecological index, the European Deprivation Index (EDI). Excess death rates were studied according to SES using additive excess hazard models with multidimensional penalised splines.
Results: A total of 34,169 patients with MS were included (88% relapsing onset MS (R-MS), 12% progressive onset MS (PPMS), Female/Male sex ratio 2.7 for R-MS and 1.3 for PPMS). Mean age at disease onset was 31.6 (SD=9.8) for R-MS and 42.7 (SD=10.8) for PPMS. At the end of follow-up, 1,849 patients had died (4.4% for R-MS and 13.2% for PPMS). A socio-economic gradient was found for R-MS; more deprived patients had a greater excess death rate. At thirty years of disease duration, net survival for less deprived R-MS patients (EDI=-6) was 93.4% (95% confidence interval(CI)[90.1%-95.7%]) for men and 95.4% (95%CI[93.1%-96.9%]) for women. For most deprived R-MS patients (EDI=12), it was 80.9% (95%CI[75.3%-85.4%]) for men and 86.3% (95%CI[82.5%-89.4%]) for women. No clear socio-economic mortality gradient was found in PPMS patients.
Conclusion: SES was found to be associated with excess mortality in patients with R-MS. The mechanisms behind this association merit further exploration with information on treatments and disability. Improvements in overall care of more socio-economically deprived patients with MS could help reduce these SES inequalities in MS-related mortality.

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Prevalence of chronic comorbidities in people with Multiple Sclerosis: descriptive study based on administrative data in Tuscany (Central Italy)

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Introduction: The identification of comorbidities has a key role in the management of people with multiple sclerosis (PwMS), as they can worsen prognosis and quality of life, influence disability status, healthcare utilization and hospitalization, treatment decisions and response, and increase the risk of death. Comorbidities are common in PwMS due to the disease itself or related to the side effects of drugs, or to behavioural risk factors. Further, chronic diseases may be more easily diagnosed in PwMS due to higher number of follow-up and a widespread use of the health service than general population (GP).
Aims: Among the currently available sources to capture comorbidities, administrative databases are the most cost- and time-saving, as they cover the whole population for a long period, and they are routinely collected for the health system management. The aims of the present study were to evaluate the prevalence of common chronic comorbidities in PwMS in Tuscany (Central Italy) and to compare it with the one in GP.
Methods: Prevalence of comorbidities, including diabetes, chronic obstructive pulmonary disease (COPD), hypertension, stroke, heart failure (HF), cardiac infarction (CI) and ischemic heart disease, was assessed in PwMS and in GP resident in Tuscany, aged >20 years, using validated case-finding algorithms based on administrative data (hospital discharge, drug dispensation, exemption and home and residential long-term care registers).
Results: In total, we identified 8,274 PwMS. Among them, 34% had at least one comorbidity, with hypertension being the most common (28.5%). Comparing PwMS with GP, we observed statistically higher prevalence rates in PwMS for stroke in both sexes, for diabetes and COPD only in females, and for hypertension only in males; whereas CI were more common in GP for both sexes, and HF only in female.

This increased risk was especially evident in the young and intermediate age groups, where MS may play an important role as risk factor for some comorbidities.In PwMS, as well as in GP, prevalence of chronic diseases was higher in males and increased with age.
Conclusions: Comorbidities frequently coexist with MS and they may have an impact on this complex disease, from the health, clinical and socio-economic points of view. Therefore, a routine screening for chronic comorbidities should be a crucial step in the clinical practice, as well as the promotion of healthy lifestyles to prevent the onset and to reduce their burden.

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P468
Patterns and risks for cognitive impairment in multiple sclerosis: a UK biobank study

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Introduction: Cognitive dysfunction is common in people with Multiple Sclerosis (MS). It is unclear whether MS preferentially affects specific cognitive domains, or to what extent risk factors for cognitive impairment in the general population overlap with those in MS.
Objectives/Aims:
1. To determine patterns of cognitive impairment in MS
2. To assess the role of conventional dementia risk factors in MS-associated cognitive impairment
Methods: We obtained linked healthcare records, demographic data and cognitive test outcomes for 2500 people with MS and 10000 age and sex-matched healthy controls without neurological disease from UK Biobank. We evaluated the effect of MS on cognitive test outcomes using linear regression models, adjusted for age, sex, ethnicity and deprivation. We then evaluated the effect of dementia risk factors on cognitive test outcomes, with and without MS in the models.
Results: The study population had a mean age of 55 (SD 7.7) and was predominantly female (73%).
MS was associated with a specific pattern of cognitive impairment, characterised by diminished processing speed, executive function and prospective memory. Working, short-term and episodic memory were relatively preserved.
MS was independently associated with increased (slower) reaction time (mean difference (MD) 40ms, 95%CI 35-46ms, $p<0.05$). This effect persisted after adjusting for conventional dementia risk factors.
The individual effects of dementia risk factors on reaction time were small in comparison to the effect of MS. BMI, air pollution and hearing loss had no significant effect on reaction time, while depression (MD 13.13ms), diabetes (MD 10.56ms), hypertension (MD 6.93ms), loneliness (MD 8.50ms), fewer years of full time education (MD 1.40ms), smoking (MD 0.18ms) and physical inactivity (MD 0.0014ms) were independently associated (all $p<0.05$) with longer reaction times across the cohort.
Conclusion: Using a large cohort of deeply-phenotyped UK adults, we observed a distinct pattern of cognitive impairment among people with MS compared to healthy controls. Longer reaction time was independently associated with MS after adjusting for conventional dementia risk factors. Further work will examine how MS-specific factors, such as physical disability, disease duration, and treatment, influence cognitive outcomes.

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P469
Frequency and risk factors of fingolimod rebound – a retrospective population-based study

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Introduction: Based on reports in small cohorts, the frequency of fingolimod (FTY) rebound, a phenomenon of severe disease activity following FTY discontinuation, has varied between 5-20%. Large population-based cohorts have not been analyzed, and to our knowledge only one study has addressed risk factors for rebound.
Objectives: FTY discontinuation results in rebound risk, but the frequency and risk factors of a rebound are still unclear.
Aims: To analyze the frequency and risk factors of an FTY rebound in a population-based setting.
Methods: We searched the Finnish MS-register for patients who were previous or current users of FTY and who lived in the hospital district of Helsinki and Uusimaa in November 2020 (population of 1.7 million). We assessed medical records and collected basic demographic data for the whole cohort. Of patients who discontinued FTY, we collected clinical, MRI and laboratory data. Patients who used FTY for less than 6 months were excluded. Criteria for rebound were to have either an increase of at least 2 EDSS points during a relapse occurring within 6 months from FTY cessation, or to have more than one relapse within 6 months after FTY discontinuation and one of these relapses was the most severe in the patient's history.
Results: Among 3840 patients, we found 331 patients who had started to use FTY. In total, we discovered 114 events of discontinuation: 81 patients (71%) discontinued without a relapse, 21 (17.5%) experienced a relapse not fulfilling rebound criteria, and 12 patients (10.5%) experienced a rebound. The median time to a rebound was 9.9 weeks (range 5.9-15.9) and 8.5 weeks (1.3-23) to an ordinary relapse. The rebound group were younger at diagnosis and had used FTY for a longer time before discontinuation compared to the group without a relapse. Change in lymphocyte counts between discontinuation and relapse was smaller in the rebound group as compared to the ordinary relapse group (p=0.037).
Conclusions: In this study, 10.5% of patients experienced a rebound, which is in line with previous estimates of 5-20% in smaller cohorts. Younger age at diagnosis and longer exposure to FTY were risk factors for a rebound relapse. The differences in blood lymphocyte levels indicate that a rebound and an ordinary relapse after FTY discontinuation might be distinct pathophysiological phenomena and this warrants further research.

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Is benign multiple sclerosis truly benign? A socioeconomic investigative nationwide cohort study

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Introduction: A subpopulation of patients with multiple sclerosis (MS) experience a benign disease course with limited disability accumulation. This is termed benign multiple sclerosis (BMS) and is clinically recognized but has no formal diagnostic criteria and the merit of the term has been debated. Previous studies have demonstrated that patients with MS have a substantially higher risk of socioeconomic decline, however, it is unknown if this holds true for patients with BMS. The ability to work requires retained ambulatory function, cognition, and limited fatigue consistent with the concept of BMS. Receiving disability pension represents a significant loss of function and meaningful patient centered outcome.
Objectives: To compare the risk of disability pension in patients fulfilling a consensus-definition for BMS with matched controls from the Danish background population.
Methods: Using the nationwide Danish Multiple Sclerosis Registry, we identified patients with BMS defined as ten years of disease duration with no expanded disability status scale (EDSS)-records above three. The study period was from 1. January 1998 to 1. January 2021. Main inclusion criteria were a ten-year disease anniversary in the study period, 30-64 years of age at baseline and no prior history of disability pension. Patients were matched 1:10 with controls from the background population on age, sex, educational level, municipality and calendar year. Individuals were followed until disability pension, censoring or a competing risk (death, 65 years of age, emigration). We estimated the absolute risk and adjusted cause-specific hazard ratio (HR) of receiving disability pension.
Results: The cohort of BMS patients consisted of 1868 patients. The mean age was 43.1 (SD: ±8.0) years and the male-female ratio 1:2. The mean EDSS was 1.4 (SD: ±0.9) and 87% were receiving treatment with a disease modifying drug. The absolute risk of receiving disability pension 20 years after disease onset was 13.7% (95% CI: 11.6-16.1) for the BMS-patients, significantly higher than that of the controls from the background population: 3.9% (95% CI: 3.5-4.3), P<0.001. Correspondingly, the BMS-patients displayed a fourfold increase in the hazard of receiving disability pension compared with controls, HR: 4.1 (95% CI: 3.4-4.8).
Conclusions: Patients with BMS have a significantly higher risk of receiving disability pension compared to matched controls from the Danish background population.

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Untangling the effect of relapse on disability worsening

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Introduction: The impact of relapses on multiple sclerosis (MS) disability worsening has been extensively studied, with a consensus on the impact of relapses in the short-term and a debate on the long-term impacts. In previous studies relapses as a variable was used as a binary or a frequency variable.
Objective: To estimate the short- and long-term impact of individual relapses on MS disability worsening.
Aim: To investigate the patterns behind accumulation of physical disability in association with relapse.
Methods: From theSwedish MS registry (SMSreg),we extracted information ofRRMS patients with disease onset between 1990 and 2019. Variables included EDSS score,relapse and treatment. Flexible relative survival analysiswas used to study the effect of individual relapses as atime-varying co-variantonreaching the EDSS milestones 3, 4 and 6(long-term effect). In addition, using a linear mixed model we evaluated the changes in the EDSS score in in the five months pre- and post-relapse (short-term effect).
Results: From 7482 patients with $\geqslant$1 relapse and $\geqslant$3 EDSS scores registered, we found an increased risk of reaching sustained EDSS 3(HR=1.09, 95%CI: 1.07 to 1.10, P$<$0.001) and 4 (HR=1.04, 95%CI: 1.03 to 1.06,P$<$0.001)with each additional relapse, but no effect on reaching EDSS 6(HR=1.00, 95%CI: 0.98 to 1.02, P$>$0.05). Furthermore, we observed a gradual increase in EDSS from two months pre-relapse onset peaking at one month post-relapse. The EDSS peak was highest in non-treated patients (β-coef: 0.84, 95%CI: 0.79 to 0.89).On average, the increase in EDSS diminished gradually and remained above the pre-relapse state at 4 monthspostrelapse(β-coef: 0.22, 95%CI: 0.17 to 0.26). Patients treated with monoclonal antibodies had the lowest change in EDSS during the whole post-relapse period, their EDSS at four month post relapse was similar to the pre-relapse EDSS (β-coef: 0.03, 95%CI: -0.20 to 0.26).
Conclusion: Relapses are associated with short- and long-term disease worsening in MS. The choice of treatment effects the EDSS increase during relapse as well as improvement during post relapse period.

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Clinical aspects of MS - MS and gender

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Ponesimod compared with teriflunomide in female patients of childbearing age with relapsing multiple sclerosis: Results of the phase 3 OPTIMUM study

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Background: Multiple Sclerosis (MS) is more prevalent in women and has a significant impact on family planning.
Objectives: To present a post-hoc, subgroup analysis of safety and efficacy on ponesimod (PON) vs teriflunomide (TER) in reproductive-age women with MS from the phase 3, multicenter, double-blind, active comparator, randomized OPTIMUM study.
Methods: Patients were randomized (1:1) to 20-mg PON or 14-mg TER once-daily for up to 108 weeks. The primary endpoint was annualized relapse rate (ARR). Secondary endpoints included change in the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ–RMS), number of combined unique active MRI lesions per year (CUALs), and time-to-12- and 24-week confirmed disability accumulation (CDA). Exploratory end points included the % change in brain volume and no evidence of disease activity (NEDA-3 and NEDA-4) status. Safety and tolerability were assessed.
Results: Of 1133 patients enrolled in OPTIMUM study, 602 were females of childbearing potential [ages 18-45], randomized to either PON 20 mg [294; 48.8%] or TER 14 mg (308; 51.2%). Groups were well matched by demographic and disease characteristics. Baseline/disease characteristics were similar. For females of childbearing age, the relative rate reduction (RRR) for PON vs

TER in the ARR was 36% (0.198 vs 0.309, p<.001). The mean difference in FSIQ-RMS receiving PON vs TER was -4.66 (-0.02, 4.64; p<.003). The RRR for PON vs TER in CUAL was 41%; (1.63 vs 2.76, p<.001) and the reduction in time to 12-week and 24-week CDA risk estimates was 31% (9.5% vs 13.3%; p=0.13) and 26% (7.5% vs 9.7%; p=.29), respectively. Brain volume loss at week 108 was lower by 0.44% (−0.86% vs −1.30%; p<.001); the odds ratio for NEDA-3 was 1.76 (23.9% vs 15.1%; p=.007) and 2.18 (12.0% vs 5.9%; p<.005) for NEDA-4.At least one treatment-emergent AE was reported in 87.8% and 89.9% and serious AEs in 10.2% and 7.8% in PON and TER female patients. Treatment discontinuations due to adverse events in the PON group was 24 [8.2%] and 22 [7.1%] with TER. There were no deaths.

Conclusion: In this subgroup analysis PON vs TER in females of childbearing age with MS, both safety and efficacy were consistent with the overall OPTIMUM results. PON may be a safe and effective therapy for this patient population.

Disclosure

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Could follicle reserve disclose cognition and physical disability in MS?

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Introduction: The close relationship of MS with sex hormones draws attention to the possible relationship of follicle reserve on both the physical and cognitive course of MS.

Aims: In this study, it was aimed to investigate the correlation between follicle reserve and physical and cognitive status in women with MS.

Methods: Relapsing or progressive MS patients were included in the study, and their physical status was evaluated by EDSS. In addition to sex hormones, antimullerian hormone (AMH) levels were measured to evaluate the follicle reserve, and antral follicle counts were evaluated by transvaginal USG. The cognitive status was evaluated with the Brief International Cognitive Assessment for MS (BICAMS) battery and Trail Making Test (TMT).

Results: A total of 50 MS patients were included in the study. A negative correlation was found between EDSS and FSH, AMH, and antral follicle count (respectively; p=0.014, p<0.0001, p=0.001). A negative correlation was observed between EDSS and AMH and in the number of antral follicles (respectively; p=0.01, p=0.029). However, when the effect of age and disease duration was removed, no significant relationship was found between the amount of IVMP and the level of AMH. When the relationship between cognitive tests, sex hormones and the number of antral follicles is evaluated by taking the effect of age and disease duration; a negative correlation was observed between BVMT-R and antral follicle number (p=0.027). A positive correlation was observed between the duration of TMT and the number of antral follicles (p=0.044).

Conclusions: When evaluated together with the negative correlation between AMH/antral follicle number and EDSS, and the correlation between cognitive tests and follicle reserve, our results show that the course of the disease is related to the follicle reserve regardless of age, and that the high-dose steroid treatment does not have a negative effect on the follicle reserve.

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Clinical aspects of MS - Pregnancy in MS

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Use of pregnancy-related healthcare in women with multiple sclerosis

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Introduction: Few studies have described the level of adherence to recommendations related to pregnancy care in women with multiple sclerosis (MS). Such guidelines from general population aim to improve quality of antenatal care to reduce the risks of stillbirths and pregnancy complications. French health authorities recommend for women with MS regular follow-up by a gynecologist-obstetrician.

Objectives: Our objective was to measure the level of compliance to pregnancy-related care recommendations among women with MS, using data from the French national insurance database.

Aims: This study aims to identify a potential gap in management of pregnancy in MS.

Methods: This retrospective cohort study included all pregnant women with MS between 2010 and 2015 in France. Using the national insurance database, we were able to identify visits with gynecologists, midwives and general practitioners (GP), as well as ultrasounds and biological tests. Based on the Adequacy of Prenatal Care Use (APNCU) and the Content and Timing of care in Pregnancy (CTP) indexes, a new tool adapted to French recommendations was developed to measure the antenatal care trajectory, and classify it as adequate or not. Explicative factors were identified using multivariate logistic regression models. A random effect was included, as women may experience several pregnancies over the period.
Results: Overall, 4,804 women with MS accounting for 5,448 pregnancies ending in live births were included. When considering only visits with gynecologists/midwives, 2,277 pregnancies (41.8%) were considered as "Adequate", and when adding visits with GP, it increased to 3,646 pregnancies (66.9%). Multivariate models showed that multiple pregnancy and higher medical density were associated with better adherence to recommendations. In contrast, women aged 25-29 years and over 40 years had lower adherence, as people with specific insurance coverage (related to low income), agricultural and self-employed workers. Details of visits and tests will be provided. Only 87 women (1.6%) did not have any visit or biological test. In 50.1% of pregnancies, women had at least one visit with a neurologist during the pregnancy.
Conclusions: Despite French recommendations, it is obvious that many women rather consult GP. It seems to be linked with density of gynecologists, but may also reflect women's preferences. The present study cannot reveal if the lack of adherence is related to MS or similar to that of general population.

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Comparison of anti-CD20 therapies versus other disease modifying therapies on postpartum disease activity in patients with multiple sclerosis

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Introduction: Disease activity in multiple sclerosis varies during pregnancy. Pregnancy, especially in the third trimester, appears to be protective against relapses. However, the postpartum period is associated with an increased risk of disease activity particularly within the first three months after delivery. The appropriate treatment in the peripartum period is still not known. Reducing the risk of harmful drug exposure to the fetus while reducing postpartum disease activity is important to minimize patient disability and optimize the health of the newborn. Anti-CD20 therapy has prolonged biologic activity that may protect throughout pregnancy and the vulnerable postpartum period, while reducing exposure to the fetus. Practice at the University of Colorado has included pregnancy planning 1-5 months after anti-CD20 therapy with re-treatment 1 month postpartum.
Objectives: We compared postpartum disease activity with anti-CD20 therapy versus other therapies.
Methods: We retrospectively reviewed cases from the University of Colorado, and compared postpartum disease activity from patients who have been treated with an anti-CD20 therapy versus other disease modifying therapies prior to or after conception. We evaluated disease activity (relapses and MRI activity) in the 2 years prior to pregnancy, during pregnancy, and up to 1 year postpartum. The primary outcome is development of new T2 hyperintense lesions or gadolinium enhancing lesions in the post-partum MRI.
Results: We report an interim analysis of 20 patients who were treated with an anti-CD20 therapy in the prepartum period. Seventeen of the 20 had stable post-partum MRI scans. Two of the 3 subjects with new lesions did not have a baseline MRI while on anti-CD20 therapy prior to conception. One of 20 subjects (5%) had one new confirmed MRI lesion while on anti-CD20 therapy. In the comparison group, 34 patients had postpartum MRIs for review. Seventeen of the 34 (50%) had new lesions on postpartum MRIs, and 7 subjects (20.5%) had multiple new lesions. Treatments were heterogeneous and included: no disease modifying therapy in the year prior to conception, fingolimod, natalizumab, glatiramer acetate, dimethyl fumarate, interferon beta 1a. Additional subjects will continue to be included.
Conclusions: This data suggests that anti-CD20 therapy in the pre-conception stage reduces postpartum disease activity. Further studies are needed to confirm these findings.

Disclosure
No relevant disclosures

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Brain MRI activity during the year before pregnancy can predict long term clinical worsening in females with multiple sclerosis

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Introduction: There are fewer multiple sclerosis (MS) relapses during pregnancy, although relapse risk increases in the early post-partum period, as has been predicted by pre-pregnancy or disease activity, as assessed clinically or radiologically.

Objective: The aim of this study was to evaluate the correlation between magnetic resonance imaging(MRI)changes in the year before pregnancy and the long-term(5 years)clinically meaningful worsening inExpandedDisabilityStatusScale(EDSS).
Methods: An observational retrospective case–control study included171pregnancies in99females with MS. All patients had a follow-up period of at least 5 years post-partum. For each pregnancy, we evaluated the clinically meaningful worsening in EDSS from pre-pregnancy baseline to last available within the end of follow-up period (for baseline score of 0: 1.5-point increase; baseline score 1.0–5.5: 1.0-point increase; baseline score ⩾6: 0.5-point increase, as previously defined). Statistical analyses were used to evaluate the correlation between MRI and post-partum relapses during 5-years follow-up. Clustered logistic regression was used to investigate the predictors of long-termclinically meaningful worsening in EDSS.
Results: We found a significant correlation for an active-MRI pre-pregnancy and long-term clinically meaningful worsening in EDSS(p=0.0006). EDSS pre-pregnancy and long-term clinically meaningful worsening in EDSS were also significantly correlated (p=0.043). Using a multivariate model, we predicted which women will not experience post-partum relapse by a stable-MRI pre-pregnancy (89.6% specificity; p=0.012).
Conclusions: Our study examined the value of routine MRI in MS patients during the year before pregnancy as a predictor of long-term clinically worsening. This study revealed that an active-MRI pre-conception is a strong predictor of long-term worsening in EDSS and higher ARR during the follow-up period, regardless of whether the woman had clinical evidence of disease activity prior to conception and delivery.These findings emphasize the need to optimize disease control and achieve both clinical and imaging stability pre-conception, to reduce the risk of long-term clinical deterioration.

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Interferon beta exposure during pregnancy and breastfeeding: Impact on birth outcome and child development – results from the post-authorisation safety study PRIMA

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Introduction: Since 9/2019 a label change in the EU for the class of interferon beta (IFNβ) therapies allows the use of IFNβ during pregnancy and breastfeeding.
Objectives: To assess pregnancy outcomes of women with multiple sclerosis (MS) exposed to IFNβ therapies.
Aims: Here we focus on results pertaining to child development.
Methods: The post-authorisation safety study PRIMA was conducted from 4-10/2021. Retrospective pregnancy data were retrieved from peginterferon beta-1a (PegIFNβ-1a) or intramuscular (IM) IFNβ-1a treated MS patients registered in the MS Service Center patient support program (PSP) 2001-2020. To systematically collect data on developmental milestones of the newborn, MS patients reporting live birth outcomes completed a questionnaire based on the standardised German paediatric check-up booklet via telephone interview. The primary objective was to evaluate the impact of exposure to PegIFNβ-1a or IFNβ-1a before and during pregnancy on pregnancy outcomes.
Results: Out of 542 pregnancies reported by 426 women (mean age ± standard deviation 32.9±4.7 years) 466 (86.0%) resulted in live birth (78.2% without defect, 2.8% with defects, 5.0% born prematurely). IFN exposure was documented during 374 pregnancies. As most registered pregnancies occurred before the label change, treatment was paused or stopped during 57.7%, taken continuously before and during 8.7%, and started during 2.6% of pregnancies (31% stopped before pregnancy or unknown). A total of 162 women completed the questionnaire for 192 live births (53.1% male). Newborns had Apgar scores indicative of healthy infants. Newborn screenings were inconspicuous with few exceptions. No differences in weight, height and head circumference at birth could be discerned between exposed and unexposed subgroups. Among 158 breastfed children (82.3%), 113 (71.5%) were breastfed exclusively until month 5, and 34 (21.5%) were breastfed during their mother's IFN intake. Physical growth curves up to 48 months lay within the expected range of the general German population.
Conclusions: These real-world data obtained within the scope of a PSP confirmed results from previous studies that exposure to interferon beta therapies during pregnancy or lactation had no adverse effects on the development of the child and did not affect intrauterine growth. Data support and complement the label update of all interferon beta therapies and here especially PegIFNβ-1a and IM IFNβ-1a. Study Support: Biogen.

Disclosure
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Trends in the use of disease-modifying therapies in pre-pregnant women with multiple sclerosis in the United States: a claims database analysis

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Introduction: Most disease-modifying therapies (DMTs) in multiple sclerosis (MS) are not approved for pregnant women. Up to 45% of pregnancies are unplanned and little is known about current DMT use in pre-pregnant women with MS.

Objective: To evaluate DMT use in pre-pregnant women with MS in the United States from 2016-2020.
Methods: A retrospective cohort study in women with MS aged 12-55 years with pre-pregnancy start date between 2016 (to allow 12 months prior to confirm MS) and 2019 (to allow 12 months after to confirm pre-pregnancy) was conducted using IBM MarketScan data. The pre-pregnant cohort was defined as those reaching the last menstrual period in the next 12 months; sensitivity analysis with 6 months was also performed. MS was confirmed using a validated claims-based algorithm before the pre-pregnancy start date. Pregnancy outcome was determined by diagnosis and procedure codes. Women without continuous medical and prescription coverage were excluded. DMTs for the pre-pregnant cohort included injectables (glatiramer acetate, [pegylated] interferon β-1a/-1b), infused (alemtuzumab, mitoxantrone, natalizumab [NTZ], ocrelizumab [OCR]) and orals (cladribine, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, fingolimod [FTY], ozanimod, siponimod, teriflunomide). Monthly prevalence was calculated based on number of women with DMT use in a month (per prescribing information [infused], procedure codes [injectable] or prescription fills [oral]), divided by number of eligible women in that month.
Results: Preliminary analyses included NTZ, OCR and FTY. Among 443 pre-pregnant women over 5316 person-months, OCR use increased after approval in 2017, peaking at 12.9% in April 2019. FTY use remained stable over time, peaking at 10.8% in 2017 and decreasing slightly until February 2019. NTZ use was stable across years, peaking at 14.5% in April 2017, followed by a slight decrease until October 2019. Further data on all DMTs in the pre-pregnancy cohort as well as the pregnant and postpartum cohorts will be shown.
Conclusions: Preliminary results suggest a sharp increase in OCR use since 2017, while NTZ and FTY remained stable since 2016. DMT use duration may not account for pre-pregnancy extended dosing, potentially underestimating DMT use. Further data are needed to better understand potential paradigm shifts in DMT use in women of childbearing age. Counseling remains an important approach to ensure optimal outcomes for women and infants.

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Assisted reproductive technology treatment and risk of multiple sclerosis – a danish cohort study

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Introduction: Hormone fluctuations in the lifespan of a woman appears to affect both multiple sclerosis (MS) risk and MS disease course. Several case series have reported that women with MS are at risk of relapses following assisted reproductive technology (ART) treatment. However, whether ART treatment may trigger development of MS is less clear.
Objective: To compare the incidence of MS among women who had undergone ART treatment to women who had conceived a child without prior ART treatment using national health registries.
Methods: We included women with a first ovarian stimulation cycle prior to in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (i.e. ART treatment) recorded in the Danish IVF register between January 1, 1996 and December 31, 2018; and women recorded in the Danish Medical Birth Register with the birth of their first child where date of conception is between January 1, 1996 and December 31, 2018. Outcome was a diagnosis of MS recorded in the Danish Multiple Sclerosis Registry. The cohort was followed until March 10th, 2021. Crude and adjusted hazard ratios (aHRs) with 95% confidence intervals were calculated based on Cox proportional hazard regression.
Results: 585,716 women where included in the cohort of which 63,791 (11%) were exposed to at least one initiated IVF/ICSI cycle during the study period. The median follow-up time for the entire cohort was 12.4 years (Q1-Q3=6.6-18.1). Compared to women conceiving without prior ART, ART treated women were older (31.8 years versus 27.5 years), more often had a university degree (45% versus 36%), and more often had received other fertility treatments than IVF/ICSI prior to cohort entry (26% versus 2.1%). We found no association between incident MS and exposure to ART compared to non-ART pregnancy (aHR=1.07; 95 % CI 0.92-1.24). An intention-to-treat analysis on a propensity score matched sub-cohort confirmed our results. Including all ART cycles among the ART treated women, we found no increased risk of MS within two years of ART cycle start for successful ART cycles (i.e. pregnancy) compared with failed ART cycles (no pregnancy) (aHR=1.01; 95% CI 0.58-1.76). We found a non-significant trend towards increased risk of MS with increasing numbers of ART cycles although based on small numbers.
Conclusions: Women treated with ART do not seem to be at increased risk of developing MS compared to women not exposed to ART.

Disclosure
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Immune cell alterations during pregnancy in patients with multiple sclerosis

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Introduction: Pregnancy in women with multiple sclerosis (MS) has protective effects on the rate of relapses. The post-partum period, however, is associated with an increased risk of relapses. Immunological mechanisms driving those changes in disease activity are still incompletely understood. Recently, Eomesodermin-expressing T-helper cells (Eomes+ Th cells) were found to enhance neuroinflammation and disease progression in MS. Interestingly, extrapituitary prolactin can induce the expression of Eomes in Th cells*ex vivo*. We hypothesize that prolactin release at the end of pregnancy and following delivery might shape a cytotoxic and inflammatory immune cell compartment causative for MS worsening.
Aim of the study: Longitudinal investigation of immune cell alterations and prolactin release during pregnancy in MS and evaluation of their pathophysiological role.
Methods: Clinical course, immune cell alterations, and prolactin were assessed at different time points during pregnancy or in patients with planned pregnancy. Peripheral blood mononuclear cells (PBMCs) were isolated using density centrifugation following incubation with fluorochrome-conjugated antibodies against surface and intracellular antigens. Frequencies of Eomes+ Th-cells, Eomes+ cytotoxic T-cells, regulatory T-cells, Th cells, Tc cells and B cells were analysed using flow cytometry (BD FACS-Canto™ II).
Results: The cohort comprised n=26 non-pregnant and n=40 pregnant patients with sampling at several time points during pregnancy (1st trimester n=22, 2nd trimester n=18, 3rd trimester n=26, post-partum n=24). Overall, immune cell subsets (CD3, CD4, CD8, HLADR activated cells, B cells, NK cells) did not differ. Pregnant patients tended to have higher expression of Eomes in T-helper cells (p=0.1528). Prolactin in serum rose continuously during the course of pregnancy, associated with a trend for a positive correlation between frequencies of Eomes+ Th cells and prolactin especially in the 2nd trimester (r=0.37, p=0.19). Of note, expression of Eomes+ Th cells was associated with lower frequency of regulatory T cells in pregnant patients, particularly in the 3rd trimester (r=-0.45, p=0.03) but not in non-pregnant patients (r=-0.30, p=0.14).
Conclusion: Pregnancy in MS induces lower regulatory T cells presumably via a prolactin induced Eomes+ T cell axis. Whether those alterations are also associated with enhanced disease activity remains to be studied in an extended cohort.

Disclosure
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Disease activity in multiple sclerosis patients after assisted reproductive technology

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Introduction and objectives: An increase in relapses in multiple sclerosis (MS) patients after undergoing assisted reproductive technologies (ART) has been described. The objective is to

analyse the relapse rate after ART depending on the procedure outcome.
Methods: Patients followed up in our MS unit with the diagnosis of relapsing-remitting MS (RRMS) by McDonald criteria who underwent ART from January 2001 to April 2021 were selected for the study. Each ART cycle was considered an event. MS relapses that occurred during the previous 12 months and the 3 and 12 months after the ART procedure were studied. The annualised relapse rate (ARR) in the 12 months before ART and the ARR in the following 3 and 12 months were compared. The ARR after ART cycles which led to pregnancy, and the ARR after the unsuccess cycles (no pregnancy, miscarriage or other) were also compared.
Results: The cohort included 46 RRMS patients and 101 ART cycles. Protocols of 48 ART cycles were retrieved and included GnRH agonists (12.5%), GnRH antagonists (20.8%) and others (66.7%). The mean age of patients at the ART was 35.4±3.9 years. The outcomes of the 101 procedures were as follows: pregnancy (33.7%), no pregnancy (55.4%), miscarriage (6.9%) and other (4%). The mean ARR during the 12 months before the ART was similar to the ARR the three months after (0.41±0.67 vs 0.44±1.25, p=0.88). Likewise, the mean ARR the 12 months before and the 12 months after was maintained (0.41±0.67 vs 0.35±0.65, p=0.44). There were statistically significant differences in the ARR among the different outcomes. The mean ARR was lower when the result was pregnancy than when it was unsuccess, in the three months after (0±0 vs 0.66±1.49, p=0.013) and the 12 months after (0.12±0.41 vs 0.46±0.72, p=0.006). When analysing the 67 unsuccess cycles, the mean ARR during the 12 months before the ART was similar to the mean ARR in the three months after (0.42±0.63 vs 0.66±1.49, p=0.31) as in the 12 months after (0.42±0.63 vs 0.46±0.72, p=0.75). Nevertheless, analysing the 34 cycles that led to a pregnancy, the ARR was significantly reduced from 0.38±0.74 in the 12 previous months to 0±0 in the 3 months after (p=0.006) and to 0.12±0.41 in the 12 months after (p=0.034).
Conclusions: The annualised relapse rate is maintained after ART in those patients with unsuccess procedures and reduced the year after when the outcome is pregnancy.

Disclosure
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Mario Jato and Marc Barahona declare nothing to disclose.

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B cell subset dynamic during pregnancy and early post-partum in women with multiple sclerosis

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Introduction: Pregnancy in Multiple Sclerosis (MS) patients is associated with a reduction of disease relapses due to the down-regulation of inflammation functional to fetal tolerance. In the post-partum inflammatory rebound may occur as the result of immunocompetence restoration. Such hormonal-driven immunological adaptation is thought to involve T cell compartment. Nevertheless, B cell subset dynamic, whose role in MS disease pathogenesis is now well established, have been poorly explored during pregnancy and post-partum.
Aims: To investigate the dynamic of B cell subsets in pregnant women with Multiple Sclerosis (MS) during pregnancy and early post-partum.
Methods: We designed a monocentric non interventional study (BABIES study) enrolling untreated pregnant MS women within 8 weeks±5 days from last menstrual period. Clinical and immunological data were collected during the first (T1), the second (T2) or the third (T3) trimester of pregnancy, as well as 2 weeks (T4), 3 (T5) and 6 (T6) months from delivery. B cell subpopulations were analyzed by multi-parametric flow cytometry in peripheral blood mononuclear cells (PBMCs) freshly isolated from peripheral blood sampling.
Results: Preliminary results on 9 women followed up at least until T4 show that absolute number and percentage of circulating total CD19+ B cells drop during pregnancy overall. Looking at subpopulations, while CD24+CD38+ naive transitional immature B cells and CD27+ memory B cells rapidly decrease, CD27- mature naïve B lymphocytes slightly increase. CD27+ memory compartment also reorganizes with an increase in the IgG/IgA switched memory cells. Consistently with this result, antibody producing CD27hiCD38hi plasmablasts are also rapidly and dramatically augmented in peripheral blood of pregnant women.
Conclusions: In MS women, pregnancy induces specific B cell depletion and reorganization with a dramatic reassortment in subpopulation composition. Very interestingly, such immunological adaptations are rapidly reverted after delivery. If B cell dynamic during pregnancy and post-partum is associated with disease remission and rebound has still to be elucidated.

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Clinical aspects of MS - MS symptoms

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Sleep apnea and periodic limb movements are highly prevalent in patients with multiple sclerosis

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Introduction: The pathogenesis of multiple sclerosis (MS)-related fatigue is multi-factorial, including neurogenic, inflammatory, endocrine, metabolic, mood, as well as sleep disorder-related mechanisms. The confounding effect of sleep disorders on the association between fatigue and neurodegenerative changes in the brain has not been investigated.
Objectives: To assess the prevalence of sleep apnea and periodic limb movements in the framework of a prospective study which investigates the neurogenic causation of treatment-resistant fatigue in MS.
Methods: MS patients enrolled in a National MS Society-funded prospective study (grant identifier RG-1501-03141) underwent a one-night at-home sleep test (HST) using a NOX T3 portable monitor. HST recordings were scored by a registered polysomnographic technologist. Respiratory Event (REI) and Periodic Limb Movement (PLMI) Indices were calculated for each patient.
Results: Out of 36 patients, 7 (20%) had mild (REI=5-14), 1 (3%) had moderate (REI=15-29), and 1 (3%) had severe sleep-disordered breathing (REI⩾30). Fourteen (42%) of the patients had mild (PLMI=5-24), 4 (11%) had moderate (PLMI=25-49), and 7 (19%) had severe periodic limb movements (PLMI⩾50). Overall, 81% of the patients had at least mild sleep-disordered breathing and/or periodic limb movements.
Conclusion: Sleep abnormalities (i.e., sleep apnea and periodic limb movements) are highly prevalent in patients with MS. We plan to compare the MRI exams of subgroups of MS patients with fatigue, to test the hypothesis that fronto-striatal circuitry is more affected by lesions in patients without sleep apnea compared to those with sleep apnea.

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Impaired visual discrimination and object recognition in RRMS patients despite intact visual pathway

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Objective and aim: To assess visual discrimination and object recognition in relapsing-remitting multiple sclerosis (RRMS) patients who have no history of optic neuritis and unremarkable visual evoked potentials (VEP).
Methods: 20 RRMS patients between 18 and 65 years old with an Expanded Disability Status Scale (EDSS) score ⩽ 3 with no relapse or corticosteroide treatment in the last 4 weeks were eligible for the study. A progressive disease course, history of optic neuritis or impaired VEPs were exclusion criteria. 20 healthy and age/sex-matched controls were included.
The test battery consisted of the Farnsworth-Munsell (FM) 100-Hue test for visual color discrimination, object recognition by the Birmingham object recognition battery (BORP), anxiety and depression measured by the hospital anxiety depression scale questionnaire (HADS-A and D), concentration, cognition and decision-making by the symbol digit modalities test (SDMT), and learning and memory by the auditory verbal learning and memory test (German version VLMT 1-5 and VLMT 7). Additionally, serum neurofilament light chain (sNfL) levels were determined.
Results: RRMS patients (mean age ± standard deviation (sd) = 35.2±11.4) had a mean disease duration of 7.7 years (sd = 5.7);

their last relapse was 5 years ago (sd = 4.5). The median EDSS was 1.25 (range 0-2.5). Two RRMS patients were treatment naïve whereas 18 received a disease-modifying therapy.
Strikingly, visual discrimination in the FM 100-Hue color test was significantly worse in RRMS patients (mean±sd, RRMS: 67.4±35.3; controls: 35.0±16.1, ***p<0.001). In line with this, object recognition was also impaired in RRMS patients compared to healthy control subjects (mean±sd, RRMS: 28.9±2.1; controls: 30.3±1.2, *p=0.014), whereas concentration and decision-making (SDMT) as well as verbal learning and memory (VLMT 1-5 and VLMT 7) were comparable. sNfL levels were nonsignificantly increased in RRMS patients (sNfL in pg/ml, mean±sd, RRMS: 9.2±13.1; controls: 4.8±1.6, p=0.08).
Conclusions: RRMS patients show a worse visual discrimination and object recognition despite an intact visual pathway and normal performance in cognition tests and memory performance. Recent data from animal experiments point towards a dysregulation of local cortical networks which are compromised by distant focal lesions. These network dysregulations should be given more attention as they have functional consequences and are not targeted by current immunotherapies.

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Isolated genital numbness in multiple sclerosis: urogenital profile and neurophysiological correlates

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Background: Urogenital dysfunction has a significant effect on quality of life in MS and is often underreported. Sensory impairment over the external genitalia contributes to sexual dysfunction however usually occurs in the context of sensory loss elsewhere. Numbness limited to the external genitalia is uncommon and lesions may localise to the conus medullaris. Neurological lesions affecting the cauda equina or pudendal nerve can also present with genital numbness, as well as non-structural causes such as exposure to selective serotonin reuptake inhibitors (SSRI). Complex pelvic innervation conveying somatic and erogenous sensations can be interrogated by pelvic neurophysiology.
Aim: To investigate urogenital symptoms and pelvic neurophysiological characteristics of patient with MS reporting genital numbness.
Methods: Consecutive patients with MS referred to the Department of Uro-Neurology with 'genital numbness', between January 2018 to January 2022. Genital numbness related symptoms (sexual, bladder and bowel dysfunction), contributing factors (medication exposure, cycling), clinical examination findings (Von Frey Hairs (vFH), and neurophysiology findings (pudendal somatosensory evoked potentials (SEP), bulbocavernosus reflex (BCR) and anal sphincter EMG), and MS clinical history were recorded.
Results: Four patients (1 female; median age 45.8 years (range 29.3-59.6 years)) were referred with genital numbness. Two had numbness extending to the perineum. The median duration of genital numbness was 3 years (2 to 5 years). Median duration of MS was 5 years (3 to 16 years), and mean EDSS score 4.0. All patients had spinal cord lesions, with one conus medullaris lesion on MRI. Two patients had abnormal tibial and pudendal SEPs, and one patient an abnormal BCR. No patients had associated medication exposure. All patients had additional bladder symptoms (storage) and reduced bladder sensations. Sexual function was impaired in two patients.
Conclusion: Isolatedgenital numbness is an uncommon symptom in MS without accompanying leg numbness and is associated with bladder dysfunction. Pelvic neurophysiology is able to interrogate the sacral somatic sensory/motor innervation, which can be affected by conus medullaris lesions as found with an abnormal BCR. Abnormal tibial and pudendal SEP's are commonly seen in MS and do not further localise the genital numbness. Urogenital symptoms are common in MS and altered genital sensation and sexual function are under-reported.

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Clinical aspects of MS - Clinical assessment tools

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MSReactor is an acceptable long-term web-based cognitive monitoring platform for patients with multiple sclerosis

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Introduction: Routine cognitive monitoring in multiple sclerosis (MS) outpatient clinics is currently an unmet need. Computerised cognitive batteries are brief and reliable but long-term usability is yet to be assessed. MSReactor is a web-based, reaction time cognitive battery assessing processing speed, attention and working memory.
Aims: To assess the long-term acceptability of MSReactor.
Methods: Participants completed MSReactor testing 6 monthly at outpatient clinic visits and rated their willingness to repeat testing, levels of anxiety whilst testing, interest, enjoyment and duration of tasks. Depression, anxiety and quality of life surveys were completed at each visit. MSReactor acceptability and relationship to depression, anxiety and quality of life was assessed at 12, 24 and 36 months using summary and descriptive statistics.
Results: In total, 456 participants completed testing at the 12-month timepoint, 230 at 24 months and 191 at 36 months. Mean age at baseline was 42 years (standard deviation (sd) 11 years), mean disease duration 9.9 years (sd 7.2 years) and median Expanded Disability Status Scale 2 (interquartile range 1-2.5). Most participants would be happy or very happy to repeat testing at 12 (n=292, 64%), 24 (n=152, 66%) and 36 months (n=117, 61%). Most patients (n=433, 95%) rated the duration of testing as being "about right" at 12 months and this continued at 24 (n=213, 93%) and 36 months (n=178, 93%). In terms of interest in the MSReactor tests, a majority were either neutral, found them a little bit interesting or very interesting (n=378, 82%; n=182, 79% and n=159, 83% at 12, 24 and 36 months, respectively).
At 12 months, patients who rated the testing as anxiety-inducing had higher depression scores (mean 10.0, 95% confidence interval (CI) 6.7-13.2) and anxiety scores (mean 49.1, 95% CI 40.0-58.2) compared to patients who did not find testing anxiety-inducing (depression mean 5.6, 95% CI 5.0-6.2 and anxiety mean 37.1, 95% CI 35.0-39.1). Further, at 24 months, patients who rated testing as anxiety-inducing had higher anxiety scores (mean 50.5, 95% CI 41.4-59.6) compared to patients who rated testing as non-anxiety-inducing (mean 36.7, 95% CI 33.9-39.4). There was no difference in quality of life between any of the acceptability measures.
Conclusion: MSReactor is an acceptable platform for long-term computerised cognitive monitoring in patients with MS. Increased levels of anxiety may impact the acceptability of long-term monitoring.

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Oligoclonal M bands distinguish two MS populations based on neurofilament light chain levels in patients without inflammatory activity

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Background: Recent works have demonstrated the value of oligoclonal M bands (OCMB) as a biomarker of conversion to secondary progressive multiple sclerosis, having been suggesting that could indicated a distinct pathophysiology pathway in patients with multiple sclerosis (pwMS).
Objectives: To analyze the relationship of the serum neurofilament light chain (NFL) in absence of inflammatory activity, in pwMS stratified by the presence or not of OCMB, versus healthy controls (HC).

Methods: Two cohorts of HC, have been compared with a cohort of pwMS without clinical or radiological signs of acute inflammation. The absence of inflammation was defined as the absence of relapses OR brain MR gadolinium enhanced lesions (GEL), in the three months before and after the NFL determination. Serum NFL have been determinate by the SIMOA technology. The OCMB in the cerebrospinal fluid(CSF) were analyzed by isoelectric focusing and immunoblotting.
Results: 254 people have been studied: 124 healthy voluntary controls and 130 pwMS. In pwMS with OCMB in the CSF, NFL in absence of inflammation was higher than in pwMS without OCMB and HC (11.4 pg/mL, 8.9 pg/mL and 9.0 pg/mL, respectively). Exponential correlation between the age and the NFL was demonstrated, with accelerating increases in patients with progressive MS, and with OCMB.
Conclusions: In absence of evident inflammatory activity, pwMS and OCMB exhibit higher NFL levels. Thus, OCMB could portray an underlying inflammatory process not detected by conventional MRI studies and may explain the poorer prognosis of these patients.
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P489
Scoring methods of cognitive fatigability in people with multiple sclerosis

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Background: Cognitive fatigability (CF) is considered as the measurable change in the performance within cognitive tasks due to fatigue. Currently there is no consensus on the scoring methods that should reflect CF within different tests. Therefore the aim of this study is to explore different methods of the Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT) to assess CF.
Methods: A sample of people with MS (PwMS) and healthy controls (HC) is collected using convenience sampling at the local MS Center. All participants completed in following order the: SDMT, PASAT2 and -3 (PASAT with respectively 2 or 3 seconds interstimuli interval). Besides the absolute scores reflecting the amount of correct answers, also the dyad scores (two or more consecutive correct answers)are calculated solely for the PASAT2 and -3. To detect changes throughout the test performance, each administration was split in two and three equal segments.
Results: A sample of 48 PwMS and 49 HC was collected. Absolute scores decreased significantly when using the split in three segments for the SDMT within the group of PwMS (part1:19.50±4.07; part3:17.29±4.25; z=-4.29; p<.001) and in HC (part1:20.47±3.86; part3:19.24±4.04; z=-2.98, p=.002); and for the PASAT2 in the group of PwMS (Part1:14.35±3.39; part3:11.02±3.57; z=-5.50, p<.001) and in HC (part1:15.04±3.26; part3:12.96±3.96; z=-3.82, p<.001); and for the PASAT3 scores in the group of PwMS (part1:16.90±2.69; part3:15.15±3.60; z=-4.64, p<.001) and in HC (part1:17.98±2.33; part3:16.71±3.21; z=-3.24, p=.001). The PASAT dyad scores decreased significantly for the PASAT2 in PwMS (part1:10.35±4.79; part3:5.94±3.89; z=-5.63; p<.001) and HC (part1:11.33±4.24; part3:8.63±5.03; z=-3.71; p<.001); and the PASAT3 in PwMS (part1:13.71±4.30; part3:11.38±4.92; z=-4.53; p<.001) and HC (Part1: 15.57±3.56; part3: 13.49±4.62; z=-3.49; p<.001).
Conclusion: A decline in performance within cognitive tasks, is found with scoring methods using absolute and dyad scores in both the SDMT and the PASAT3 and -2. Suggesting cognitive fatigability in PwMS and HC.

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P490
The relationship between swallowing function, pulmonary functions and respiratory muscle strength in patients with multiple sclerosis

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Introduction: Patients with Multipe Sclerosis (MS) experience respiratory muscle weakness, impaired lung functions, and swallowing disturbances even in the early stages of the disease.
Aim: To investigate the relationship between swallowing function, pulmonary functions and respiratory muscle strength in subjects with MS.
Methods: Twenty-one patients diagnosed with MS (mean age:41.52±10.06, 11 women, 10 male, mean EDSS: 1.73±1.14, disease duration MS: 1.38±1.77/year) were included in the study. Pulmonary functions (%$FEV1_{pred}$, %FVC_{pred}, %FEV1/FVC_{pred}, %PEF_{pred},%$FEF25\text{-}75_{pred}$) of the patients evaluated using MicroQuark Spirometer (COSMED) and respiratory muscle strength (maximal inspiratory pressure-MIP, maximal expiratory pressure-MEP) assessed with "MD Diagnostics RP Check" . Swallowing function was evaluated with "Questionnaire for the Assessment of DYsphagia in Multiple Sclerosis (DYMUS)" and "EAT-10".
Results: The averages of respiratory muscle strength, respiratory functions, DYMUS and EAT-10 were as follows; MIP: 79.80±30.19 cmH2O, MEP: 101.85±26.90 cmH2O, %FEV1pred:

80.80±14.57, %FVCpred: 85.14±16.33, %FEV1/FVCpred: 79.13±5.91, DYMUS: 3.23±2.62, EAT-10: 5.47±6.24. Ten patients (47.6 %) were at high risk of dysphagia (DYMUS ⩾3 and EAT-10⩾3). There were negative moderate significant correlations between DYMUS and MIP (r=-0.536, p=0.012) and MEP (r=-0,475, p=0.029). In addition EAT-10 was negatively correlated with MIP (r=-0.433, p=0.049). No correlation was found between DYMUS or EAT-10 and pulmonary functions.

Conclusion: This study showed that swallowing function is related with inspiratory and expiratory respiratory muscle strength but not pulmonary functions. Implementation of techniques to increase inspiratory and expiratory respiratory muscle strength to rehabilitation programs may be preferred to improve swallowing functions in this population.

Disclosure
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P491

Remote web-based assessment of cognition, mood and fatigue in people with multiple sclerosis

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Introduction: Cognitive dysfunction is a common, debilitating but often overlooked aspect of multiple sclerosis (MS). Given the short and infrequent nature of traditional clinical visits there is a need for broad, sensitive and practical assessments that people with MS can complete at home to enhance monitoring for cognitive decline.

Objectives: To demonstrate that web-based computerized assessments can be used to remotely assess a wide range of cognitive domains known to be adversely affected in people with MS.

Methods: All study data was collected online between February and March 2020 using Cambridge Cognition's secure web-based testing application. Participants were recruited using an online recruitment platform. In order to participate, individuals had to meet the following self-reported eligibility criteria: diagnosis of MS, aged ⩾18 years, fluent English speaker and normal (or corrected to normal) vision. Participants were asked to provide basic demographic information and to complete a series of questionnaires assessing their mood, fatigue and level of physical disability. They also completed a battery of computerized CANTAB cognitive assessments, providing measures of episodic memory, working memory, executive function, social cognition and sustained attention. All tasks included automated voiceover instructions and scoring. To reduce burden on participants, the assessments were available to complete at their convenience in two separate parts, each taking approximately 30 minutes. Participants were instructed to perform all of the tasks on their own, in a quiet room and to the best of their ability. All subjects provided informed consent prior to their participation and were reimbursed for their time on completion of the study.

Results: 102 participants (62% female) were recruited into the study. At the group-level, normative comparisons of participants cognitive test scores relative to age, sex and education matched individuals in the general population indicated that MS patients in this study performed similarly to controls across these measures. Inspection of individual participant profiles suggested that there was substantial heterogeneity across cognitive domains both within and between individuals with MS, ranging from very high to very poor performance, highlighting the importance of assessing each of these aspects of cognition.

Conclusions: Web-based CANTAB assessments can be used to remotely assess cognitive functioning in people with MS.

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P492

Learning from pseudo-labels: deep networks improve classical longitudinal brain volume change estimation for patients with MS

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Introduction: Deep learning networks are capable of learning robust predictions from noisy distributions. The application of these techniques to estimate longitudinal percentage brain volume change (PBVC), an imaging biomarker of multiple sclerosis (MS) disease progression, is hampered by difficulty acquiring ground-truth atrophy labels, which are limited to the predictions of classical methods such as SIENA. However, it is not clear whether deep networks can learn from such methods and outperform them.

Objective: To develop and validate a novel deep learning model (SNACA) by comparison with the accepted gold standard, SIENA in terms of error in controlled scenarios and correlation with lesion metrics.

Methods: Voxel-wise pseudo-atrophy labels were generated based on SIENA's predicted deformations for 90 pairs of MRI scans from patients with relapsing-remitting MS (RRMS) patients and used to train a 3D U-Net convolutional neural network. Finally, the PBVC estimation module in SIENA pipeline was replaced with our model for consistency and correlation experiments.

Results: *Consistency experiment.* In 100 patients with RRMS, PBVC was estimated using SIENA and SNACA between 3 scan timepoints (t0, t1, t2). [PBVC(t0-t1) + PBVC(t1-t2)] and [PBVC(t0-t2)] were calculated. The difference between these measures was lower for SNACA (-0.038 +/- 0.104%) than SIENA (-0.075 +/- 0.275%).

Correlation experiment. In 68 patients with RRMS, PBVC was calculated using SNACA between baseline and follow-up (36-48 months); and lesion volume calculated on baseline T2 imaging with manual annotation. PBVC-SNACA had a slightly stronger

monotonic correlation with baseline lesion volume (ρ = -0.2353, p = 0.0019) than PBVC-SIENA (ρ = -0.2289, p = 0.0025). A similar trend was observed on partial correlation controlled for age and disease duration, with ρ = -0.373 and p = 0.002 for the deep learning model, and ρ = -0.339 and p = 0.005 for SIENA.
Conclusions: We demonstrate that a deep learning model (SNACA) trained for partial brain volume change estimation with pseudo-labels derived from SIENA can achieve better performance in terms of consistency; and a stronger correlation between PBVC and baseline lesion volume. Incorporated into neuroimaging analysis pipelines for clinical trials, SNACA is a fast and robust tool for estimating PBVC.

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P493
Neurostatus-eEDSS results in high consistency of expanded disability status scale assessments: experience from 13 clinical trials

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Introduction: In the setting of Multiple Sclerosis (MS) randomized clinical trials (RCT) Neurostatus-eEDSS is increasingly implemented as the preferred method to quantify disability. By providing an algorithm based real-time feedback and interaction with expert neurologists from the University Hospital Basel (UHB) Neurostatus-eEDSS improves consistency in assessments. The algorithm alerts users to scoring inconsistencies or missing data. After data entry, users can request up to four feedback rounds, one is mandatory. Users can correct scores and view feedback. If the scoring algorithm detects no inconsistencies the form is stored in the database.If inconsistencies are detected or comments were added, an expert review is triggered.The expert neurologist can view assessments in a web portal and interact with site users to resolve remaining inconsistencies. The final decision on scores remains with the examining neurologist.
Objective: Analyze the operational performance of the Neurostatus-eEDSS in 13 global clinical MS trials implementing the Clario system.
Methods: Assessments captured using the Neurostatus-eEDSS in 13 global clinical trials with 4 different sponsors from 25 January 2019 until 25 April 2022 were analyzed.
Results: Trials included patients with relapsing MS (8 trials), primary progressive MS (4 trials), and non-relapsing secondary progressive MS (1 trial).The analysis included 41,874 Neurostatus-eEDSS assessments.72% of the Neurostatus-eEDSS assessments were completed on the tablet in 30 minutes or less. Of the final assessments obtained after 1-4 real time feedback rounds on site, 86% were stored as final and required no expert review, 2% required 1 round, 7% 2 rounds, 3% required 3 rounds, and 2% required 4 or more rounds of expert review. The expert review process resulted in changing EDSS Step scores in 4.3% of all assessments.Of the EDSS functional systems, Pyramidal had the greatest number of functional system score changes (2.8% of assessments).
Conclusion: The Neurostatus-eEDSS system results in a high consistency of EDSS scoring through real time on-device feedback on scoring inconsistencies and by assuring completeness of assessment data. The system allows further improvement and individualized patient evaluation based on timely remote feedback and interaction between users at sites and expert neurologists.

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P494
Multiple sclerosis and ambulation: the relationships of the 25 foot timed walk to quantitative gait parameters during preferred walking speed and dual task walking

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Introduction: People with Multiple Sclerosis (PwMS) experience disease courses characterized as having either relapses and/or progression of disease impact. Some features of accumulative disability in PwMS are currently measured by EDSS and/or a 25-foot timed walk (25FTW) and the changes in these parameters. Ambulation however is a complex function and one ordinal outcome measure does not likely provide sufficient information to assess and quantify such impact or change. Quantified gait analysis includes multiple unique and critical parameters that underlie walking performance and can be quantitatively captured along a continuum. These gait parameters also significantly vary along the EDSS and also vary within homologous EDSS disability groups. Current approaches to identify "no evidence of disease activity" (NEDA) as a measure of disease stability or change are likely insufficiently granular and quantitative to identify such early changes along a continuum with ordinal outcome measures.
Objectives: To enhance insight into the relationship of the one measure of 25FTW to several critical measures underlying the gait cycle.
Methods: A retrospective review of data collected in the course of routine care of PwMS including: demographics (age, gender), digital gait analysis (GA), and the 25FTW on the same day. GA captured the following gait parameters: Velocity (V), Double Support (DST), Cadence (C), Functional Ambulation Profile (FAP), Gait Variability Index (eGVI), and Walk Ratio (WR) averaged across 3 trials during preferred walking speed and then dual task walking. Regression analysis was completed.
Results: PwMS (N=105), gender 69% female, average age 53.7 +/- 11 years.Along a continuum the 25FTW values related to the following gait parameters during preferred walking speed: V R^2=0.63, DST R^2=0.65, C R^2=0.56, FAP R^2=0.61, eGVI R^2=0.54, WR R^2=0.05; dual tasking walking: V R^2=0.55, DST R^2=0.31, C R^2=0.42, FAP R^2=0.64, eGVI R^2=0.46, WR R^2=0.01.
Conclusions: Walking ability reflects a complex integration of multiple factors. Although the 25FTW represents one of the traditional outcome measures to gauge MS impact and disease progression, the complex relationship of the one value obtained to the many underlying aspects of ambulation ability that can be easily measured raises the question as to whether our current measures of disease impact, disease change and NEDA sufficient and whether they are sufficiently recognize important change.

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P495
Multiple sclerosis, multi-domain computerized cognitive testing and employment: real world value of validated cognitive testing

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Introduction: Multiple Sclerosis (MS) is a chronic relapsing and progressive disease. Cognitive impairment (CI) is common in people with MS (PwMS). CI in PwMS is not objectively quantified in routine care and may be "invisible."Multiple computerized cognitive batteries have been "validated", but few have been validated both directly to Minimal Assessment of Cognitive Function in MS (MACFIMS) and related to quantitative Magnetic Resonance Imaging (MRI) measures.Unemployment rates among PwMS are high and a common area of concern. Identifying CI along a continuum of multiple cognitive domains might provide patient centric proactive opportunities for targeted rehabilitative interventions to maintain employment or consider disease-modifying therapies (DMT) that might stabilize or improve CI.
Objectives: To enhance understanding of cognitive factors influencing employment among PwMS.
Methods: Retrospective analysis of data collected prospectively in PwMS who completed assessments in the course of routine care between January 2020 – June 2021. Outcomes measures included a standardized validated computerized cognitive assessment battery (CAB, Neurotrax), and patient reported outcome (PRO): Modified Fatigue Impact Scale (MFIS), Patient Determined Disease Steps (PDDS) and Multiple Sclerosis Impact Scale (MSIS-29). A logistic regression model was run to examine factors associated with employment among PwMS. Significance was set a priori at $p < 0.05$.
Results: 324 PwMS, mean age of 56 (+/- 10) years old, 68% female, PDDS 0-8, and MS disease duration 15 (+/- 10) years. The majority of participants completed a high school degree

(n = 110, 38%) or bachelor's degree (n = 62, 22%).PwMS who reported they were currently employed had significantly higher scores on all outcomes assessed except for the verbal function section of the CAB compared to those who are unemployed (p = <0.01 – 0.017). Factors found to be associated with employment included age (p <0.001) and MSIS scores (p = 0.05).
Conclusion: This specific computerized multi-domain CAB can differentiate employed vs unemployed PwMS. This analysis provides real world ecological value to cognitive testing across multiple cognitive domains.Identifying patient centric CI profile might provide a unique opportunity for targeted cognitive interventions addressing specific CI or provide an opportunity to change impaired cognitive domains across multiple domains or change DMT to one with efficacy across a broad range of CI.

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P496
LUN-MS: validity, reliability and acceptability of a new questionnaire to identify the unmet needs of people with multiple sclerosis

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Introduction: People with multiple sclerosis (pwMS) experience a variety of biopsychosocial problems, the majority of which remain unmet by supporting services. At present, there are no Patient-Reported Outcome Measures that can be used in clinical settings to identify the unmet needs of pwMS. We developed a 29-item questionnaire, Long-term Unmet Needs in MS (LUN-MS) which was adapted from a questionnaire used for assessing the unmet needs of people with stroke[1].
Objective: The objective of this study is to check the psychometric properties of the LUN-MS questionnaire.
Aim: To assess the reliability, validity and acceptability of the LUN-MS questionnaire.
Methods: PwMS were asked to complete the LUN-MS and Multiple Sclerosis Impact Scale (MSIS-29) twice, 4 weeks apart, during which time participants clinical status remained stable. They also completed a questionnaire to assess satisfaction with the LUN-MS. Relative validity was tested using surrogate data analysis comparing number of unmet needs against MSIS-29 using Spearman's rho. The internal consistency was assessed using Cronbach's alpha. The reliability for each response was calculated by comparing the response during Time point-1 and Time point-2 using weighted kappa. Agreement was graded as no agreement (0), slight (0.10-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0-61 to 0.80), near-perfect (0.81 to 0.99) and perfect (1). P values of less than 0.05 were taken as significant.
Results: Eighty-eight pwMS completed the study. Mean age was 43.3 years (range 17-74) and 93.2% (n=82) of them had relapsing-remitting MS. They had an illness duration, from diagnosis, of 121.4 months (range 2-610) and a median Extended Disability Status Scale (EDSS) score of 5.5 (range 0-7.5) Correlation between the number of unmet needs and total MSIS-29 score was significant (Spearman's rho=0.631, p<0.001). Internal consistency was high (Cronbach's alpha 0.907). The satisfaction questionnaire showed high level of acceptability (T1=90.9%, T2=81.8%). Item reliability was: fair-3 items, moderate-20 items and substantial-6 items (weighted kappa 0.334-0.793).
Conclusion: LUN-MS is a reliable, valid and acceptable tool which can be used by clinicians to identify the unmet needs of pwMS.
Reference:
1.LoTS care LUNS study team. Validation of the Longer-term Unmet Needs after Stroke (LUNS) monitoring tool: a multicentre study. Clinical Rehabilitation 2013; 27(11) :1020–1028.

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P497
Extraction of lesion activity information in multiple sclerosis from unformatted MRI reports using advanced natural language processing techniques

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Introduction: New and active lesion activity in magnetic resonance imaging (MRI) is one of the 3 core criteria used to evaluate treatment responses in MS, as seen in the no evident disease activity (NEDA) method. However, identifying such criteria currently relies exclusively on human effort, which is time-consuming and prone to human errors.
Objectives (Aims): Our goal was to take advantage of recent development in natural language processing (NLP) technologies,

such as name entities Recognition (NER). The NER is a method capable of classifying named entities into predetermined categories.

Methods: In this study, we used a convenience sample of 270 unformatted MRI reports of the brain and spinal cord for people with MS. The variables of interest were: lesion entity, including new enhancing lesions, new or enlarging T2 lesions; and lesion location entity. A cutting-edge, semi-supervised NLP model was used, namely, bidirectional encoder representations from transformers (Bert) with conditional random field (CRF). Further, we implemented several new techniques to improve model performance and generalizability, including an attached training mechanism and a regularity approach. The latter enabled the classification of different subtypes of an entity. To provide ground truth, the aforementioned entities were labeled manually first. Data splitting used an 80:20 scheme, providing 185 reports for training and 46 for validation. The model evaluation used a metric called flexible F1 score, a modified measure of accuracy.

Results: Preliminary results showed that after 18 epochs of training, the overall flexible F1 score at validation was 68%. It was 68% for lesion entities, and 78% for location entities, respectively.

Conclusions: These results suggest that our model has the potential to automatically extract clinically significant information from unformatted radiology reports even based on extremely small sample size. This ability would be critical for improving the efficiency of research in similar areas in MS and establishing ground truth labels for other projects.

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P498

No evidence of disease activity can predict long-term disease course

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Introduction: No evidence of disease activity with three composites (NEDA-3) is achieved if the person with MS (pwMS) has no new MRI lesions, no new relapses and no change in Expanded disability status scale (EDSS). NEDA-3 is not a perfect tool, but it is superior to the individual parameters separately. There is disagreement on whether NEDA-3 is a good predictor of long-term disability.

Methods: A retrospective cohort study using real-world data, with limited selection bias from the complete MS population at two hospitals in the southeast of Norway. We included pwMS diagnosed between 2006 and 2017.

Results: Sufficient information for determining NEDA was available for n= 536. Only 37% of achieved NEDA one year after diagnosis with no demographic differences between pwMS achieving NEDA and not. Time to NEDA failure was 3.3 (95% CI 2.9-3.7) years. PwMS who achieved NEDA had a time to EDSS 6 of 33.8 (95% CI 30.9-36.8) years vs 30.8 (95% CI 25.0-36.6) years in pwMS who did not achieve NEDA, $p<0.001$. When rebaselining NEDA at year two, 51% achieved NEDA in the first year after rebaseline, time to NEDA failure was 3.4 (95% CI 3.0-3.7)years and time to EDSS 6 was 44.5 (95% CI 40.4-48.5) years in pwMS achieving NEDA vs 29.6 (95% CI 24.72-35.0) years in pwMS not achieving NEDA, $p=0.003$. At rebaseline, pwMS with a high efficacy therapy as the initial drug had a time from diagnosis to NEDA fail of 4.8 years (95% CI 3.9-5.8) vs 3.1 years (95% CI 2.7-3.5) in pwMS started on a moderate efficacy therapy, $p=0.001$. In pwMS with NEDA failure at year one, 70% failed one, 28% failed two and 2% failed three composites. New MRI lesions were the most common cause of NEDA failure (63%), followed by new relapses (50%) and EDSS change (25%).

Conclusions: NEDA-3 at year one can predict the long-term disease course in MS. Starting a high efficacy DMT is associated with longer time to NEDA failure than moderate therapies. However, calculating NEDA from rebaseline year two is more accurate than using NEDA from time of diagnosis. Finally, most patients only fail one composite and new MRI lesions are the most likely cause of NEDA failure.

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P499

Motion capture of the Manual dexterity test to categorize hand function in multiple sclerosis

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Introduction: The 9-Hole Peg Test (9HPT) is an established neuroperformance assessment of upper extremity function in multiple sclerosis (MS), but the conventional test is limited to a single outcome (total time). A technology-enabled iPad® adaptation of the 9HPT, the manual dexterity test (MDT), allows intra-task biomechanical outcomes to be measured.
Objectives/Aims: To use motion capture to develop novel upper extremity biomechanical outcomes and explore the relationship of these outcomes with clinical characteristics.
Methods: A Kinect® device was used to capture patient bilateral 3-dimensional, multi-joint hand motion (n=10) while performing the MDT. An advanced mathematical model, using MDT data and closure coefficients derived from motion capture analysis, was constructed to yield novel outcomes regarding peg insertion time, removal time, and bulk movement time, which provide key insights into specific mechanisms of fine and gross motor control. Clinical measures included disease course (relapsing vs progressive), Patient Determined Disease Steps (PDDS), and patient and clinician reported spasticity, dysmetria and neuropathic pain. Point-Biserial correlation coefficients, Spearman correlation coefficients, and t-tests were used to examine the relation of conventional and novel MDT outcomes with clinical measures.
Results: The study population comprised 10 patients, mean age 60.0 years (+/-9.58), disease duration 15.5 years (+/-6.7), 50% progressive MS course, median PDDS 4, 90% right hand dominant. Strong correlations (>0.7) and significant mean differences ($p<0.05$) with the clinical presence of arm spasticity were observed for the novel measures of bulk peg insertion movement, peg insertion time, empty hand retrieval movement, and traditional outcome of total time. Strong correlations (>0.7) and significant mean differences ($p<0.05$) with the clinical use of neuropathic pain medications were observed for the novel measures of peg grab time, bulk peg insertion movement, peg insertion time, empty hand retrieval movement, and traditional outcome of total time. The novel measure of peg grab time had a stronger correlation (0.73) than total time (0.61) with the presence of upper extremity weakness.
Conclusions: Measurement of upper extremity function using a digital adaptation of the 9HPT allows more detailed interrogation of function.Novel biomechanical measures may help better characterize the clinical phenotypes leading to impaired function.

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P500
Self perception of cognitive impairment is not influenced by disease related variables and educational level

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Introduction: Cognitive impairment (CI) is frequent in people with Multiple Sclerosis (PwMS), affecting 45% to 65% of them. Despite the potential for negative impact on social functioning, occupation, quality of life (QoL) of PwMS, CI is underdiagnosed and few tools as the Brief International Assessment of Cognition for MS (BICAMS) are recommended to monitor. To understand self-perception of cognitive functioning, the Perceived Deficits Questionnaire (PDQ) has been largely used. Although lot of studies have tried to understand its correlation with mood, QoL and objective cognitive functioning, the influence of others clinical aspects has been scarcely investigated.
Aims: This study aimed to understand whether any other parameters influence self-perception of CI (e.g., educational level, disease course and duration) and to contribute in investigating its correlation with the objective CI.
Methods: We administered BICAMS and PDQ to PwMS of the Italian MS Society Rehabilitation Center who underwent a medical visit for CI. Age, gender, educational level, disease course and duration, educational level were collected from all participants.
Results: The majority of the sample (N=97) were females (68) and an average 53.5 years of age (SD 10.2) with a disease duration of 13.22 years (SD 10.10). Most of the PwMS have relapsing-remitting MS (58), while 26 and 13 have secondary progressive MS (SP) primary progressive (PP), respectively. Mean educational level reported were 11.91 (SD 3.90). Mean SDMT was 39.04 (SD 13.53), 9.75 (SD 2.39) on the CVLT II, 18.4 (SD 9.75) on the BVMT-R. Mean PDQ was 31.27 (SD 15.84). No significant relationship was found between PDQ and BICAMS scores (SDMT: r= .009, p= 939; CVLT II: r=-.117, p=291; BVMT-R: r=.061, p= .583), between PDQ and other variables analysed (schooling: p= .758; disease duration: p= .076; disease course: p= .197). According with literature PwMS with RR course showed better results on BICAMS and higher perception of cognitive deficits.
Conclusions: According with literature, results suggest that PDQ has no significant correlation with objective cognitive functioning. Therefore, it seemed not to be influenced by educational level, MS duration and course. Future investigation needs to focus on the possible features that could early affect both the self-perception of cognitive functioning and the objective one.

Disclosure
Bergamaschi Valeria and **Jessica Podda** declare no conflict of interest.
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Clinical aspects of MS - Patient reported outcomes

P502
Patient-reported outcome parameters support estimating and predicting progression independent of relapse activity in people with multiple sclerosis

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Introduction: Accurate detection of disability progression is a significant unmet need in people with progressive multiple sclerosis (PwPMS). Government and health agencies have deemed the application of patient-reported outcomes measures (PROMs) in clinical practice and clinical trials a major strategic priority. Nevertheless, data documenting the clinical utility of PROMs in neurological diseases is scarce.
Objective: To evaluate whether the assessment of PROMs contributes to detecting and predicting disability progression independent of relapse activity in PMS.
Methods: PROMs were evaluated in two independent cohorts; the EMerging blood BIOmarkers in PROgressive Multiple Sclerosis (EmBioProMS) investigated PROMs (Beck depression inventory-II (BDI-II), multiple sclerosis impact scale-29 (MSIS-29), fatigue scale for motor and cognition (FSMC)) in PwPMS (primary and secondary PMS). In the other cohort, the placebo arm of the phase III ORATORIO trial in PPMS, the 36-Item Short Form Survey [SF-36] was evaluated. PROMs were compared between participants with evidence of disability progression (EDP) and those with no evidence of disability progression (NEDP).
Results: Participants in EmBioProMS with EDP in the two years prior to inclusion (114/185 [61.6%]) had worse BDI-II, MSIS-29, and FSMC scores at baseline compared to PwPMS with NEDP. PwPMS with any of the included PROMs above the 90th percentile had an odds ratio of 3.8 (P= 0.007) for having EDP in the last two years. Sensitivity analysis revealed a similar pattern at lower percentiles (e.g., 80th and 70th) and for single PROMs scores separately. In the placebo arm of ORATORIO (n= 137), the physical component score (PCS) of SF-36 at week 120 was worse, compared to baseline, in cases who experienced EDP over the preceding trial period (P= 0.007). Worse PCS at baseline was associated with higher hazard ratios of disability accumulation over the subsequent 120 weeks (HR: 2.01 [30th-], 2.11 [20th-], and 2.8 [10thpercentile],P= 0.007, 0.012 and 0.005, respectively).
Conclusions: PROMs could provide a practical, cost-efficient, and remotely accessible subsidiary tool to assess and predict disability progression in chronic neurological conditions like PMS through standardised, structured, and quantifiable patient feedback.

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Therapeutic adherence and quality of care of MS patients during COVID-19 pandemic: an italian multicenter patient-centered survey (COVIMPSAT)

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Introduction and aims: Multiple Sclerosis (MS) Centers experienced a significant disruption of their clinical activities during the first waves of COVID-19 pandemic. As part of a national multicenter survey (COVId Ms Patients SATisfaction survey – COVIMPSAT), we collected i) the opinion on quality of care (QoC) received by people with MS (pwMS) from MS Centers (MSC), and ii) data on therapeutic adherence and discontinuation, during the lockdown period (March-May 2020) in Italy.
Methods: In April-May 2021, 16 Italian MSC compiled and sent a digital (35-item) survey to their patients. Statistical analyses were performed with SPSS, version 25.
Results: 1670 pwMS (67.3% women) completed the survey. Most of them (89.9%) were on disease-modifying therapies (DMTs). The most used DMTs were dimethyl fumarate (18.6%),

ocrelizumab (14.4%) and natalizumab (13.9%). During the lockdown period, 88% did not modify their DMT regimen, while 11% reported a change in DMT intake, with a reduction in 7.8% and a drug discontinuation in only 4.2% cases.
Almost 9 out of 10 pwMS (89.1%) were able to get in contact with their MSC without difficulties. Thirty-six percent of pwMS contacted their MSC for getting information about COVID-19, while 30% were directly contacted from the MSC personnel to provide information on MS and COVID-19 and preventive behaviours. More than half of the patients (63.5%) performed their check-up visits at the MSC with the same schedule as the pre-pandemic period, while 36.5% of pwMS voluntary skipped follow-up visits mainly because of fear of getting COVID-19 infection (46%) and the sensation of feeling well without an absolute/urgent need of a check-up visit (16.8%). Interestingly, although only 1.3% of pwMS underwent a teleneurology follow-up visit, 80% of patients suggested to invest more in telemedicine programs in order to expand contact channels with MSC. The overall opinion of pwMS on MSC during the pandemic period in Italy was more than positive, with 32% of pwMS declaring a significant increase in trust in their MSC.
Conclusions: Italian pwMS judged globally well the activity, accessibility and information received by their MSC during the first wave of COVID-19 pandemic. Only 1 out of 10 pwMS underwent a change in their DMT regimen, showing a high drug adherence. Our data also demonstrate that implementing telemedicine programs would further improve the QoC of patients, particularly those with higher disability or living far from the MSC.

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Validation of the MS-IADL-Q to measure cognitive functioning in daily life

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Objective: To assess the psychometric properties of the recently developed Multiple Sclerosis Instrumental Activities of Daily Living Questionnaire (MS-IADL-Q) to measure cognitive functioning in daily life.
Methods: MS patients (N=100, 73 RRMS, 77 females, age = 48.3±11.2 years) and their proxies (N=100, 62 females, age = 49.7±13.5 years) filled out the MS-IADL-Q (51 activities, 8 categories) twice with a two-week interval. Inter-rater agreement and test-retest reliability was assessed using the intra-class correlation coefficient (ICC). Scores on the MS-IADL-Q were correlated (Pearson) with mood and anxiety (Hospital Anxiety and

Depression Scale), fatigue (Checklist Individual Strength-20R), cognitive complaints (Multiple Sclerosis Neuropsychological Questionnaire) and caregiver burden (Caregiver Strain Index) to measure construct validity.
Results: We found poor agreement between patients and proxies (*ICC*<0.5) for three items ("Being responsible for own medication", "Using social media on a smartphone", "Taking care of others"), moderate agreement (*ICC*=0.5-0.75) for 27 items and good/excellent agreement (*ICC*>0.75) for 21 items. For patients, the test-retest reliability could be considered moderate for six items and good/excellent for the other items (*N*=45). For proxies, the test-retest reliability could be considered moderate for eight items and good/excellent for 42 items. Only for one item, "Operating other devices", poor reliability was found. Scores on the MS-IADL-Q were moderately associated with mood (*r*=0.507), anxiety (*r*=0.352), cognitive complaints reported by proxy (*r*=0.633) and caregiver burden (*r*=0.648), whereas strong correlations with fatigue (*r*=0.698) and cognitive complaints – patient version (*r*=0.792) were found (all*p*<0.001).
Discussion: This interim analysis shows favorable test-retest reliability for both versions of the MS-IADL-Q. A few items (*N*=3) need reconsideration as a consequence of low inter-rater agreement between patients and proxies. Only one item showed poor test-retest reliability in the proxy version of the questionnaire. The construct validity of the questionnaire needs to be further explored compared to a neuropsychological examination.

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Safety of a third SARS-CoV-2 mRNA vaccine dose in people with multiple sclerosis

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Background and goals: The goal of this study was to assess the rate of self-reported side effects, need for medical assistance and hospitalizations after a third COVID-19 vaccination in people with multiple sclerosis (pwMS) with or without disease-modifying treatments. We also wanted to investigate if SARS-CoV2 antibody levels correlate with side effects.
Methods: Participants enrolled in the vaccination trial Nevrovax were invited to complete a questionnaire on side effects after the third dose of SARS-CoV-2 vaccination. SARS-CoV2 antibodies were measured in BAU/mL after 3 weeks or longer after vaccination. The results were linked to data from the Norwegian Immunization Registry. Statistical analyses were performed using SPSS Stastistics version 26. Group comparisons were analyzed using independent samples t-tests and chi-square tests with a significance level of 0.05.
Results: In total 606 pwMS (77.4% female, mean age 48.3 years) were included in this study. At the time of immunization, 61.7% of all pwMS were treated with anti-CD20 monoclonal antibodies and 19%with sphingosine 1-phosphate receptor modulators. Mean time to follow up from third dose to answering the questionnaire was 29.9 days.586 patients received an mRNA-vaccine (257 BNT162b2 and 344 mRNA1273 as dose 3) while 20 received a viral vector vaccine-AZD1222 (One as dose 3). Data on vaccine type of dose 3 was missing in 4 patients. Side effects were reported by 66.2% of all pwMS. Mean age of patients with and without side effects were 47.0and 50.7 years, respectively ($p < 0.01$). We found a higher rate of side effects among women (68.8%) than men (59.1%) ($p=0.047$), and a higher rate among those using anti-CD20 therapy (73.3%) ($p<0.05$). Blood samples of SARS-CoV2 antibodies were obtained in 547 patients. There were no significant difference in antibody levels in patients with side effects (mean 1185 BAU/mL) and patients without side effects (mean 1174 BAU/mL),$p=0.66$. 16 pwMS (2.6%) sought medical help after vaccination. No pwMS needed hospitalization.
Conclusions: Our results demonstrate that a third dose of SARS-Cov2 vaccines are safe in pwMS using different DMTs. Rate and severity of side effects vary with both treatment and demographic factors. SARS-CoV2 IgG levels did not correlate with side effects. There were no hospitalizations after vaccination with a 3rd dose.

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Multiple sclerosis and ambulation: a comparison of the relationship of traditional outcome measures and quantitative gait analysis as they both relate to perception of balance and falling in people with multiple sclerosis

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Introduction: People with Multiple Sclerosis (PwMS) experience disease courses with relapses and/or progression. Accumulative disease burden in PwMS are measured by EDSS and/or MRI. Neither of these two outcome measures reflect the PwMS's real-world experience (RWE). Current outcome measures of ambulation, 25-foot timed walk (25FTW) & Timed Up and Go (TUG), multidimensional, quantitative gait analysis (GA) have not been examined with patient perspective. GA includes critical parameters that underlie walking performance and are quantitatively captured. Current approaches to identify "no evidence of disease activity" (NEDA) or RWE as a measure of disease stability are likely insufficiently granular to identify changes. Exploring multiple gait parameters as opposed to measures with limited dimensionality of performance with PwMS RWE as reflected by patient reported outcomes (PRO) may provide better insight.
Objectives: To gain insight into the relationship of current outcome measures to multiple objective critical measures underlying the gait cycle as they relate to PRO.
Methods: A retrospective review of data collected in routine care of PwMS including: Activities Balance Confidence scale (ABC), Modified Falls Efficacy Scale (MFES), 25FTW, TUG, and GA on the same day. GA captured gait parameters: Velocity (V), Double Support (DST), Cadence (C), Functional Ambulation Profile (FAP),& Gait Variability Index (eGVI) for preferred walking speed (PWS) and dual task (DT) walking.
Results: PwMS (N=105), gender 69% female, average age 53.7 +/- 11 years. The following correlations were found with ABC: 25FTW V R^2=0.43; TUG R^2=0.21; PWS: V R^2=0.43, DST R^2=0.36, C R^2=0.45, FAP R^2=0.31, eGVI R^2=0.39; DT: V R^2=0.40, DST R^2=0.25, C R^2=0.45, FAP R^2=0.35, eGVI R^2=0.36. MFES: 25FTW V R^2=0.27; TUG R^2=0.26; PWS: V R^2=0.31, DST R^2=0.29, C R^2=0.35, FAP R^2=0.12, eGVI R^2=0.25; DT: V R^2=0.28, DST R^2=0.25, C R^2=0.31, FAP R^2=0.14, eGVI R^2=0.18.
Conclusions: Although the 25FTW and TUG gauge MS impact with RWE PRO, the complex relationship of multidimensional outcome measures of the gait cycle to ABC and MFES along a continuum of gait parameters suggest that our current measures of disease impact, change and NEDA as they reflect the patient experience are likely insufficiently sensitive. This combination of RWE and quantitative multi-dimensional objective measures of disease impact & change can enhance insight into disease impact, the definition of NEDA and targeted treatment timing and value.

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Experiences of post-traumatic stress disorder in people living with multiple sclerosis

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Introduction: Receiving an MS diagnosis is a potential and significant threat to a person's wellbeing. Post-traumatic stress disorder (PTSD) is an anxiety disorder that is usually caused by experiencing traumatic events. While there is limited research on the association between PTSD and MS, research has found a significant proportion of pwMS have experienced PTSD-related symptoms.
Aims: To understand people's experiences of PTSD in relation to their MS.
Objectives:
1) Explore the experience of PTSD among pwMS using a web-based survey
2) Understand how clinicians can better support pwMS who have experienced PTSD

Methods: We posted a survey on Shift.ms from 18-Dec-20 to 4-Jan-21. Shift.ms is a global social network for, and founded by, pwMS. The contained 10 questions regarding people's age, gender, year of diagnosis, country of residence, PTSD symptoms and diagnosis. This analysis examined responses to the question "Please tell us more about your experience of PTSD as a result of living with MS?" We used NVivo12, a qualitative data analysis software, to code and analyse comments to identify common themes.
Results: We received 467 qualitative responses out of 1,079 who completed the survey. We identified four main themes: 1) experiences and diagnoses, 2) symptoms, 3) social impact and 4) coping strategies. People reported experiencing PTSD both prior to or following an MS diagnosis. Additionally, some believed that their PTSD had caused them to develop MS. Several people felt receiving their MS diagnosis had been traumatic and did not receive any support from clinicians. Anxiety was the most common symptom people experienced, followed by depression, disturbed sleep, fear, panic attacks, flashbacks and nightmares respectively. PTSD had a significant impact on pwMS's ability to work, socialise with friends and family and participate in previously enjoyed activities. Despite the difficulties of living with MS and PTSD, some people identified coping strategies including self-care, social support and professional psychological treatment.
Conclusions: It is important for clinicians to reconsider how they deliver an MS diagnosis, as many pwMS reported this as a traumatic experience. Clinicians should signpost people to support, such as counselling or therapy, which people reported helped them to cope. Finally, clinicians should consider how a previous experience of PTSD can impact pwMS and how an MS diagnosis/living with MS can be a traumatic experience.

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A provisional multidimensional computerized adaptive testing version of the MSQOL-54: Individualizing health-related quality of life measures in multiple sclerosis

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Introduction: The Multiple Sclerosis Quality of Life-54 (MSQOL-54) is one of the most used MS-specific health-related quality of life (HRQOL) inventories. Availability of an adaptive short version that immediately processes and scores the items may improve instrument usability and validity. Multidimensional computerized adaptive testing (MCAT) has not previously applied to MSQOL-54 items.
Aims: To develop an MCAT version of the MSQOL-54, and assess its performance.
Methods: Responses from a large international sample of MS patients were assessed. We calibrated 52 (out of 54) items using bifactor item response theory for graded response data model, with 10 group factors and one general HRQOL factor. Eight simulations were implemented with different termination criteria using a 2X2X2 factorial design. We set standard errors (SE) to 0.40 and 0.32 (i.e. corresponding to Cronbach's alpha thresholds of 0.85 and 0.90, respectively) for general HRQOL factor. We also set SE to 0.50 (i.e., Cronbach's alpha of 0.75) and 'no SE threshold' for group factors. In addition to the SE rules, in half of the simulations the MCAT terminated if the change in the general HRQOL factor score from one item to the next was <0.01. MCAT factor score estimates were evaluated in terms of number of administered items, root mean square difference (RMSD), and correlation.
Results: Our dataset included 3669 MS patients (mean age 43 years [range 18-87], 74% women, 54% mild level of disability). The bifactor model fit the data well. Local dependency was apparent between nine item pairs. By inspecting the item information function within pairs, we removed eight items having the lower information function from the subsequent analysis. Thus, 44 items were used in the simulation studies. Among the 8 simulations, that with SE set to 0.32 (general factor), and no SE thresholds for group factors provided satisfactory performance (mean number of administered items 26 [range 16-44], 41% reduction in respondent burden); the correlation with the full-length questionnaire was 0.94, and the RMSD was 0.32.
Conclusions: Compared to the original MSQOL-54, the MCAT version required fewer items without loss of precision for the HRQOL general factor, at the same time reducing respondent burden. Further work should be conducted to revise MSQOL-54 items, in order to make the calibration and MCAT performance efficient also on group factors, so that the MCAT version may be used in clinical practice and research.

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Predicting expanded disability status scale (EDSS) Using patient reported outcomes (PROs)

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Introduction: Patient Reported Outcomes (PROs) have previously been used in Multiple Sclerosis (MS) studies as a complement to clinical outcomes, such as the Expanded Disability Status Scale (EDSS), to get the patients' own perspective of the disease. The Multiple Sclerosis Impact Scale (MSIS-29) is a PRO consisting of 29 questions that capture two specific domains, a physical domain (20 questions) and a psychological domain (9 questions). Previous studies have shown that these two domains can be used as a prognostic tool for clinical outcomes. Given the richness of the questionnaire, there may be even more domains that together could increase the correlation with clinical outcomes.
Objectives: The aim of this study was to use a neural network variational autoencoder to derive a richer domain space of five latent variables from MSIS-29 and use these domains to get a better prediction of EDSS using a feed forward neural network.
Methods: The Swedish MS registry was used to obtain MSIS-29 and EDSS scores from 9421 patients and 42776 observations, where each MSIS-29 observation had a related EDSS observation

within ±6 months. The data was divided into a training set (7421 patients, 33749 observations) and a validation set (2000 patients, 9027 observations). Both the variational autoencoder and the EDSS predictor networks were trained using the training set, where the five latent variables were used as input to the EDSS predictor. For comparison, a separate EDSS predictor was also constructed using the original two domains as input. The validation set was used to calculate the correlations.

Results: The physical and psychological domains of the MSIS-29 had a correlation of 0.66 and 0.32 with EDSS. Using these two domains as input to a neural network EDSS predictor increased the correlation with EDSS to 0.68. Each of the five domains obtained from the variational autoencoder correlated to a lower degree with EDSS (0.58, 0.51, 0.63, 0.51, 0.45), but when combining them to predict EDSS the correlation increased to 0.71.

Conclusions: The two original domains of the MSIS-29 correlated well with EDSS, especially when used jointly in a feed forward neural network. However, by constructing a larger domain space of five variables it was possible to increase the correlation further, demonstrating a richness of the MSIS-29 that goes beyond the two original domains. This reflects also that EDSS is indeed a composite of separate domains.

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Multiple sclerosis and ambulation: the relationships of the neuro QoL lower extremity function patient reported outcome to quantitative gait parameters during preferred walking speed and dual task walking

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Introduction: People with Multiple Sclerosis (PwMS, MS) experience disease courses characterized as having relapses and/or progression of disease impact. Some features of accumulative disease burden in PwMS are measured by EDSS and/or MRI. However, neither of these two outcome measures holistically reflect the PwMS experience or disease impact on real world experience (RWE). Patient perspective of disease impact has also become an important measure of disease and disability change but the relationships of some of these reported measures reflecting the patient experience are not well defined in relation to multidimensional objective examiner independent quantitative gait analysis. Current approaches to identify "no evidence of disease activity" (NEDA) or RWE as a measure of disease stability or change are likely insufficiently granular and quantitative to identify early changes along a continuum with the patient RWE. The Neuro-QoL Lower Extremity Function (LEF) is one such PRO developed to capture the patient experience.

Objectives: To enhance insight into the relationship of the patient RWE by PRO to several critical quantitative objective measures underlying gait cycle.

Methods: A retrospective review of data collected in routine care of PwMS including: demographics, Neuro-QoL-LEF PRO and digital gait analysis (GA) on the same day. GA captured the following gait parameters: Velocity (V), Double Support (DST), Cadence (C), Functional Ambulation Profile (FAP), Gait Variability Index (eGVI), and Walk Ratio (WR) averaged across 3 trials during preferred walking speed and then dual task walking. Regression analysis was completed.

Results: PwMS (N=105), gender 69% female, average age 53.7 +/- 11 years. Along a continuum the LEF values related to the following gait parameters during preferred walking speed: V R^2=0.54, DST R^2=0.36, C R^2=0.44, FAP R^2=0.32, eGVI R^2=0.44, WR R^2=0.01; dual tasking walking: V R^2=0.46, DST R^2=0.17, C R^2=0.4, FAP R^2=0.38, eGVI R^2=0.36, WR R^2=0.004.

Conclusions: Walking ability reflects a complex integration of multiple factors. Effective or safe ambulation ability represents a combination of not only multiple underlying abilities but incorporating the patient perspective with multi-dimensional measures of ambulation together can add more value to identify RWE of disease impact and or progression. This combination of RWE and objective measures of disease impact and disease change can enhance the definition of NEDA and treatment value.

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The relation between age, symptoms onset and physical disability: a prospective registry study

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Introduction: Age has a role determining the impact of MS on individuals with later onset, who appear to accumulate disability more rapidly. However, in progressive forms the mean age at onset of progression does not differ and the ages at which disability landmarks are attained are similar among all MS subtypes.
Objectives: We looked at the relation between age and physical disability as described by two patient reported outcomes (PROs), namely the Multiple Sclerosis Impact Scale (MSIS-29) and the Multiple Sclerosis Walking Scale (MSWS-12). We wanted to determine whether these PROs are sensitive to age and capture any age-related decline and if this decline can be attributed to ageing with the disease or to normal ageing.
Methods: We studied >90,000 MSIS-29 and MSWS-12 questionnaires generated over 10 years by 14,533 patients and grouped them into 5 years age groups. Control data (~500) was available only for MSIS-29; based on this data the benign MS subgroup (milder form of MS) offered a good approximation to controls and it was therefore compared to the remaining MS population. Permutation testing was used to evaluate the influence of age group on the PROs and how this varied based on benign subgroup membership. Moreover, we looked at how the correlation between PROs and age was modulated by disease duration.
Results: Age group was associated with PROs for MS patients (MSIS-29: $p<0.0001$; MSWS-12: $p<0.0001$) who are not benign (MSIS-29: $p=0.6299$; MSWS-12: $p=0.4723$). The correlation between age and PROs for this group was positive (MSIS-29: $r=0.221$, $p<0.0001$; MSWS-12: $r=0.288$, $p<0.0001$). In contrast the correlation for the benign subgroup was negligible (MSIS-29: $r=0.099$, $p<0.0001$; MSWS-12: $r=0.049$, $p=0.0655$). When evaluating the correlation between age and PROs separately at different disease durations, the correlation was found to be larger and positive in the earlier stages of the disease and reducing progressively in the more advanced stages.
Conclusion: Both MSIS-29 and MSWS-12 worsen with increasing age and this worsening cannot only be attributed to normal ageing, as it is not observed in the benign subgroup. Age appears to be modulating MSIS-29 and MSWS-12 in the first few years since MS onset. As disease duration increases, the symptoms slowly overpower this effect and even up the differences among individuals of different ages. More work should go into understanding the mechanism behind the interaction of MS onset, age and age at onset.

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Neuroimaging correlates of patient-reported outcomes in multiple sclerosis

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Introduction: Patient-reported outcomes (PROs) are increasingly associated with concurrent and future impairments in persons with multiple sclerosis (pwMS). The structural and pathological relationship between MS pathology and PROs in pwMS is currently unknown.
Objective and aim: To investigate the relationship between PROs and magnetic resonance imaging (MRI) measures of inflammatory and neurodegenerative changes in a heterogenous group of pwMS and age and sex-matched healthy controls (HCs).
Methods: Total of 142 pwMS and 47 HCs were scanned using 3T MRI scanner and completed a Likert-style PRO questionnaire named Lifeware®that outlines the ability to stand up from low seat, climb a flight of stairs, upper or lower extremity limitation, bladder or bowel continence, fatiguability and life satisfaction. Beck's Depression Inventory (BDI) for assessment of depression was also completed. MRI-derived T1/T2-lesion volume (LV), and volumes of the whole brain (WBV), gray matter (GMV), white matter (WMV) and lateral ventricle (LVV) were derived using SIENAX software. Additional volumes of the deep GM (DGMV) and nuclei-specific volumes of thalamus, caudate, globus pallidus, putamen, and hippocampus were calculated using FIRST. Ordinal regression models adjusted for age and depression were used.
Results: The extent of patient-reported limitations in standing up from low seat or climbing flight of stairs were explained by age, BDI and all DGM nuclei volumes ($p<0.029$). Limitations due to

fatiguability and the extent of life satisfaction were only related to the level of depression (BDI $p<0.001$), and not associated with any MRI-based outcomes. Most relationships between structural pathology and PROs were modulated by BDI scores.
Conclusion: PROs in PwMS are associated with neurodegenerative changes specifically to the DGM nuclei. Contrarily, PROs were not associated with the MS lesion load. Depression is a significant modulator of PROs and of pwMS life satisfaction.

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Participation and barriers for work in individuals with multiple sclerosis in Nordland county (Norway): a survey study

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Introduction: Multiple sclerosis (MS) is a chronic, neurological disease affecting young individuals in working age. Most people with MS(pwMS) have mild to moderate disability (level 0-4 at the Expanded Disability Status Scale (EDSS)), still, many are unemployed or in reduced positions.
Objective: Knowledge regarding work status and barriers for work in pwMS is needed.
Aim: To explore work status and barriers for work in pwMS in Nordland county, Norway.
Methods: This cross sectional survey study was sent by post to all pwMS in Nordland county, Norway, who were over 18 years old and registered at the Nordland Hospital Trust (N=512). Work status, clinical and demographical characteristics and a questionnaire exploring barriers forwork (MS Work Difficulties Questionnaire-23) were recorded. The survey was sent out in June 2021, with a reminder in October 2021 and January 2022. The inclusion ended in February 2022. Descriptive statistics in IBM SPSS is used to describe status for work participation and barriers for work in pwMS.
Results: There were 250 pwMS participating in the survey (approximately 50% of pwMS in Nordland answered). The EDSS score among those under 67 years old was mean 2.8 (SD 2.4) and median 2, which indicate mild disability. Within those under 67 years old, 57% had been working the past year, and these were working on average 61%. There were no difference between pwMS` current % of employment and the % they desired to work if the job was specifically adapted to their needs. Both physical, cognitive and social barriers for work were reported in persons of all ages. More detailed calculations and correlations between factors will be conducted.
Conclusion: Only 57% of the MS population in this study who were in working age were actually working, even though having mild disability. As there were no difference between current work percentage and desired percentage, this may indicate that these individuals were comfortable with being in reduced positions. Both physical, cognitive and social barriers for work were reported. Interventions that adress work participation in pwMS are needed.

Disclosure
Nothing to disclose

Clinical aspects of MS - Economic burden

P514
Sustained decrease of income in multiple sclerosis: a new possible disability outcome measure of disease progression

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Introduction: Conventional disability multiple sclerosis (MS) outcome measures such as those based on expanded disability status scale (EDSS), are hampered by several factors including frequency of clinical visits. Alternative independent measures are needed for studying MS characteristics and the effect of interventions such as disease modifying treatments (DMT) on MS progression.
Objectives: We aim to utilise linked data from the Swedish MS-registry and the longitudinal integrated database for health insurance and labour market studies (LISA) from Statistics Sweden to establish a new method based on the patients' sustained decrease of annual income (i.e., declared earnings) as an outcome measure for disease progression and disability.
Methods: We have previously reported that treatment delay increased the risk of progressing to EDSS 4 by 7% per year (95% confidence interval (CI), 1.048−1.101,$p< 0.001$) in patients from Stockholm. Here, we reproduced the results for all adult patients in the Swedish MS registry with relapsing-remitting or secondary progressive MS, exposed to DMT for at least 3 months (N=8713). We examined the benefit of early treatment using a socioeconomic outcome measure, the sustained decrease of income (SDI).

We define SDI as a sequence of negative linear regression coefficients generated for each additional annual income from MS onset for each patient. Such a sustained series of negative coefficients indicate an irreversible drop of income that we believe is associated with disease progression. The time from the MS onset to the first DMT was used as the exposure variable in multivariate Cox regression analysis, revealing the risk of reaching SDI before the age of 65 years.

Results: Cox regression analysis with uncategorized time to DMT initiation showed a statistically significant hazard ratio (HR) of 1.03 (95% CI, 1.02−1.04,$p < 0.001$), increasing the risk to reach SDI by 3% for every year of delaying DMT use after MS onset. The Cox model was adjusted for age at onset, baseline EDSS, treatment year, gender, but also education which correlates highly with income.

Conclusion: We developed and present a new MS outcome measure based on the patients' sustained decrease of income (SDI) after onset and we confirm that similarly to EDSS-based disability progression, early exposure to DMT is associated with more favourable outcomes on the patients' ability to work and maintain their earnings after treatment initiation.

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Clinical aspects of MS - Comorbidity

P515

Long-term outcome after COVID-19 infection in multiple sclerosis: a matched-controlled study in a nation-wide Austrian registry

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Background: Long-term outcome after COVID-19 in patients with multiple sclerosis (pwMS) is scarcely studied and controlled data are lacking.

Objective: To describe long-term outcome after COVID-19 in pwMS in comparison to a matched control group of pwMS.

Methods: From the AutMuSC registry,we included pwMS with PCR-confirmed diagnosis of COVID-19 and ⩾6 months of follow-up available. As a control group, we recruited pwMS from the Vienna MS database (VMSD) matched for age, sex, disability level (Expanded Disability Status Scale [EDSS]) and disease-modifying treatment type (no vs. immunomodulatory vs. immunosuppressive DMT).

Results: Of 142 pwMS with COVID-19 (mean age 43.2 years [SD 11.8], 63.4% female, median EDSS 1.5 [range: 0-7.5], 54.2%immunomodulatory DMT, 20.4% immunosuppressive DMT), 90.1% initially had a mild COVID-19 course not requiring hospitalization.

Three months (M3) afterCOVID-19, 76% had recovered completely, 84% after 6 months (M6) and 92% after 12 months (M12). Most frequent residual symptoms were new or worsened fatigue (M3: 18.4%, M6: 12.8%, M12: 7.8%), new or worsened hyposmia (M3: 8.5%, M6: 4.3%, M12: 1.4%) and new or worsened dyspnea (M3: 7.1%, M6: 6.4%, M12: 2.8%). Compared to matched controls (fatigue: 7.1%, hyposmia: 0.7%, dyspnea: 1.4%), fatigue and hyposmia were significantly more frequent only at M3, while dyspnea remained increased until M6.Occurrence of relapse (8.6% vs. 7.0%) and EDSS progression (5.6% vs. 4.2%) were not significantly increased in pwMS with COVID-19 compared to control group during the observation period.Employment status remained unchanged in 96.5% after COVID-19 and 97.9% in controls.

Conclusions: Long-term outcome of COVID-19 is favourable in a large majority of pwMS with only a small proportion of patients suffering from persistent fatigue, hyposmia or dyspnea, usually resolving after 3-6 months.Against the background of a closely matched control group, COVID-19 is neither associated with increased risk of relapse or EDSS progression nor a persistent increase in fatigue.

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P516

Cardiovascular comorbidities and cardiovascular risk assessment in Aquaporin-4 and MOG antibody disorders

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Introduction: Patients with autoimmune disorders may have increased risk of cardiovascular disease, which could influence management and clinical outcomes. However, little is known about vascular comorbidities in Neuromyelitis Optica Spectrum Disorders (NMOSD).
Objectives: To assess the frequency of cardiovascular comorbidities and determine cardiovascular risk in NMOSD Aquaporin-4 positive (AQP4+) and MOG antibody associated disease (MOGAD) patients, at diagnosis.
Methods: Adult patients with confirmed NMOSD AQP4+ and MOGAD consented to participate at the prospective cohort at Oxford Demyelinating Tissue Bank (United Kingdom), and filled in a Cardiovascular Risk Score (QRISK2) questionnaire at their first appointment, between August 2016 and April 2022. Items included were age (25-84 years old), sex, ethnicity, family history of heart disease, smoking, diabetes, hypertension, chronic kidney disease, atrial fibrillation, rheumatoid arthritis, body mass index (BMI), cholesterol/HDL ratio and systolic blood pressure. QRISK2 calculates the individual risk of having a heart attack, transient ischaemic attack (TIA) or stroke in the following ten years, if no previous vascular events. Binary logistic regression adjusting for confounding factors was used to compare MOGAD and NMOSD AQP4+patients.
Results: Included 71 NMOSD AQP4+ patients (median age 53 (IQR 20.0) years, 84.5% female, 56.1% white, median disease duration 3.0 (IQR 10.0) years) and 121 MOGAD patients (median age 38.0 (IQR 18.0) years, 63.6% female, 67.8% white, median disease duration 1.0 (IQR 4.0) years). Twenty-two (31.0%) NMOSD AQP4+ and 14 (11.6%) MOGAD patients had moderate or high cardiovascular risk (>10%). Frequency of diabetes was 7 (9.9%) and 5 (4.1%), hypertension 5 (7.0%) and 5 (4.1%), ever smokers 20 (28.2%) and 44 (36.4%), obesity (BMI > 30 mg/kg^2) 15 (28.3%) and 37 (41.1%), in NMOSD AQP4+ and MOGAD respectively. Differences were not significant between diseases when adjusted for age, sex, ethnicity, disease duration.
Conclusions: NMOSD patients have a considerable high burden of cardiovascular risk factors, hence close monitoring during follow-up is required.

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P517
Characterizing the relationship between white matter lesions and depression in patients with multiple sclerosis

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Introduction: Multiple sclerosis (MS) is an immune-mediated neurological disorder that affects one million people in the United States, with up to 50% of patients experiencing a lifetime depression. However, mechanisms of depression in MS remain underinvestigated. Previous research using lesion network mapping has demonstrated that strokes in gray matter associated with depression disrupt a reproducible depression network but this has not been expanded to white matter disease.
Objectives: To investigate the comorbidity of depression in MS.
Aims: This study aims to define how depression in adults with MS is associated with white matter lesion (WML) location and burden in a retrospective sample.
Methods: Participants with MS were identified from the electronic medical record. The depressed individuals (DI) included persons with evidence of depression as indicated by a ICD-10 depression diagnosis(F32-F34.*), a prescription for antidepressant medication, or screening positive via PHQ2/9(n=232, age(SD)=49(12), %females=86). The age- and sex-matched non-depressed comparators (NDC) included persons with no prior depression diagnosis, psychiatric medications, and were asymptomatic on PHQ2/9 (n=148, age(SD)=47(13); %females=79). Structural MRI was obtained as part of routine care at 3T using a research-quality protocol. WMLs were automatically segmented using the algorithm Method for Inter-Modal Segmentation Analysis and projected onto a standard template. Eighty-seven white matter tracts(WMT) were evaluated. The volume of WMTs intersecting each lesion was computed via streamline filtering in DSI Studio. Age and diagnostic effects were assessed with general linear models and T-tests. Enrichment of effects in a previously described depression network (Siddiqi et al., 2021) was also evaluated.
Results: Streamline filtering recapitulated previously known patterns of MS disease, with high proportions of streamlines impacted in the optic radiations, inferior fronto-occipital fasciculi, medial longitudinal fasciculi, and corticopontine tracts. Greater age was associated with higher disease burden in 54/87 WMTs ($P_{FDR}<0.05$). The burden of MS lesions was higher within versus outside the depression network ($P<2.2$ x10^-16). DIs had a higher mean disease burden across all WMTs ($P<0.05$).
Conclusions: We present a novel approach for calculating the relationship of WML to disease burden and provide new evidence supporting a relationship between WML and depression in MS.

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I have nothing to disclose.

P518
Clinical course of multiple sclerosis and patient experiences during breast cancer treatment

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Introduction: Over one third of people living with multiple sclerosis (MS) are post-menopausal women, a demographic disproportionately affected by breast cancer.
Objective: To characterize oncologic outcomes, MS trajectory, and qualitative experiences of women with MS diagnosed with breast cancer.
Methods: A single-center retrospective review of prospectively collected medical record data was performed for patients with both MS by 2017 McDonald Criteria and breast cancer. Demographic, oncologic (pathology and treatment), and MS (duration, disease modifying treatment (DMT) use, relapses, pseudo-relapses, and EDSS scores) data were reviewed following cancer diagnosis. Clinical notes and communications were reviewed using grounded theory to identify themes pertaining to patients' experiences with the dual diagnoses.
Results: Of 81 patients with both MS and breast cancer diagnoses at UCSF, 43 had informative records for analysis. At time of

cancer diagnosis, mean age was 56.7 years (range 47-81) and MS duration 16.5 years (SD 11.6). Cancer stage was mostly 1 (30%) or 2 (52.5%); 88.3% had hormone receptor positive disease. Oncologic treatment included surgical resection in 42/43 (97.6%), estrogen modulation (48.8%), chemotherapy (42.9%, including cyclophosphamide 7%), and radiation (31%).At cancer diagnosis, 51.2% of patients were on MS DMT; 27.9% subsequently changed DMT. Altogether, 6 patients (14.0%) experienced MS relapse(s) during the follow-up period (median 5 years); mean annualized relapse rate was 0.03 (SD 0.07); relapses were more common if DMTs were held/discontinued (p=0.045). Pseudo-relapses occurred in 12 (27.9%). EDSS scores remained stable over pre-treatment (2.25, IQR 1.5-6), mid-course (3, IQR 2-6), and follow-up (3, IQR 2-6) periods. Qualitative insights included: concern for immunosuppression in cancer setting, variable choices of oncologic treatment, MS vs. chemotherapy-induced neurologic symptoms, patient perspectives on self-care, and curiosity about hormonal therapies and MS course.

Conclusions: Breast cancer episodes punctuate the course of chronic conditions like MS, raising questions about impact on neurologic outcomes. Reassuringly, we did not detect increased MS relapse rate or disability progression. Qualitative themes central to MS treatment planning warrant further investigation. Decisions regarding MS DMT during breast cancer treatment will be further complicated by the approval of immunotherapies for breast cancer.

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P519

Smoking and health-related quality of life in patients with multiple sclerosis from Latin America

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Tobacco smoke is an important modifiable environmental risk factor for multiple sclerosis (MS) with a relevant impact on health-related quality of life (HRQoL) in affected patients. We aimed to assess the use of tobacco in patients with MS (PwMS) from Latin America (LATAM), and its impact on health-related aspects.

Methods: cross-sectional study with a web-based survey conducted between January and March 2022 in a large cohort of pwMS from LATAM using a self-administered, anonymous questionnaire delivered by treating neurologists and MS organizations. The survey was developed and underwent a pilot process to ensure that the items addressed accurately the purposed research questions. The survey collected data on demographics, social and clinical data, HRQoL (MS Impact Scale-29), Fatigue Severity Scale, The Hospital Anxiety and Depression Scale, and physical disability (self-administrated EDSS). PwMS were classified as follows: "Current user", those who use tobacco currently (at least one cigarette per day) within the past year. "Former users", those who had tried tobacco but had not used currently within the past year. "Never users", patients who never tried tobacco. For the analysis, patients were dichotomized as follows: current user + former users (CS+FS) and never users (NU). Descriptive and comparative measurement were done between groups in clinical and health related measurements.

Results: 425 patients from 17 countries of LATAM were included, mean age 43.6±11 years, 317 (74.6%) female, median EDSS 2 (range 0-9). A total of 300 (CS+FS) and 125 (NU) were analyzed. No significant differences were observed between groups in mean age (43.2 vs. 44.5 p=0.26), RRMS (81.6% vs. 71.2% p= 0.09), DMT received (84.3% vs. 81.6% p= 0.23) and EDSS (2.66 vs. 2.52 p=0.65). Significant differences were observed in CS+FS vs. NU in fatigue (39.4±1.0 vs. 32.2 ±1.1, p=0.01), MSIS-29 physical (50.3 ±1.7 vs. 45.5±1.2, p= 0.01) and anxiety (11.1±3.1 vs. 6.3±2.3 $p<0.001$) adjusted by co-variables. In CS+FS group, 30% of treating neurologist do not discuss with their patients about ceasing smoking habit.

Conclusion: in MS patients that smoke, health related aspects like fatigue and MS impact scale are significantly more affected compared with those in patients that never smoked. It is critical that providers caring for pwMS assess smoking status and educate patients about the relationship between this habit and its impact over progression and health related effects.

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P520

Enhanced detection of JCPyV DNA based on extracellular vesicle-associated cell-free DNA

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Introduction: Progressive multifocal leukoencephalopathy (PML) is a rare and potentially fatal demyelinating brain infection caused by JC polyomavirus (JCPyV). PML is a severe side effect of immunotherapy, particularly of natalizumab treatment of MS patients. Diagnosis can be challenging. Clinical or MRI-based suspicion requires sensitive methods to confirm the presence of JCPyV in cerebrospinal fluid (CSF). Polymerase chain reaction (PCR) is crucial for detecting JCPyV DNA. Nonetheless, PCR sensitivity is frequently limited, requiring repeated lumbar punctures or even the need for brain biopsies.

In recent years, extracellular vesicles (EVs) in health and disease have gained increasing attention. JCPyV particles, like many other viruses, have been found both on the exterior of EVs and packaged inside, possibly playing a role in intercellular transmission, viral spread across membranes, and facilitating immune escape.

Objectives/Aims: Increasing the sensitivity of JCPyV molecular assays using EV-associated cell-free DNA as a template.

Methods: Wild-type JCPyV particles deriving from a urine sample of a healthy individual and PML-type JCPyV of a brain biopsy from an HIV-1-infected PML patient were propagated on 293TT cells for four weeks. Cell culture supernatant was collected two, three, and four weeks post-infection, and JCPyV DNA was quantified in the combined cell culture supernatant using total DNA and EV-associated circulating cell-free DNA (ccfDNA) as template. EV-associated ccfDNA was isolated, enriching EVs from cell culture supernatant using a spin-column-based technique followed by a bead-based method to purify ccfDNA.

Results: The concentration of wild-type JCPyV DNA could be increased 1.5-fold ($1.44*10^7$ copies/mL vs. $9.28*10^6$copies/mL) when using EV-associated ccfDNA as PCR template over total DNA, while PML-type JCPyV could be increased 3.9-fold ($4.10*10^4$ copies/mL vs. $1.04*10^4$).

Conclusion: Highly sensitive methods are required to improve clinical diagnostics of PML, especially early in the disease. Of particular importance are PML cases associated with immunotherapy such as natalizumab for MS, as CSF JCPyV viral load is often low and remains repetitively undetected. In vitro, we could show that the concentration of detectable JCPyV DNA could be increased using EV-associated ccfDNA as PCR template as one way to increase molecular assay sensitivity. We now work on confirming this finding for clinical samples when PML is suspected.

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Clinical aspects of MS - Digital health and global networks

P521

Views from an international multiple sclerosis patient community on the future of their clinical care

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Background: The COVID-19 pandemic led to changes in healthcare delivery for people living with multiple sclerosis (MSers), largely due to the rapid increase in the use of telemedicine. The learnings from this change may influence the future of MS care, providing an opportunity for MSers to shape the framework of clinical care.

Goals: The goals of this research were to 1) gain lived experience insights to understand the impact of the pandemic on MSers' access to, and delivery of, clinical care about 18 months into the pandemic, and 2) understand MSers' experiences of telemedicine, including the adoption, feasibility, benefits, drawbacks, and preferences relative to their previous experience with in-person appointments.

Methods: An online volunteer survey (in English), available 27 August 2021 to 22 September 2021, was emailed or accessed through social media for adults (⩾18) who self-reported an MS diagnosis.

Results: 2,214 respondents answered at least the first question and 1,469 completed it. Most respondents lived in the UK (65%), were white (89%), female (77%), with diagnosis of relapsing-remitting MS (66%). Despite the pandemic, 42% of respondents were dissatisfied with the level of contact with their MS neurologist. Attending in-person appointments with MS clinical team was challenging for 51%, primarily due to symptoms/disability. Over the past year, 74% of respondents had a telemedicine (telephone or video) appointment and 51% had in-person appointments. More than half (60%) considered telemedicine to be the same or better than in-person appointments, especially if via video. Various types of appointments were identified as 'acceptable' or 'unacceptable' for telemedicine. Although there were varying

degrees of confidence with technology and use of telemedicine for remote care, the majority indicated recognition of the role of telemedicine in the future of MS clinical care and believe technology improves their lives.
Conclusions: Best practice for implementing video appointments by MS healthcare teams should include recognition of the patient perspectives and managing their expectations around the limitations. Considerations should include MSers' different confidence levels in engaging in telemedicine, understanding of appointment types better suited for in-person vs video, and heterogeneity of MS, including greater symptom burden for MSers with progressive MS, potentially impacting their ability to travel to in-person appointments.

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P522
Remote passive monitoring in people living with progressive multiple sclerosis during the COVID-19 pandemic shows a measurable reduction in daily activity

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Introduction: Government-led restrictions during the coronavirus disease 2019 (COVID-19) pandemic provided an opportunity to assess whether digital remote monitoring tools could effectively measure changes in daily activity in people with progressive multiple sclerosis (PwPMS).
Objectives: To assess the impact of COVID-19 restrictions on daily activity and clinical change in PwPMS using smartphone sensor data.
Methods: Using a precursor to Floodlight™ MS, we collected sensor data on daily activity and functional performance from June 2018 to August 2020 in a cohort of 427 PwPMS treated with ocrelizumab in CONSONANCE (NCT03523858). We developed a method for identifying individuals with an abrupt change in daily activity corresponding to local restrictions using life-space (the spatial range of mobility in everyday life [km]). Clinical measurements of the Timed 25-Foot Walk (T25FW) and Nine-Hole Peg Test (9HPT) were taken at baseline, Weeks 24, 48 and 72. Changes in digital (daily steps) and clinical outcome measures were correlated to changes in life-space.
Results: Patients with at least 50 days of life-space data with no more than 28 days between measurements in 2020 (n=122/427) were selected. Of these, 54 (44%) patients experienced a measurable reduction in life-space, with a median occurrence on 11 March 2020 ($\pm$19 days); 68 (56%) had no detectable change, of whom 13 (11%) had a consistently low life-space (mean=$<$1 km). Patients with a measurable reduction in life-space experienced a 28% reduction in daily step count in the first 4 weeks following restrictions ($p<0.0001$, Wilcoxon paired test). Longer duration of life-space restriction was correlated with greater reduction in step count (Spearman's $r=-0.86$, $p<0.00001$; n=31). A significant worsening (16% increase, p=0.011) in T25FW from Week 48 to 72 was observed in 30 eligible PwPMS with detected reduction in life-space between clinical visits, whereas a nonsignificant change (7% increase, p=0.23) was observed for 37 eligible PwPMS with a mean life-space consistently $>$1 km and no detectable reduction. No significant change was found for 9HPT in either group. There was no significant difference in baseline demographics and clinical measures between groups.
Conclusions: Prolonged reduction in mobility due to COVID-19 restrictions may impact physical activity and clinical disability in PwPMS. Remote digital monitoring using Floodlight MS may be useful for assessing activity and functional performance in PwPMS.

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M Usdin is an employee of Genentech, Inc. and shareholder in F. Hoffmann-La Roche Ltd.
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P523
Geography and a changing technology landscape: analysing coverage of German multiple sclerosis care networks and digital health technology adoption in multiple sclerosis trials

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Introduction: Due to the growing complexity of optimising multiple sclerosis (MS) monitoring and treatment, physicians increasingly need to specialise and engage in interprofessional communication. For this reason, disease-specific care and research

networks have been established, offering patients certified healthcare in participating centres. However, the ability of care networks to provide healthcare services to patients close to home usually remains vague. Digital Health Technologies (DHT) could help improve remote care.

Aims: In this study, we analyse the coverage of the German MS focused networks 'Kompetenznetz Multiple Sklerose (KKNMS)' and 'Deutsche Multiple Sklerose Gesellschaft (DMSG)' using a driving time-based isochrone approach. Additionally, we characterise the use of DHT in MS clinical trials.

Methods: Diagnostic and treatment focused network centres were mapped to OpenStreetMap locations, and isochrones for 30, 60, 90, and 120 minutes were calculated using a local installation of openrouteservice. The resulting geometric figures were aggregated and used to mask the publicly available global human settlement population grid 2019 (GHS-POP19) to estimate German inhabitants that can reach centres within the given periods. MS trials registered on ClinicalTrials.gov between 2010 - 2021 were screened for DHT usage and further characterised.

Results: Approximately 96.48 % of Germans can drive to a DMSG/KKNMS centre within one hour, while an estimated 99.98 % can reach one within two hours (30 minutes: 64.24 %, 90 minutes 99.71 %). When focusing on KKNMS, a network based on large academic hospital centres specialised in MS, an estimated 65.1 % of patients can reach a centre within one hour of driving, with approximately 98.42 % of Germans able to do so within two hours (30 minutes: 26.05 %, 90 minutes 90.92 %). MS trials on ClinicalTrials.gov show a trend toward adoption of DHT, with up to 15 % using such technology in 2020. Assessed outcomes using DHT focus on motor function but increasingly also include other concepts such as cognition.

Conclusion: Germany's coverage of MS-specific research and care networks is comparably good. However, there are certain regions where specialised care is hard to reach, which might be especially troublesome in the case of an often disabled patient collective. DHT, such as telemedicine or remote patient monitoring, could help to improve care in such areas and is already increasingly used in clinical trials.

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ADS declares that she serves as a member of the Scientific Advisory Board of HumanFirst.

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Group counselling consultations: the way forward?

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Introduction: Virtual patient consultations have become increasingly common following the COVID-19 pandemic. In our region, we have utilised virtual group meetings of up to 30 patients to deliver education sessions regarding drug therapy for multiple sclerosis. Counselling sessions using Microsoft Teams provided information for either Siponimod, Fampridine, or Ocrelizumab and Ofatumumab, with opportunity following the presentation for questions. Patients were subsequently offered an individual Consultant review for a personalised discussion.

Objectives: All individuals who attend a virtual session during February 2021 – March 2022 will be sent an online questionnaire to complete.

Aims: To determine the effectiveness of online group counselling consultations in providing information on medication.

Methods: Patients attending a virtual session during February 2021 – March 2022 were contacted to complete an online questionnaire.

Results: More than half (42/80) of patients who responded had no previous experience of using MS Teams. Sessions were considered easy to access (average rating 8.8/10) and technical issues with sound or connection were only reported by 9/80. Average knowledge of the drug prior to the session was 3.8/10 and following the session this improved to 7.9/10. A virtual group session allowed the opportunity to hear the questions of other patients and this was felt to be beneficial (average rating 8.9/10). The vast majority (78/80) had no concerns regarding their confidentiality. Preference for this session to be delivered virtually rather than in person, favoured virtual delivery (7.6/10). Final comments highlighted the time and travel savings, with no significant concerns raised.

Conclusions: Virtual group counselling sessions provide clear advantages to both patients and clinicians, saving time for the clinicians, but also giving patients group support around medication decisions. This review confirms that the majority of patients report group sessions are an effective, convenient and safe method of discussing medication. As treatment options for patients with MS expand and demand on services increases, this group

counselling platform will allow greater flexibility to deliver information to patients.

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Pathology and pathogenesis of MS - Pathology

P525
Neuronal loss in the thalamus and pons correlates with disease severity: Interim analysis of a large digital pathology study

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Introduction: Neurodegeneration plays a crucial role in determining disease severity and regional brain volume changes are predictive of disability progression.
Aims: We hypothesised that the extent of neuronal loss at extensively interconnected sites, such as the thalamus and brain stem, would be predictive of disease severity.
Methods: Sections of cortical (frontal, cingulate, occipital) and non-cortical grey matter (thalamus, pons and cerebellar dentate nucleus) were routinely sampled, immunostained and scanned (n=308 progressive MS cases; age=62, IQR 34-98; female= 199; UK MS Tissue Bank, REC 18/WA/0238). Digital slides were annotated and quantified (QuPath, v0.2.3) and the density of HuC+ neurons (mm^2), lesion area (percent of total block area, MOG+), microglia/ macrophage density (HLA-D+ immunoreactivity) and lymphocyte infiltration in meningeal and perivascular sites (CD20+ and CD3+ immunoreactivity) reported and compared to clinical measures.
Results: An interim analysis of neuron density (n=253), demyelination (n=40) and lymphocyte infiltration (n=30) are presented. Average demyelination was highly variable across cases (0-75%) and blocks (2-16%; greatest in cingulate and occipital cortex). Correlation analysis revealed significant associations between neuron density in the thalamus and occipital lobe and pons (Spearman $r>0.45$, $p<0.01$). Neuron density in the thalamus correlated with disease duration ($r=0.77$, $p<0.0001$), time to progression ($r=0.41$, $p<0.023$), and time from EDSS7 to death ($r=0.56$, $p<0.001$). Neuron density in the pons correlated with disease duration ($r=0.76$, $p<0.0001$), onset to progression ($r=0.56$, $p<0.001$), onset to EDSS7 ($r=0.68$, $p<0.0001$) and age died ($r=0.64$, $p<0.0001$). The area of CD3+ and CD20+ immunoreactivity was greatest in the pons ($p<0.05$) in comparison to other sampled blocks.
Conclusions: We reveal the significant association between neuron loss in the thalamus and pons with measures of disease outcome in this large pathological analysis. Monitoring regional tissue atrophy at these extensively connected sites could be an important surrogate of disability progression.

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P526
The prevalence and topography of spinal cord demyelination and inflammatory activity in multiple sclerosis

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Introduction: The demyelinated lesion is a cardinal feature of progressive multiple sclerosis (MS) pathology that commonly affects the spinal cord. Given its well-characterized anatomy, the distribution of spinal cord lesion topography and inflammatory activity may provide important clues about disease pathogenesis. Early observations demonstrated that spinal cord lesion distribution mirrors the venous architecture whilst recent imaging studies highlighted an outside-in gradient in which demyelination is most pronounced at surfaces nearest cerebrospinal fluid (CSF).
Objectives: Given the lack of consensus regarding the vascular and CSF contributions to spinal cord pathology, we aimed to characterise the prevalence and topography of spinal cord demyelination in a large post-mortem cohort using immunohistochemistry (IHC), the gold standard method for lesion detection.
Methods: Cervical, thoracic, and lumbar spinal cord tissue derived from 119 MS cases was available for study. IHC was used to detect demyelination (proteolipid protein) and classify its inflammatory activity (CD68). Lesions were standardised onto anatomical templates before mixed models and permutation-

based cluster analysis were used to identify patterns in the prevalence and topography of demyelination.
Results: Spinal cord lesions were observed in 76.5% of cases. Cases were more likely to harbour lesions at the cervical compared to the lumbar level. Inflammatory activity (active or mixed active/inactive) was a salient feature observed in 87.9% of cases. Lesions were vascularly distributed and consistently affected the dorsal columns, lateral corticospinal tracts, and the grey matter. The subpial surface was commonly spared with only a limited circumference impacted (less than 15%). The presence of lesions also exhibited a strong relationship with clinical disease milestones.
Conclusions: Our findings demonstrate that demyelination is common and highly inflammatory, biased towards the cervical level, and relates to clinical disability measures even at late disease stages. The subpial surface is commonly spared with a vascularly-associated predilection observed for white matter tracts and the grey matter. This argues against an outside-in gradient of spinal cord demyelination in MS. Taken together, our study highlights the importance of early intervention to target persistent inflammatory demyelination and nominates vascular dysfunction as an important potential target to study further.

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P527
Ultrastructural alterations in the normal appearing white matter in MS correlate with activated microglia and lymphocytes

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Introduction: In the normal appearing white matter (NAWM) in multiple sclerosis (MS) an increase in phospholipids and decrease of sphingolipids due to a lipid metabolism defect and deimination of myelin basic protein are modelled to lead to an increase in the repulsive force between myelin sheaths. Myelin blistering is observed in the NAWM, and myelin obtained from MS donors is phagocytosed more efficiently by microglia than myelin from control donors.
Objectives: Here we set out to systematically quantify the axon-myelin unit in MS NAWM and control white matter (WM) at the ultrastructural and subcellular level, and to correlate these characteristics with inflammation.
Aims: The aim of the project is to study alterations in the axon-myelin unit in the NAWM in MS that may predispose the tissue for lesion formation.
Methods: Transmission electron microscopy (TEM) and high resolution immuno-histochemistry (IHC) were performed on the normal appearing white matter of n=8 MS and n=8 control donors. The axonal density, g-ratio, axon caliber, inner tongue area, number of myelinoid bodies and myelin outfoldings, mitochondria size and mitochondria frequency were quantified, and the length and overlap of nodes, paranodes and juxtaparanodes were measured. The number of P2RY12-HLA+ microglia, iba1+CD68+ microglia and CD3+ T-cells were quantified, and were correlated to the ultrastructural characteristics.
Results: In MS there was a lower g-ratio (p=0.02), a lower myelin density (p=0.01) and a higher frequency of axonal mitochondria (p=1.5e-4). Furthermore, in MS there was a disorganization of the nodes of Ranvier with longer paranodes (p=0.03) and juxtaparanodes (p=0.01) and a larger overlap between paranodes and juxtaparanodes (p=7.12e-5). This range of ultrastructural characteristics correlated positively with the number of active and phagocytic microglia and lymphocytes in the optic nerve.
Conclusions: In MS optic nerve NAWM the myelin layers are less compact, there is an altered organization of the Nodes of Ranvier, potassium channels are unmasked at the nodes of Ranvier and axons contain more mitochondria, accompanied by increased presence of activated and phagocytic microglia and T cells. Together, this may predispose the myelin in MS NAWM for lesion formation and thereby contribute to disease progression.

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P528
Microfibril-associated protein 4 (MFAP4) Is a marker for disease activity and extracellular matrix remodeling in the active disease stage of inflammatory demyelinating diseases

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Introduction: Active disease stages of inflammatory demyelinating diseases (IDDs) are frequently associated with inflammation and subsequent disruption of the blood-brain barrier. Microfibrillar-associated protein 4 (MFAP4) is an extracellular matrix protein and a marker of matrix remodeling in peripheral diseases. MFAP4 has never been described in the CNS.

Objectives: to evaluate MFAP4 CNS expression and measure CSF and serum MFAP4 levels in patients with IDDs.

Methods: MFAP4 levels were determined with an AlphaLISA immunoassay. Two other CNS proteins, glial fibrillary acidic protein(GFAP) and neurofilament light chain (NfL), were measured with ultrasensitive single-molecule array assays. The study included 161 IDDs patients from eight centers (62 NMOSD all AQP4-IgG positive, 22 MOG-IgG+ associated disease (MOGAD), 19 optic neuritis (ON), and 49 MS). Serum from healthy controls (HC) (64, of those in addition 14 CSF) were tested. Tissues sampled at CNS autopsy were from patients with acute MS (n=3), progressive MS (n=3), NMOSD (n=2), disease controls (n=3, from patients with stroke) and HC (n=6). Paraffin sections were stained using antibodies against MFAP4.

Results: CSF MFAP4 levels were reduced in the acute stage of IDDs (⩽60 days); the reduction was more pronounced in patients with acute ON relapse (mean 14.6 U/mL vs. 17.9 U/ml HC, p=0.009) compared to other CNS attacks (17.2 U/ml, p=0.031). CSF MFAP4 levels in acute stage IDDs were negatively correlated with the severity of the relapse (r=-0.42, p=0.015). CSF MFAP4 levels were positively correlated with NfL levels in IDDs (r=0.21, p=0.0431), and with GFAP levels in NMOSD (r=0.38, p=0.023). In tissues, MFAP4 immunoreactivity was observed in the meninges and the vascular/perivascular spaces in HC; reactivity was enhanced in the optic nerve. At sites of active inflammation, a downregulation of MFAP4 reactivity was observed in NMOSD and to a lesser degree in MS.

Conclusions: CSF MFAP4 may serve as a marker of disease activity and contribute to extracellular matrix remodeling as a consequence of inflammation in active IDDs.

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P529

Microglial and iron heterogeneity in progressive multiple sclerosis

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Introduction: Modulation of microglia is being considered as a therapeutic approach for delaying progressive disability in multiple sclerosis (MS). Microglial cells associated with demyelinated lesions are prominent in chronic active white-matter (CAWM) inflammation, which varies based upon lesion location, mechanism of demyelination, and age of the lesion. This study was focused on establishing a database of cerebral white-matter lesions (WMLs) and investigating whether these WMLs were associated with iron-sequestering microglia. Iron is the major paramagnetic component of paramagnetic rim lesions which can be detected on a single MRI scan and is associated with disability progression in MS.

Objectives: To identify and characterize a pathological database of CAWM lesion types in postmortem brains from progressive MS patients.

Aims: 1) To characterize microglial associations with CAWM lesions. 2) To investigate associations of CAWM lesions with iron-positive and iron-negative microglial lines.

Methods: Macroscopic visible WMLs (280) were dissected from cm-thick coronal brain slices from a cohort of progressive MS patients. These lesions were sectioned and stained for myelin (proteolipid protein), microglia (MHC Class II), and iron (Turnbull method).

Results: CAWM lesions are characterized by a microglial line at the lesion border and a hypocellular demyelinated core. Over 280 macroscopic cerebral WMLs were harvested from 19 MS brains, and the lesions were stained for myelin and MHC Class II antibodies. Of these, 35 lesions (12%) were active, 155 lesions (55%) were chronic active, and 91 lesions (33%) were chronic inactive. The deposition of iron in 144 CAWM lesions was investigated using the Turnbull method: 39 lesions (25%) had a prominent iron ring, while 116 lesions were negative for iron despite having a prominent microglial line at the lesion border.

Conclusions: This database of cerebral WMLs will afford further investigation into the mechanisms of MS disease progression by characterizing microglial lines associated with CAWM lesions. It has been proposed that expansion of perilesional iron rings could serve as a surrogate marker for lesion expansion and progression of disability. Seventy-five percent of CAWM lesions were iron-negative, and iron can accumulate without enrichment of microglia. If expansion of chronic active lesions contributes to disease progression, then demyelination at the lesion edge should be associated with microglial lines.

Disclosure

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K Cyncynatus and T Chomyk have no disclosures.

P530

Lipocalin 2 regulates blood-brain barrier integrity under inflammatory conditions

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Endothelial cells are, together with astrocytes and pericytes, an integral part of the blood-brain barrier (BBB). The complex pathogenesis of multiple sclerosis (MS) includes a significant contribution of vascular inflammatory processes, in which circulating immune cells enter the central nervous system, a process called diapedesis. In previous studies, by using mouse models for MS, we identified lipocalin 2 (LCN2) as a protective molecule that partly protects oligodendrocytes in the toxic cuprizone model. Since LCN2 is a secreted protein and endothelial cells are known to express LCN2 receptors, we hypothesized that LCN2 might additionally be able to stabilize the integrity of the BBB by restoring endothelial permeability under inflammatory conditions. Indeed, *Lcn2*-deficient mice showed increased perivascular infiltrations in the combinatory Cup/EAE model. Furthermore, LCN2 may regulate the expression of tight junction molecules and/or integrins. To investigate this, we first analysed astrocytic LCN2 expression at the *Glia limitans perivascularis* using transmission electron microscopy. Further, *in vitro* endothelial cell cultures were used to investigate LCN2 effects on endothelial permeability under inflammatory conditions. Pro-inflammatory stimuli resulted in a disruption of endothelial barrier as measured in transwell permeability assays and electrical impedance sensing measurements (EIS). Gene and protein expression levels of tight junction molecules and integrins were evaluated in response to inflammatory stimuli and/or additional LCN2 treatment.

Using *in vivo* MS models, we found astrocytes to express LCN2 in close spatial proximity to endothelial cells, indicating that astrocytes might mediate inflammatory signalling within the CNS by secreting LCN2 at the astrocyte-endothelial interface. *In vitro*, endothelial permeability was improved by LCN2 treatment and EIS showed enhanced impedance after co-stimulation with LCN2. Tight junction molecules were stabilized in the cell membrane by LCN2 as observed in immunofluorescence-based time-lapse microscopy.

Taken together, our data indicate a possible role of LCN2 in maintaining BBB integrity during inflammatory lesion formation and progression. Future studies will include a novel astrocyte-specific *Lcn2*-deficent mouse strain to further elucidate the precise role of astrocytic LCN2 in the context of MS-related inflammation in the CNS.

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P531

Accelerated cellular senescence in progressive multiple sclerosis

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Background: Age-related neurodegenerative processes have been implicated in the pathogenesis progressive MS (P-MS) and recent evidence support a role for cellular senescence (CS) in age-related neurodegeneration.

Aim: To seek pathological evidence of accelerated CS in P-MS and determine its pattern.

Methods: Three to four post-mortem tissue blocks per case of P-MS (n=30) and controls (n=14) from the UK-MS tissue bank were analyzed. MOG, GFAP, HLA-II TMEM119, Olig-2, Iba-1, GAD67, MAP2 immunostaning was used to quantify demyelination and inflammation and identify cell types. 53BP1 (DNA damage response-DDR marker) and p16 and GL-13 (lipofuscin detection system) were used as markers of CS in 7μm-sections of demyelinated white matter lesions (WML), normal appearing white matter (NAWM), normal appearing cortical gray matter (NAGM) and control white (CWM) and gray matter (CGM). Senescence-associated secretory phenotype (SASP) factors were quantified in CSF using Bioplex assay.

Results: The %53BP1$^+$ cells in MS WML were found increased 2.1-fold compared to NAWM and 3.8-fold compared to CWM ($P< 0.01$ for both). The % GL13$^+$ cells were increased in WMLs 1.6-fold compared to NAWM ($P<0.05$) and 2.6-fold compared to CWM ($P<0.01$), indicating more extensive CS in demyelinated areas. P16$^+$ cell counts were also more numerous in WMLs compared to NAWM ($P<0.05$) and CWM($P<0.001$) and in GMLs compared to NAGM ($P<0.05$) and CGM ($P<0.001$). Co-localization studies showed evidence of DDR and CS in neurons, astrocytes, oligodendrocytes but notmicroglia. The %53BP1$^+$ cells correlated with GFAP (rp= 0.50, $P<0.05$) and HLA II IR (rp=0.42, $P<0.05$) in WMLs but not in NAWM or NAGM, indicating increased DDR in demyelinated lesions, associated with astrogliosis and microgliosis. 53BP1$^+$ and p16$^+$NAGM cell counts exhibit an inverse correlation with age of death (rp=-0.49, P= 0.015 and rs= -0.45, P= 0.029), suggesting that the greater the senescent cell load in NAGM the earlier the death in P-MS.

SASP factors IL-6, IL-10, Gro-β, MCP-1, MCP-3, MIP1a, MIP3a, CCL-25, TNF-a, and MIF were significantly increased in the CSF

of MS cases. CSF IL-6, MIF and MIP1a levels correlated with 53BP1$^+$ cell counts in NAGM, (rp=0.60, P=0.012; rp= 0.56, P= 0.024, rp= 0.57, P= 0.020, respectively), while IL-10 levels correlated with p16$^+$cell counts in NAWM (rp=0.62, P= 0.01).
Conclusions: Our study provides evidence of accelerated CS, primarily affecting demyelinating lesions and the presence of CSF SASP factors in P-MS.

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19: Experimental models

P532
Interferon-gamma restricts the immune responses in neuromyelitis optica disease: a novel animal model

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Introduction: Neuromyelitis Optica (NMO) is an autoimmune disease of the Central Nervous System (CNS) mediated by Th17 cells and antibody response to the water channel protein Aquaporin 4 (AQP4), associated with chronic damage of the optic nerves and spinal cord, leading to paralysis and loss of sight. NMO animal models are substandard inducing disease inconsistently and weakly.
Objectives: Develop and characterize a new NMO mouse model, which best represents the human disease in terms of incidence and chronicity of the disease, severity of symptoms and underlying molecular mechanisms.
Aims: Describe the role of Interferon-gamma (IFN-g) on the induction of an AQP4 animal model.
Methods: C57BL/6 (WT) and IFN-g knockout (GKO), IFN-g receptor KO (IFNRKO) and IFN-alpha/beta receptor 1 KO (IFNARKO) mice were immunized subcutaneously with the $AQP4_{201-220}$peptide in Complete Freund's Adjuvant and treated with pertussis toxin at day 0 and +2. WT mice were treated weakly with neutralizing anti-IFN-g antibodies. mRNA expression and flow cytometry analysis of infiltrating CNS cells were performed. CNS histopathology was determined by immunofluorescence.*In vivo*anti-IL-6R antibodies were used to interfere with IL-6 signaling and, B-cell depletion was made using anti-CD20 antibodies.
Results: WT mice treated with anti-IFN-g antibodies, GKO and IFNGRKO mice showed ascendant paralysis starting from the tail to complete hind limb paralysis with higher incidence and more severe chronic symptoms, but not IFNARKO mice. CNS Th17 cells and associated genes were upregulated in the absence of IFN-g. CNS histological analysis showed an increased presence of T and B cells, and complement, in lesion sites, associated with astrocytes, myelin, oligodendrocytes and neuron loss. Mechanistically, IL-6 signaling is necessary for the development of plasma cells, and disease incidence, and B-cell depletion diminished the disease incidence, severity and Th17 phenotype, confirming B cell pathogenicity.
Conclusions: AQP4 mouse model is strictly regulated byIFN-g and its signaling, controlling the disease onset, progression and severity, by restraining pathogenic Th17 and B cells through modulation of IL-6 signaling. This model shows high similarity with human Neuromyelitis Optica in terms of clinical severity and molecular mechanisms.

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Identifying the molecular underpinnings of blood-brain barrier dysfunction in multiple sclerosis

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Introduction: Blood-brain barrier (BBB) breakdown is amongst the earliest pathological hallmarks observed in multiple sclerosis (MS). The mechanisms leading to BBB dysfunction are incompletely understood and are generally thought to be a consequence of the autoimmune neuroinflammatory process in MS.
Objective/Aims: We challenge this view and ask if intrinsic alterations in BBB endothelial cells manifested at the genetic or epigenetic, transcriptional, and ultimately phenotypic level cause or contribute to altered BBB function in MS.
Methods: We made use of human induced pluripotent stem cells (hiPSCs) derived from 3 healthy controls (HC) and 4 MS patients and differentiated them using a newly established extended endothelial cell culture (EECM) protocol into EECM-brain microvascular endothelial cell (BMEC)-like cells as *in vitro* model of the BBB. We performed transcriptional profiling of HC and MS-derived EECM-BMEC-like cells stimulated or not with TNF-α and IFN-γ by RNA sequencing.
Results: The RNA sequencing analysis showed 438 and 282 differentially regulated genes in unstimulated and stimulated EECM-BMEC-like cells derived from HC and MS patients, respectively. Reactome Pathway analysis identified a strong modulation of the Semaphorin-4D (SEMA4D) signalling pathway in unstimulated

MS-derived EECM-BMEC-like cells compared to the controls. Our ongoing studies confirm expression of SEMA4D and its downstream effectors, RHOB and ROCK2 in EECM-BMEC-like cells and a contribution of this signalling pathway in junction maturation.
Conclusion: Our study suggests that SEMA4D and its downstream effectors may contribute to junctional impairment of the BBB in MS.

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Patient-derived 3D brainspheres as a platform to model chronic neuroinflammation and interrogate its molecular mechanisms in multiple sclerosis

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Introduction: Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS), whose pathophysiology impacts on the function of immune and CNS cell types. Advances in human stem cell technologies have enabled the generation of human induced pluripotent stem cells (hiPSCs) from MS patients as a valuable tool for disease modelling.
Objectives: We optimized a protocol to generate 3D Brainspheres (BS) consisting of neurons, astrocytes, and oligodendrocytes and to co-culture BS with hiPSC-derived microglia, where we modelled the effects of MS-specific inflammation in enhancing neurodegeneration, by exposing BS to MS patient-cerebrospinal fluid (CSF).
Methods: hiPSC lines derived from 2 MS patients and 2 healthy donors were used. Based on data from the literature, we generated neural precursors (NPCs) containing a*SOX10*-enhanced green fluorescent protein cassette under a doxycycline-inducible promoter to stimulate the differentiation of mature oligodendrocytes. 3D BS were generated and co-cultured with iPSC-derived microglia, whose differentiation was characterized by flow cytometry and immunofluorescence. During differentiation, the expression of neuronal, astrocyte, and oligodendrocyte's markers was assessed by RT-qPCR and immunofluorescence. Electron microscopy analysis was performed to visualize the presence of wrapping myelinating processes and synapses. After 8 weeks of differentiation, BS were stimulated with 10% CSF for 24 hours and the transcriptome of the different CNS cells was profiled by single cell RNA-sequencing.
Results: We established a protocol to generate human 3D BS, displaying the diversity of CNS cells, as assessed by gene expression and immunostaining analysis. We confirmed in 3D cultures that *SOX10* over expression in human NPCs promoted the differentiation of oligodendrocyte's resembling the primary humans. Ultrastructure analysis by electron microscopy revealed a variety of differentiated and mature cell types in the BS, including functional myelinating oligodendrocytes. Notably, exposure to CSF induced a marked alteration of intracellular signalling pathways related to inflammatory and oxidative stress response, paving the way for future investigations dissecting the underlying molecular mechanisms.
Conclusions: We implemented BS as a valuable 3D organotypic model, providing a reproducible protocol for modelling chronic inflammation in MS and drug discovery effort.

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P535

Pharmacological microglia depletion followed by repopulation ameliorates recurrent cuprizone-induced demyelination

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Introduction: Remyelination failure is a hallmark of progressive MS and is associated with neuronal loss. Thus, pro-remyelinative strategies have therapeutic potential for MS. Microglia, innate immune cells in the central nervous system (CNS) parenchyma, are implicated in MS. As CNS sentinels, microglia respond to homeostatic disturbances with a range of activation states. Microglia support remyelination by removal of myelin debris, lesion remodelling, and secretion of trophic factors. However, their supportive abilities are reduced during MS progression and with age. Therefore, we hypothesize that rejuvenating microglia through a repopulation cycle could improve remyelination.
Objectives/Aims: To determine the effects of microglia depletion and repopulation on remyelination efficiency, oligodendroglial differentiation, and microglia morphology and gene expression. Hereto we used mice repeatedly exposed to cuprizone to model reduced remyelination capacity.

Methods: In a recurrent cuprizone-induced demyelination mouse model, we acutely depleted microglia using the colony-stimulating factor-1 (CSF1R) inhibitor BLZ945 and allowed them to repopulate. In brief, two weeks after a five-week cuprizone diet, microglia were depleted with daily administration of BLZ945 (p.o.) for five days, and mice were allowed to recover for 10 weeks before a second five-week cuprizone diet. To assess remyelination efficiency and quality, we used electron microscopy to measure g-ratios and assess myelin quality. To investigate oligodendroglial differentiation and microglia morphology, we performed immunohistochemical analysis. We further assessed the repopulation effects on microglia by profiling microglia gene expression via RNA sequencing.
Results: BLZ954 depleted ~85% of microglia, and microglia numbers were restored within 10 days after withdrawal. While repopulated microglia showed a distinct baseline gene expression profile, their transcriptional response to cuprizone was similar to that of microglia from vehicle-treated animals. Nonetheless, BLZ945 treatment improved the myelin quality after a secondary demyelination event.
Conclusion: Microglia repopulation ameliorates secondary demyelination. These results indicate a therapeutic potential of microglia repopulation strategies for demyelinating diseases such as MS.

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Single-cell transcriptomics identifies brain inflammatory networks in experimental autoimmune encephalomyelitis (EAE)

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Background: Single-cell RNA sequencing (scRNA-Seq) is a novel technique used to quantify gene expression in individual cells and is of great interest to understand molecular signatures associated with inflammation in complex tissues such as the CNS.
Objectives/Aims: 1) To unravel the cellular heterogeneity implicated in the neuroinflammatory processes of experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis. 2) To characterize CNS-resident endothelial cell (EC) heterogeneity and EAE-associated transcriptional signatures. 3) To identify the molecular crosstalk between CNS-resident ECs and infiltrating immune cells.
Methods: scRNA-Seq was used to characterize the cells implicated in the neuroinflammation of MOG_{35-55}-induced EAE (C57BL/6) mice. Single cells were isolated from whole brains from three mice at peak of disease and three healthy mice. $CD31^+$ selection was then performed to enrich for ECs and sequenced. Normalization was done with SCTransform, clustering was performed with the Louvain algorithm and cell-type identity was assigned using publicly annotated gene-sets. The R package Slingshot was used to perform pseudo-time analysis. Immunofluorescent staining was used for human validation
Results: Eighteen distinct cell populations were identified, with a significant infiltration of immune cells observed in the EAE mice. Further, a strong MHC upregulation was observed in most CNS-resident cell-types, consistent with the cellular response to increased immune mediator activity. Interestingly, a gradient of gene expression rather than distinct transcriptional profiles separated the arteriovenous zonation of the CNS vasculature. Differential gene expression analysis showed more transcriptomic perturbations in venous ECs, suggesting an important role for this particular zonation in immune infiltration. The two most upregulated genes (ACKR1, LCN2) were validated in human samples. Furthermore, ligand-receptor interaction annotation showed specific crosstalk between venous ECs and infiltrating immune subsets.
Conclusion: We demonstrate a landscape of the cellular heterogeneity involved in EAE neuroinflammation and provide important molecular insights in specific cell processes that lead to CNS immune infiltration. Furthermore, arteriovenous zonation was differentially affected by immune activation, suggesting an important role in the processes leading to immune infiltration across the BBB for venous ECs.

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P537
Co-culture of iPSC-derived microglia and iPSC-derived astrocytes: modeling multiple sclerosis white and grey matter lesion environments

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Recently, we have shown that in post-mortem brain tissue obtained from persons with the inflammatory, demyelinating disease multiple sclerosis (MS), microglia exhibit different phenotypes in demyelinated white compared to demyelinated grey matter within the same leukocortical lesion. In white matter (lesions), microglia feature a reactive morphology whereas in the grey matter, microglia seem to be more ramified and resting. Besides the difference in level of infiltrating immune cells, the different astrocyte subtypes present in white and grey matter, i.e. fibrous versus protoplasmic astrocytes, may affect microglia responsivity.
To gain more insight into the effect of astrocyte subtypes on microglial functioning, this project set up co-cultures of human iPSC-derived microglia with human iPSC derived astrocytes differentiated into a white-matter like or grey-matter like state.
iPSC-derived microglia in co-culture with iPSC-derived astrocytes showed increased morphological complexity compared to microglia cultured as a monoculture. In addition, upon treatment with MS relevant inflammatory factors, we observed that tumor necrosis factor alpha (TNFα) induced an increased ramification of microglial cells cultures with white matter astrocytes. Microglia cultured with grey matter astrocytes and treated with interferon gamma (IFNγ) became more elongated and bipolar. Functionally, microglia cultured with grey-matter like astrocytes showed increased myelin phagocytosis compared to microglia cultured with white-matter like astrocytes. Moreover, addition of IFNγ to the co-culture resulted in a further increase in myelin phagocytosis of microglia cultured with grey-matter like astrocytes which did not occur in microglia cultured with white-matter like astrocytes. Treatment of the co-culture with TNFα did not affect myelin phagocytosis by microglia. Taken together, we were able to set up an iPSC model mimicking a white and grey matter environment of astrocytes and microglia. Furthermore, inflammatory mediators, as present in MS lesions, differentially affect the phagocytic function of microglia depending on the environmental context, i.e. astrocytes, they are cultured in.

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Pathology and pathogenesis of MS - Genetics/Epigenetics

P538
Functional epigenetic networks are associated with multiple sclerosis

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Background: Genome-wide association studies (GWASs) have implicated >200 genetic loci that contribute to MS risk. Collectively, these loci provide only partial insight into the biological processes underlying MS. DNA methylation at CpG sites is an epigenetic mechanism that can influence gene expression. Epigenome-wide association studies (EWASs) of immune cells have implicated differential methylation in MS. However, the functional relevance of the findings to date is unclear.
Objectives / Aims: Here we performed a functional network EWAS of 583 people with MS and 643 controls with the aim of gaining new biological insights into disease pathology.
Methods: The study design included a discovery group comprised of early MS cases (n=208) and age, sex and region matched controls (n=402), and a replication group (n=375 MS, n=241 controls). DNA methylation data from whole blood was obtained using Illumina EPIC or 450K arrays. To identify functional epigenetic modules, we applied 'weighted gene correlation network analysis' focusing on ~11,000 CpGs previously linked to expression levels in immune (blood) cells (ie. eCpGs). This design captures the inherent clustering of functional CpGs in relation to MS. Resultant modules underwent network and pathways analysis using NetworkAnalyst with the Reactome database.
Results: We discovered and replicated three functional epigenetic modules associated with MS ($r=0.18$-0.28, $p<5e10^{-5}$). These modules formed different gene (protein) networks that mapped to pathways involved in immune structure and function (FDR<0.05). Interestingly, we revealed three pathways not implicated using the known genetic loci. These were - translocation of ZAP-70 to immune synapse, phosphorylation of CD3 and TCR chains, and regulation of signalling by CBL - all of which are involved in specific $CD4^+$ T cell signalling processes.
Conclusions: This study identified functional epigenetic networks associated with MS, three of which map to pathways not linked to the known genetic loci. These results provide new insights into the

epigenetically mediated mechanisms of MS. Future studies should examine the interaction of these epigenetic networks to both genetic and environmental factors in relation to MS.

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A genetic association study on iron metabolism genes highlights Hypoxia-Inducible Factor-1 alfa as a potential driver of chronic active inflammation in progressive MS

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Introduction: Iron enrichment has been detected by recent advanced magnetic resonance imaging at the edges of the chronic active lesions, a hallmark of progressive multiple sclerosis (pMS). Iron accumulation in such lesions mirrors the molecular profile of the disease-associated microglia but, so far, its biological meaning is not clear.

Aims: We investigated whether variants in genes implicated in iron metabolism may affect the susceptibility to develop progressive MS.

Methods: We tested the association between 66,769 Single Nucleotide Polymorphisms (SNPs) positionally or functionally mapping to 319 genes involved in iron metabolism and disease course in 946 MS patients, comparing 250 benign relapsing-remitting (disease duration $\geqslant$ 20 years, EDSS $\leqslant$ 3.5) patients versus primary (n=409) and secondary (n=287) progressive MS patients.

Results: The top-associated signal was led by the rs11621525 variant, with the A allele being protective towards the progressive course (p=5.62E-07; OR=0.53) and passing the multiple testing correction. The SNP maps to the Hypoxia-Inducible-Factor-1-alfa (*HIF1A*) gene, a key player in iron metabolism, cell response to hypoxia and regulation of Th17/Treg lymphocytes balance. *HIF1A* was also recently recognized as an important gene for the microglia of chronic active lesions in a single-nuclei RNA sequencing study [Absinta M, et al (2021)]. Previous evidence has shown that the rs11621525_A allele is able to down-regulate the expression of *HIF1A* in whole blood in healthy subjects, and to affect the methylation profile of *HIF1A* promoter. We also confirmed this effect in the Peripheral Blood Mononuclear Cells (PBMCs) of an internal cohort of 78 naïve MS patients (p=0.034). In addition, we found a trend for association between*HIF1A*expression in PBMCs and serum neurofilament levels, a marker of ongoing inflammation and neurodegeneration, in RR-MS patients (n=26, p=0.08).

Conclusions: We found that a genetic variant in *HIF1A* impacts the susceptibility to develop progressive MS. As an important factor in mechanisms shared between cell response to hypoxia, iron metabolism and Th17-related inflammation, *HIF1A* is an interesting candidate for further functional exploration in chronic inflammation in pMS.

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Single nuclei RNA sequencing stratifies multiple sclerosis patients into three distinct white matter glia responses

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In this study, we performed single nucleus RNA sequencing on the most extensive cohort of multiple sclerosis (MS) patients to date to try understanding disease variability between individuals. We analyzed 165 samples of white matter (WM) lesions, normal

appearing WM, grey matter (GM) lesions, normal appearing GM and normal brain from 55 MS patients and 28 controls including samples from multiple different lesions in single patients. We assessed cell-type specific gene expression and cellular heterogeneity profiles across WM and GM lesions, showing that GM and WM biology in MS are fundamentally different, and that non-immune cells (pericytes, endothelial cells and oligodendrocyte precursor cells) play a significant role in disease progression. We determined that the patient ID, rather than the spectrum of neuropathologically defined lesions, plays the major role in determining gene expression and cellular changes in response to MS. Gene expression changes in response to MS are highly cell-type specific but are largely shared within an individual cell-type across different lesions. They follow a continuum rather than discrete lesion-specific molecular programs and in WM, these changes are clearly associated primarily to individual patient effects and are agnostic to classical MS lesion categories. Finally, analysis of oligodendrocyte heterogeneity to identify the cause of the reduced oligodendrocyte numbers seen in MS, identified three subgroups of patients, each with distinct oligodendrocyte composition and WM glial gene expression signatures: in type 1 (stressed) oligodendrocytes show evidence of cellular stress as would follow excitotoxicity, in type 2 (standard) the regenerative sequence of oligodendrocyte developmental maturation appears normal, in type 3 (stalled) there are increased intermediate subtypes as would follow a block to complete differentiation during regeneration. Therefore we postulate engagement of different pathological/regenerative processes across the range of MS patients, but with every lesion and normal-appearing sample in each patient sharing the same pattern. The identification of three distinct patient subtypes based on pathological/regenerative processes provide, for the first time, not only convincing evidence of the need to stratify progressive MS patients but also cellular and molecular bases for doing so, allowing and different treatment strategies for patients that have up till now been regarded as a homogeneous group.

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P542

MicroRNAs can affect differentiation in an oligodendrocyte cell culture model

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Introduction: Oligodendrocytes are key players in maintaining the integrity of the central nervous system by forming myelin sheaths. During the course of multiple sclerosis (MS), oligodendrocytes and their precursor cells (OPC) are harmed and their potential to differentiate progressively declines, resulting in permanent demyelination and subsequent axonal damage. There is an increasing interest in the involvement of microRNAs in the pathophysiology of many diseases, including MS. However, their role in OPC differentiation largely remains to be investigated.
Objectives: We have previously identified a set of dysregulated microRNAs in the CSF, serum and peripheral blood mononuclear cells of patients with relapsing-remitting MS compared to healthy controls (Perdaens et al., 2020). We aim to investigate the effect of several of these microRNAs on OPC differentiation to contribute to understanding their potential role in demyelination and remyelination in MS.
Methods: MicroRNA mimics (miR-1-3p/15a-3p/20a-5p/29c-3p/33-3p/34a-5p/34c-5p/124-5p/145-5p/146a-5p/155-5p/181c-5p/214-3p/219a-5p/297 [miRCURY, Qiagen]) were individually transfected in a murine OPC cell line, called CG4, cultured for one day in a proliferation medium and 5 additional days in a differentiation medium. We assessed the relative expression ($2^{-\Delta\Delta Ct}$ method) of proliferation and differentiation markers by RT-qPCR.
Results: Several microRNAs affected the differentiation of CG4. The well-described miR-219a-5p, used as a positive control, upregulated differentiation markers as proteolipid protein (Plp) and myelin basic protein (Mbp). *Plp* and *Mbp* were both downregulated by miR-124-5p/145-5p as compared to the differentiation vehicle control (Lipofectamine 2000, invitrogen) and the negative control microRNA mimic. Interestingly, miR-33-3p reduced their expression down to the level of the proliferation vehicle control. Some microRNAs also affect proliferation, as seen by the downregulation of the marker*Hes5* by miR-1-3p and miR-34a-5p. Proliferation and differentiation are, however, not mutually exclusive.
Conclusions: In our CG4 transfection model, MS-related microRNAs can reduce OPC differentiation. We are currently investigating their messenger RNA targets to unravel the underlying

signalling pathways involved. These results are encouraging to understand remyelination defects in MS.

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Single-cell transcriptomic and epigenetic landscape of iPSCs, neural progenitors and oligodendrocytes from monozygotic twin discordant for Multiple Sclerosis

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Introduction: Hereditary factors are involved in determining multiple sclerosis (MS) risk, as suggested by familial clustering. However, a monozygotic (MZ) twin whose co-twin is afflicted with MS shows only a 25% risk of developing the pathology, suggesting that epigenetic changes directed by chromatin architecture remodeling might shape the disease phenotype.
Aims: Here, we investigated single cells gene expression and chromatin accessibility in neural precursor cells (NPCs) and oligodendrocytes (OLs) differentiated from human induced pluripotent stem cells (hiPSCs) obtained from a monozygotic (MZ) twin pair discordant for MS.
Methods: Dermal fibroblasts from an MZ twin pair discordant for MS have been reprogrammed into iPSCs and then differentiated into NPCs by dual-SMAD inhibition. NPCs transduced with a lentiviral vector carrying the inducible human Sox10 gene were differentiated into OLs. After 26 days, a heterogeneous cell population was obtained containing OLs, but also a small percentage of neurons and astrocytes. Differentiated cells underwent both single-cell RNA sequencing (scRNAseq) and single-cell Genome & Epigenome by Transposase sequencing (scGETseq), an innovative technology able to map open and close chromatin conformations, thus recapitulating its dynamics. Bioinformatics analysis was performed by *Scanpy* (Python).
Results: Transcriptomic analysis of hiPSCs and NPCs from the MZ twin pair revealed two distinct populations, recapitulating the key biological processes in which these cells are involved. Unsupervised clustering identified numerous genes describing different neuronal progenitor subtypes. Interestingly, in NPCs we found several genes differentially expressed in the MS versus the healthy twin, revealing a "stressed" phenotype, which included mediators of the immune response, cell adhesion, and lipid metabolism. Known MS-risk genes were also found to be deregulated in the MS twin suggesting that patient's derived cells recapitulate the pathology. The epigenome analysis indicated different global accessibility in chromatin architecture. Indeed, MS known and novel risk genes expression correlated with the chromatin state.
Conclusions: Single-cell transcriptome and combined chromatin state analysis have identified differentially expressed genes in the MS versus healthy NPCs. The ongoing analyses of OLs will reveal potential MS-specific heterogeneity in their regulatory landscape.

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Genetic susceptibility to multiple sclerosis is associated with earlier onset and increased disease severity

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Introduction: Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelination in the CNS. More than 200 genetic variants have been identified affecting MS risk. It is however not clear to what extent these MS risk variants affect age at onset and disease progression.
Objectives: Test the hypothesis that MS risk genes also influence age at onset and disease severity.
Aims: To examines the effects of MS genetic susceptibility on age at onset and disease severity.
Methods: MS cases were identified from Swedish population-based case-control and prospective cohorts between 2009 and 2019, with corresponding patient data obtained from the Swedish National MS Registry. Weighted genetic risk scores for MS susceptibility were calculated using previously identified non-HLA SNPs and HLA allele variants. Disability was determined by the expanded disability status scale (EDSS) and used to determine disease duration-based (MSSS) and age-related (ARMSS) severity scores. Individual and composite genetic risk associations with disease measures were assessed with a multivariable linear or logistic regression model adjusting for sex, treatment, and other relevant clinical measures.
Results: In total, 7668 MS cases were included with an average age and disease duration at assessment of 44.5 ± 12.8 years old

and 21.5 ± 11.2 years, respectively. Genetic risk scores for MS were associated with increased severity (P_{MSSS}=0.03, P_{ARMSS}=0.03) and particularly with earlier onset (P=3.76x10^{-17}). *HLA-DRB1*15:01* carriage, the primary genetic risk factor for MS, was associated with 1.15 years earlier onset (P=2.94x10^{-6}), similar to previous findings. Although most HLA risk alleles were not individually associated with severity, *A*02:01* carriage was associated with increased severity among those below 25 years of age (P_{MSSS}=0.005, P_{ARMSS}=0.001). Several non-HLA risk SNPs were also associated with earlier onset, including rs9808753 (*IFNGR2*) and rs6999228 (*PKIA*/*ZC2HC1A*/*IL7*).

Conclusion: In summary, we characterized the genetic risks of MS development with age at onset and disease severity in the Swedish population. We confirm previous reported association of carriage of *DRB1*15:01*with age at onset. We also observe additionalcontribution of MS risk variants to age at onset and severity.

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Genetic susceptibility to multiple sclerosis is associated with earlier onset and increased disease severity

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Introduction: The determination of muscle strength via manual muscle function tests (MMT) often reaches its limits due to subjective and inconsistent examination. Part of the pyramidal functional system evaluation in the Expanded Disability Status Scale (EDSS) is the strength of plantar flexion assessed by MMT. In contrast to this subjective test, the heel-rise test on a force plate could provide accurate and objective quantification of plantar flexion strength in multiple sclerosis.

Objective: Evaluation of plantar flexor force measurement by bilateral heel rise on a force plate.

Aim: To assess muscle function dependent on demographic variables in pwMs and HC.

Methods: The heel-rise test was performed with a portable force plate for 107 pwMS (age 36.2 ± 9.5, BMI 24.8 ± 5.1, median EDSS=1.0) and 67 HCs (age 37.6 ± 11.2, BMI 23.9 ± 3.8, median EDSS=1.0). All participants were instructed to raise the heels bipedally three times with the maximum strength possible. Certificated raters collected the neurostatus EDSS. A Generalized Linear Mixed Model were applied using Group effects and group interactions with EDSS, Body Mass Index (BMI), age and gender. Kendall tau-b (τb) correlations were calculated between pyramidal functional system and MMT with maximum plantar flexion strenght.

Results: The MMT of plantar flexion was not able to detect muscle weakness or differences between groups, but the heel-rise test on the force plate was able to differentiate. HCs showed significantly higher force of plantar flexors (16.1 N/kg ± 2.2) than pwMS (14.8 N/kg ± 1.7) (p=0.027). This deficit seems to be specific for plantar flexors as no correlation could be established between the MMT and the pyramidal functional system with maximum force values from the force plate with heel-rise. No significant influence were found on both groups of EDSS, BMI, age and gender on plantar flexion strength. However, between-group comparison showed significant differences (p=0.031) for pwMS with BMI 30+ and pwMs with BMI 18 to 25. Age-related strength differences were only evident in HC.

Conclusion: The heel-rise test is a quick and easy assessment of the calf muscles. The MMT was unable to detect significant plantar flexion weakness in pwMS. In contrast, the measurement of heel-rise on the force plate could distinguish between the two groups with a moderate effect size.

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Pathology and pathogenesis of MS - Immunology

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Peripheral blood immune markers associated with immunosenescence in multiple sclerosis and healthy controls

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Introduction: In people with multiple sclerosis (pwMS), aging is associated with a decline in relapses, in gadolinium-enhancing lesions, and in response to disease-modifying therapies (DMTs). On the contrary, in older pwMS there is an increased risk of overt progression outside of relapses, of slow expansion of existing lesions, and of complications on DMTs. Biological aging of the immune system (immunosenescence) is associated with a state of low grade inflammation and a higher susceptibility to infectious and neoplastic disorders. Biological sex and environmental factors like smoking and cytomegalovirus seropositivity modulate immunosenesence processes. We hypothesize that MS is associated with premature immunosenescence, and that in turn MS pathobiology and response to DMTs is affected by age-related modifications of the peripheral immune system.
Objectives: To compare levels of age-sensitive immune markers in the peripheral blood of untreated and treated pwMS, and of age-matched healthy controls (HC), in correlation with clinical outcomes.
Methods: Validated multiplex immunoassays on serum; flow cytometry assays and bulk RNA sequencing on cryopreserved peripheral blood mononuclear cells (PMBCs).
Results: We analyzed 800 biosamples from pwMS and HC, nearly half from ⩾45 years old (y.o.) subjects. A majority of MS samples (73%) and of HC samples (60%) were from women. Seropositivity for CMV was more frequent among HC (45%) than MS samples (31%). EDSS was ⩾3.0 in 10% of the samples from pwMS <45 y.o. but in more than one third of the samples from ⩾45 y.o. In the serum, we observed differences related to biological sex and age, to MS vs HC status, and/or to DMTs, in levels of different trophic factors such as β-NGF, of anti-inflammatory cytokines such as IL-27, and of adipokines such as leptin. In PBMCs, we have observed age- and sex-related differences in the frequency of immune cell subpopulations, such as an increased proportion of T lymphocytes expressing CD57, a senescence marker, in pwMS, especially women, compared to age-matched HC. Finally, RNA sequencing of PBMCs will identify differentially expressed genes before and after starting first-line DMTs in younger (⩽35 y.o.) vs older (⩾45 y.o.) pwMS, and in older pwMS showing a benign vs a progressive course.
Conclusions: Aging of the peripheral immune system is influenced by biological sex and is affected by MS and by DMTs. Such changes could contribute to the observed phenotype in older pwMS.

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P546

Upregulated complement receptors correlate with Fc gamma receptor 3A-positive natural killer cells and natural killer-T cells in neuromyelitis optica spectrum disorder

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Introduction: Inhibition of terminal complement in NMOSD using eculizumab helps prevent relapses, but the exact mechanism of action of the drug remains unclear. Similarly, genetic variants in the Fc Gamma receptor 3A are correlated with outcomes in NMOSD, but the immune cells expressing those FcGR3A receptors are unknown. We compared FcGR3A expression on immune cells modulated by complement activity in NK cells and NKT cells in NMOSD to disease and normal-healthy controls.
Objectives: To investigate the FcGR3A expression on immune cells modulated by complement activity in NMOSD.
Methods: Peripheral blood cell (PBMC) samples from 45 patients with NMOSD with AQP4-IgG, 18 disease controls, and 19 normal controls were analyzed by flow cytometry for FcGR3A expression and complement receptors*in vitro*.
Results: At baseline, the number of NKT cells was increased in NMOSD ($p < 0.001$), but the proportion that were FcGR3A positive was lower compared to normal and disease controls (p=0.0012).NK cell count was normal, but the proportion that was FcGR3A positive was also significantly lower ($p < 0.001$). In both NK cells and NKT cells from NMOSD, C5 complement receptor expression was much higher than normal and disease controls ($p < 0.001$ for both). We also evaluated activation markers CD69 and CD83, which were also significantly higher in NK and NKT cells from NMOSD patients.
Conclusions: Our results support an immunopathogenesis model in which complement pathway activation in NK/NKT cells upregulates FcGR3A expression that binds to antibody/antigen complexes. In the context of NMOSD, these complement-sensitive cells may be responsible for the escalating autoimmune activity.

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Aggressive multiple sclerosis shows an increase in a peripheral cytotoxic CD8+ T cell subset through single-cell RNA sequencing

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Introduction: Multiple sclerosis (MS) is an autoimmune disease causing chronic inflammation in the central nervous system (CNS). Using an innovative classification, we can distinguish types of MS according to disease severity: non-aggressive MS with no relapses, no appearance of new fluid attenuated inversion recovery (FLAIR) lesions and a good response to low efficacy treatments; and aggressive MS with new relapses, appearance of new FLAIR lesions, or a need for high efficacy treatments.
Aims: In an effort to anticipate disease severity, we founded the OutcoMS project, in which we aim to unravel mechanisms behind a poor outcome in MS, through the use of transcriptomics.
Methods: We collected peripheral blood mononuclear cells (PBMCs) from 22 patients at their first clinical episode during the clinically isolated syndrome (CIS) stage. After >2 years, patients were sorted into non aggressive and aggressive MS. Samples were matched with PBMCs from healthy volunteers (HV) and sequenced using single-cell CITEseq technology.
Results: We identified a subset of CD8+ T cells that are increased in CIS patients that later convert to aggressive MS compared to non-aggressive MS. This CD8+ T cell population displays a memory phenotype and cytotoxic activity similar to natural killer cells.
Conclusion: Our data suggests that severe forms of MS may be driven by a subset of cytotoxic memory CD8+ T cells.

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Mucosal associated invariant T (MAIT) cells mediate the crosstalk between the gut and the brain in people with multiple sclerosis (MS)

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Background: Mucosal associate invariant T (MAIT) cells are unconventional T cells with an innate-like phenotype. They recognize microbial-derived riboflavin derivatives presented by the major histocompatibility class (MHC) I-related protein MR1 and their mature phenotype is deeply influenced by the microbiome composition.
Objective: The overall goal of this study was to describe the role of MAIT cells in the pathogenesis of multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE).
Methods: MAIT cell activation and effect during Experimental Autoimmune Encephalomyelitis (EAE) was studied in MR1$^{-/-}$ mice, lacking completely MAIT cells, and MR1 sufficient (MR1+$^{/}$+and MR1+$^{/-}$) controls by flow cytometry. The effect of the gut microbiome composition on MAIT cells phenotype was inquired in a separate set of experiments changing housing conditions.
Peripheral blood (PB) and cerebrospinal fluid (CSF) samples were obtained from newly diagnosed, untreated people with MS (pwMS) and age-matched healthy controls (HCs). MAIT cell number, phenotype and cytokine production were characterized by flow-cytometry. The effect of MAIT cell activation on conventional T cell proliferation was determined by CFSE assay. Gut microbiome composition was determined by 16S, mWGS and ITS sequencing.
Results: MAIT cells are activated during EAE, they acquire a MAIT1 phenotype and have an immunomodulatory role, influenced by the gut microbiome composition. PwMS have lower numbers and defective activation of MAIT cells in both PB and CSF. Activated MAIT cells obtained from pwMS are less effective at suppressing in vitro conventional T cells proliferation compared to MAIT cells obtained from HCs. We linked MAIT cell phenotype to an altered gut bacterial and fungal microbiome composition consisting of low fungal richness, high abundance of *Saccharomyces* and low abundance of*Prevotella*.
Conclusions: Our study described a modulatory effect of MAIT cells on both innate and adaptive immunity. In pwMS we demonstrated a decrease and a dysregulation of MAIT cell number and function, possibly linked to an altered gut microbiome composition.

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P549
NDP-MSH improves the blood-brain barrier integrity in experimental autoimmune encephalomyelitis by inducing claudin-5 and ZO-1 expression

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In experimental autoimmune encephalomyelitis (EAE), a mouse model partially mimicking human multiple sclerosis, the dysfunction of the blood-brain barrier (BBB), is an important prerequisite for the infiltration of pathogenic immune cells into the central nervous system (CNS). The increased permeability between endothelial cells (EC), the main component of the BBB, is caused by the downregulation of Tight Junctions (TJ) proteins. We have shown previously that the neuropeptide derivative Nle4-D-Phe7–alpha-melanocyte-stimulating hormone (NDP-MSH), ameliorates EAE progression by the induction of regulatory T cells (Treg), the downregulation of T helper 17 cells (Th17), and the direct protection of neurons from excitotoxic damage. To investigate whether NDP-MSH might also modulate BBB integrity and potentially decrease the permeability of brain EC, we performed Trans-Endothelial Electrical Resistance (TEER) assays on IFNy- and TNF-stimulated EC. Interestingly, treatment with NDP-MSH reduced transendothelial migration of immune cells and markedly increased the electrical resistance of EC. To further analyze whether this effect was based on the NDP-MSH-mediated induction of TJ proteins, we quantified the expression of Zonula occludens-1 (ZO-1) and claudin-5 in EAE brain sections or EC. Immunofluorescence staining showed an increased expression of ZO-1 and claudin-5 in active lesions of NDP-MSH-treated EAE mice and NDP-MSH-stimulated brain EC cultures, which resulted in decreased transmigration of CD45^{+} leukocytes. In support of this, real-time PCR revealed an elevated mRNA expression of claudin-5 in the brain of NDP-MSH-treated EAE mice as well as NDP-MSH-stimulated EC cultures compared to controls. Altogether, these data indicate that NDP-MSH enhanced the BBB integrity by upregulating TJ proteins, such as ZO-1 and claudin-5.

Disclosure
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P550
MAIT cells from multiple sclerosis patients are modulated by the microbiome

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Background: Studies demonstrated that invariant T cells associated with mucosal (MAIT) cells play a role in MS. MAIT cells are abundant in tissues exposed to microbial antigens, and they are absent in germ-free animals. MAIT cells react to bacteria through TCR-mediated recognition of metabolites derived from Vitamins B2 (5-OP-RU) or B9 (THF), presented by MR1.
Objective: To characterize the effector functions of MAIT cell clones after exposure to the different bacterial species that are part of each patient's microbiota.
Methods: Thirty-two MAIT cell clones were isolated from 7 RRMS during remission. MAIT-specific TCR triggering was achieved by co-culturing MAIT cells with THP1 cells previously pulsed with 5-OP-RU or loaded with PFA-fixed bacteria previously identified in the microbiome of each patient. For non-specific stimulation MAIT cells were stimulated with IL-12 plus IL-18. Production of cytokines (TNF-α, IL-10, IL-17, and IFN-g), granzyme B, and perforin was measured by ELISA. The expression of the chemokine receptors CCR5, CCR6, and CXCR6 was measured by flow cytometry and expressed as mean fluorescence intensity (MFI)
Results: With all stimuli, expression of TNF-α, IFN-g, IL-17, granzyme, perforin, and chemokines receptors was significantly increased; however, these effects were significantly lower after stimulation with IL-12 + IL-18. MR1 blocking significantly inhibited TCR-dependent stimulation. Likewise, TCR-dependent stimulation demonstrated higher cytotoxicity magnitude and sensitivity compared to cytokines stimulation. Conversely, to what was observed with bacteria that produce riboflavin, MAIT cells stimulated with THF-producing bacteria significantly reduced the production of pro-inflammatory cytokines, chemokines receptors, and their cytotoxic effects. Changes in the immune response were not observed in MAIT cell clones stimulated with bacteria that do not possess the riboflavin pathway.
Conclusions: Riboflavin-synthesizing bacteria from the microbiome of MS patients can induce a pro-inflammatory profile in MAIT cells, particularly in response to specific TCR stimulation. These observations on MAIT cell triggers will pave the way to a better understanding of their role in the pathogenesis of MS.

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P551

Chemerin correlates with MS progression parameters and affects intracellular metabolism in human microglia and macrophages

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Introduction: In multiple sclerosis (MS), persistent neuroinflammation and progression may be due to dysregulation of resolution of inflammation. Chemerin, a chemoattractant hormone, produced and secreted by the white adipose tissue, has been shown to be involved in both the initiation and resolution of inflammation via Chemr23 receptor signaling in macrophages and microglia. However, the role of chemerin in MS pathophysiology remains largely unknown.
Objective: To assess whether chemerin is correlated to measures for clinical disability and neurodegeneration in MS and how chemerin regulates phenotype and function of human macrophages and microglia *in vitro.*
Methods: We measured serum chemerin using ELISA in 288 relapsing-remitting MS (RRMS), primary (PPMS) and secondary progressive MS (SPMS) from the Project Y cohort, a cross-sectional study of all people with MS born in the Netherlands in 1966, and 125 age and sex-matched healthy controls. Chemerin levels were correlated with clinical measures, expanded disability status scale (EDSS), disease duration and serum neurofilament light (NfL). Furthermore, we assessed mitochondrial respiration and glycolysis using the seahorse analyzer in human monocyte-derived macrophages and inducible pluripotent stem cell derived microglia stimulated with chemerin*in vitro*, as well as cytokine levels.
Results: No differences in chemerin levels were found between MS subtypes and controls nor between women and men. Female RRMS (n=153) patients with above median chemerin levels had higher EDSS (median 3.25 vs 2.50), and female PPMS patients (n=19) showed a positive correlation between chemerin and NfL. Lastly, chemerin correlated positively with disease duration in male patients (n=80).*In vitro*, chemerin significantly increased mitochondrial respiration and glycolysis accompanied by alterations in cytokine RNA expression and protein levels.
Conclusions: Circulating chemerin levels can serve as marker for MS severity and possibly progression and plays an important role in the inflammatory functions of macrophages and microglia *in vitro*.

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Investigating Bruton Tyrosine Kinase Inhibition in human and mouse myeloid cells to further elucidate cell-specific and disease relevant mechanisms in multiple sclerosis

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Introduction: Bruton Tyrosine Kinase (BTK) is a kinase expressed in immune and neural cells, and acts downstream of pattern recognition receptors to activate the NF-kB cascade. In MS, BTK inhibitors (BTKis) are currently in clinical trials as novel disease modifying therapies. While most research on BTKis is focused on B cells, understanding the impact of BTK inhibition in non-B cell populations is critical, given many BTKis can exert their effects in both the peripheral and central compartments.
Objectives/Aims: Here, we determine how BTK inhibition in human and murine-derived myeloid cells can alter their phenotype and function in the context of MS-relevant inflammation and repair.
Methods: Human whole blood, monocyte-derived macrophages (MDMs), and primary mouse bone marrow-derived macrophages (BMDMs) and microglia were pre-treated with evobrutinib or tolebrutinib (0.1nM – 10uM), prior to LPS stimulation. TNF and IL-6 release was measured via ELISA. Agilent Seahorse XF Cell Mito Stress Test Kit was used to measure oxygen consumption rate (OCR) and extracellular acidification rate (ECAR). Using qPCR, *btk* mRNA expression was also measured in CD14+ monocytes of relapsing remitting MS (RRMS) patients vs controls.
Results: Both TNF and IL-6 were decreased in human whole blood pre-treated with BTKi; In human MDMs, only TNF was decreased. In mouse, tolebrutinib decreased TNF in microglia but not BMDMs. In human MDMs, OCR values increased, and ECAR values decreased with BTKi treatment. In CD14+ monocytes, no differences in *btk* mRNA expression were observed between RRMS patients vs. controls.
Conclusion: Human myeloid cells are responsive to BTKis and decrease pro-inflammatory cytokine release stimulated by LPS, which may be species dependent. The ECAR decrease suggests an anti-inflammatory metabolic shift away from glycolysis with BTKis. no difference in *btk* mRNA expression between RRMS and control suggests the effect of BTKis is not transcription associated, but rather due to its direct anti-enzymatic activity.

Disclosure
nothing to disclose

P553

SARS-CoV-2 vaccine-induced immune responses and breakthrough infections in people with multiple sclerosis treated with ocrelizumab (OCR)

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Background: Attenuated antibody and robust T-cell responses following SARS-CoV-2 vaccines have been reported in people with multiple sclerosis (PwMS) treated with ocrelizumab (OCR). Factors influencing humoral and cellular responses and how these relate to clinical protection are not well understood.
Aims: To investigate the effect of OCR on antibody and T-cell responses to SARS-CoV-2 vaccines, and characterise clinical outcomes of breakthrough COVID-19 infections in PwMS.
Methods: Patients participating in three ongoing Phase IIIb studies evaluating the effectiveness and safety of OCR, who decided to receive a SARS-CoV-2 vaccine as part of national immunisation programmes, were invited to undergo optional exploratory assessment. Antibody responses to SARS-CoV-2 spike and nucleocapsid proteins were assessed using the Elecsys® electrochemiluminescence assay. Interferon-gamma ELISpot (ImmunoSpot) was used to detect SARS-CoV-2–specific T cells against 4 different peptide pools of the spike protein. Vaccine breakthrough cases were defined as suspected or laboratory-confirmed COVID-19 infections occurring ⩾14 days after completion of the recommended primary immunisation schedule.
Results: Up to Sept 2021, 111 patients provided samples for assessment of response to SARS-CoV-2 vaccination. Mean (SD) age was 41.7 (11.8) years; 63.1% were female; 72.1% had relapsing-remitting MS, 15.3% secondary progressive MS and 12.6% primary progressive MS.Most patients had been on treatment with OCR for at least 2 years. Mean (SD) of 78.5 (41.4) days elapsed between the first vaccine dose and last OCR infusion. 94/111 patients received an mRNA vaccine and 15 patients an adenoviral vaccine. Most samples were collected within 80 days following completion of the primary vaccine schedule. Antibody response

was detected in 22/103 (21%) patients and T-cell responses to ⩾1 of the 4 different peptide pools in 83/95 (87%) patients. Four breakthrough infections were reported.
Conclusions: In preliminary analysis, frequency of patients with an antibody and T-cell response were in line with published data for PwMS on OCR. Expanded analyses with a larger set of patients (approximately 450 patients, up to March 2022), including longitudinal responses, booster data, differences between vaccine platforms and assessment of factors that may affect immune responses will be presented. Correlations between level of immune responses and breakthrough infection diagnosis and severity will be explored.

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P554
FOXP3+ regulatory T cells use heparanase to access IL-2 bound within extracellular matrix to suppress neuroinflammation

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Introduction: In healthy individuals, immune tolerance is maintained by populations of regulatory T cells, including FOXP3$^+$ regulatory T cells (Treg). However, in autoimmunity, such as multiple sclerosis (MS), Treg fail to control autoreactive immune responses. Treg depend on exogenous IL-2, but circulating levels of IL-2 are low, making it unclear how Treg acquire this critical resource *in vivo*. Many cytokines are sequestered within the extracellular matrix (ECM) by heparan sulfate (HS)-containing proteoglycans. However, studies on IL-2 within the ECM pre-date knowledge about FOXP3$^+$ Treg. Contrary to Treg, conventional T cells (Tconv) do not require exogenous IL-2 *in vivo*, such that the functional relevance of tissue-bound IL-2 has remained unclear.
Objectives: To determine how Treg obtain IL-2 *in vivo* and gain an understanding of the tissue factors regulating Treg function.
Aims: 1. Determine the presence and localization of IL-2 in neuroinflammatory and lymphoid tissues. 2. Determine the mechanism by which Treg access IL-2 sequestered by HS. 3. Determine the functional consequence of the enzyme heparanase (HPSE) for Treg homeostasis, function and therapeutic potential.
Methods: Using the experimental autoimmune encephalomyelitis (EAE) model of MS, we assessed the localization of IL-2 and HS at sites of neuroinflammation and in lymphoid tissue. We then used *in vitro* cultures of the IL-2 sensitive T cell line CTLL2, as well as primary cultured murine and human Treg and Tconv to assess how Treg access HS-bound IL-2. We further used HPSE deficient (HPSE$^{-/-}$) mice and bone marrow chimera, as well as adoptive transfer approaches to determine the relevance of HPSE expression for Treg homeostasis and function in suppressing EAE. Finally, we overexpressed HPSE in chimeric antigen receptor (CAR) expressing Treg to assess its impact on the stability and function *in vitro* and *in vivo*.
Results: Treg use HPSE to access IL-2 sequestered by heparan sulfate (HS) within the ECM of EAE lesions and lymphoid tissues. HPSE expression distinguishes human and murine Treg from Tconv, and is regulated by the availability of IL-2. HPSE$^{-/-}$ Treg have impaired stability and function *in vivo*, both in homeostasis and in suppressing EAE. Conversely, endowing CAR Treg with HPSE enhances their tolerogenic function *in vivo*.
Conclusions: Together, these data identify novel roles for HPSE and the ECM in immune tolerance, providing new avenues for improving Treg-based therapy of autoimmunity.

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P555
Understanding B cell migration after personalized dosing of ocrelizumab in multiple sclerosis patients

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Introduction: Recent retrospective studies revealed that extended interval dosing of ocrelizumab does not lead to diminished effectiveness in most patients. However, it remains to be established what determines the effectiveness of extended interval dosing, which of the B cell subsets are quickly repopulated and if such subsets have a different migration across the blood-brain barrier (BBB).
Aims: In this study, we aim to compare the effect of standard versus extended interval dosing of ocrelizumab on repopulating B cell subsets. Furthermore, we aim to study if repopulated B cells have an altered migratory capacity to cross the BBB. Finally, we will correlate our findings to several CSF biomarkers of neuropathology, including neurofilament light.
Methods and results: In an ocrelizumab-treated cohort of relapsing-remitting, secondary progressive and primary progressive MS patients, 43 individuals had an increased peripheral B cell count (defined as ⩾10 cells/μL) 24 weeks after the previous dose (standard interval), whereas 38 patients had an increased B cell count on average 30 weeks after the previous dose (extended interval). We defined the peripheral immune landscape in MS patients at baseline and after standard or extended interval dosing of ocrelizumab using high-dimensional single-cell characterization by cytometry by time of flight (CyTOF). Specifically, we developed a 38-antibody panel to profile B cell subsets with a focus on changes in markers for migratory activity. In addition, we studied how these changes modify B cell migration across a human in vitro model of the BBB.
Conclusions: Our study provides a better in-depth characterization of the repopulated B cell subsets and their function after standard or extended interval dosing of ocrelizumab in a well-defined patient cohort. Combining this knowledge with the clinical parameters, we could understand which patients might benefit from extended interval dosing.

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GB7208 is a CNS-penetrant BTK inhibitor demonstrating potent activity on pathogenic pathways implicated in multiple sclerosis

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Introduction: Bruton's tyrosine Kinase (BTK) plays a critical role in B cell and myeloid cell activation and is a critical signalling node downstream of B cell receptors (BCR) and Fragment crystallisable receptors (FcR). Aberrant BTK signalling in B cells and central nervous system (CNS) resident microglia cells have been associated with driving pathogenesis in Multiple Sclerosis (MS). GB7208, a selective, CNS-penetrant small molecule BTK inhibitor has the potential to modulate multiple pathogenic mechanisms in MS.
Objectives: The present study aimed to characterise GB7208's *in vitro* and *in vivo* activity, and its impact on various cell types involved in MS pathogenesis.
Methods: Potency of GB7208 was measured in human B cells, downstream of BCR activation with receptor cross-linking antibodies. GB7208 activity was also assessed in human monocytes and induced pluripotent stem cells (iPSC) derived microglia stimulated with FcR cross-linking by immune complexes. A mouse model of anti-myelin oligodendrocyte glycoprotein (MOG) antibody driven microglia proliferation in the brain of wild-type C57BL/6 mice was used to assess the*in vivo* activity of GB7208 on microglia. Effects of GB7208 were also evaluated in an experimental autoimmune encephalomyelitis (EAE) mouse model that shares many features of human MS.
Results: GB7208 potently inhibits *in vitro* activation and function of B cells, peripheral monocytes and iPSC-derived microglia. In wild type mice with an intact blood brain barrier, GB7208 demonstrated *in vivo* activity by inhibiting microglia proliferation induced by administration of anti-MOG antibodies. In the CNS compartment of treated animals, a dose-related target occupancy effect was demonstrated for the inhibition of microglia proliferation. Finally, in a pre-clinical model of MS, GB7208 demonstrated dose-dependent reduction of in-life clinical scores. Histological assessment of spines of these EAE mice also demonstrated fewer inflammatory foci spines and significantly lower demyelination scores with GB7208 compared to vehicle.
Conclusion: GB7208 is a CNS-penetrant BTK inhibitor that potently inhibits multiple mechanisms relevant to MS pathogenesis.

Disclosure
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More efficient complement activation by anti-AQP4 compared to anti-MOG antibodies

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Introduction: Autoantibody mediated neurological autoimmune diseases comprise a broad spectrum that is rapidly evolving. Antibodies against aquaporin 4 (AQP4-IgG) are found in the majority of patients with neuromyelitis spectrum disorder (NMOSD), whereas antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) are linked to MOG-IgG associated disease (MOGAD). Both MOG-IgG and AQP4-IgG can induce complement-dependent cytotoxicity (CDC). CDC is a main pathological hallmark in NMOSD, whereas the role of complement activation in MOGAD is less clear.
Objectives: To directly compare CDC mediated by AQP4-IgG and MOG-IgG *in vitro*, to investigate correlation with antibody titers and to characterize complement activation using surface stainings on cell-based models.
Aims: We aimed to analyze CDC induced by AQP4-IgG and MOG-IgG in human serum samples from patients suffering from NMOSD or MOGAD.
Methods: A cell-based assay with HEK293 cells expressing different MOG isoforms ($MOG\alpha_{1\text{-}3}\beta_{1\text{-}3}$) or AQP4-M23 was used. Cells were incubated with human MOG-IgG or AQP4-IgG positive serum samples together with human complement and CDC was measured with a lactate-dehydrogenase assay, to quantify antibody mediated cell damage. Furthermore, immunocytochemistry of the terminal complement complex (TCC) and complement component 3 (C3) was performed.
Results: AQP4-IgG positive serum samples induced higher CDC levels than MOG-IgG positive sera. Importantly, both showed a correlation between antibody titers and CDC. Moreover, predictive values for CDC were higher for AQP4-IgG were dependent on antibody titers. Additionally, all six MOG isoforms tested ($MOG\alpha_{1\text{-}3}\beta_{1\text{-}3}$) could induce at least some CDC, however the strongest MOG-IgG induced CDC levels were found on full-length $MOG\alpha_1$ and $MOG\beta_1$. Different MOG-IgG binding patterns regarding recognition of different MOG isoforms were investigated and it was found that MOG-IgG recognizing all 6 isoforms induced highest CDC levels again on $MOG\alpha_1$ and $MOG\beta_1$. Furthermore, surface staining of TCC and C3 revealed positive staining of all six MOG isoforms and of AQP4-M23, demonstrating complement activation on a cellular level.
Conclusions: Both MOG-IgG and AQP4-IgG induced CDC in a titer dependent manner. However, AQP4-IgG showed markedly higher levels of CDC compared to MOG. This further highlights the role of complement in AQP4-IgG mediated disease, whereas the importance of complement activation in MOG-IgG mediated autoimmune disease is less pronounced.

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SARS-COV2 exposure rates and serological response of people living with MS

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Introduction: Some multiple sclerosis (MS) disease-modifying therapies (DMTs) are associated with blunted humoral vaccination responses, but relevance for SARS-CoV-2 infection is unclear.
Objectives: To determine SARS-CoV-2 exposure rates and formation of antibody memory among participants of the COMparison Between All immunoTherapies for MS (COMBAT-MS; NCT03193866) and the Immunomodulation and MS Epidemiology (IMSE) studies.
Aim: To determine SARS-CoV2 serological response of people living with MS (pwMS).
Methods: Using a multiplex bead-based assay we determined SARS-CoV-2 spike and nucleocapsid antibody levels in 3,723 pwMS in paired serum samples (n=7,157) donated prior (<January 31st 2020) and during the pandemic (July-October 2020); 16.6% had natalizumab, 6.4% fingolimod, 9.7% dimethyl fumarate, 1.9% interferon beta, 50.4% rituximab, 1.4% cladribine, 7.6% other DMTs, and 6.1% were untreated. Median fluorescent intensity (MFI) and bead-count were determined for spike and nucleocapsid antibodies, and samples were regarded as positive only when reactive to both viral antigens. Hazard ratios, from multivariable Cox regression models, were derived to assess association between antibody levels above cut-off for each antigen, comparing exposure to rituximab or fingolimod at time of sampling vs. other reference DMTs. All models were adjusted for age, sex, treatment center, time since reported infection, MS severity, disease duration, and number of previous DMTs.
Results: Specificity and sensitivity of the assay for SARS-CoV-2 was 100% and 99.7%, respectively. The proportion of positive samples for SARS-CoV-2 differed moderately across DMTs with the highest values among cladribine-treated (7.4%) and the lowest number among rituximab-treated pwMS (3.9%). Similarly, the proportion of positive cases not reported in the Swedish MS registry varied from 100% for cladribine to 33.3% among untreated pwMS. Comparing levels of antibodies titers showed that levels were lower among those treated with rituximab or fingolimod vs interferon treated pwMS. Point estimates indicated a similar trend comparing rituximab or fingolimod vs untreated pwMS.
Conclusions: Overall rates of SARS-CoV-2 antibody positivity after the first COVID-19 wave differed only moderately across DMTs, while antibody levels were lower with rituximab or fingolimod compared to interferon-treated pwMS. This indicates quantitative rather than qualitative differences in the humoral response to infection.

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Transcriptomic profile of age-related changes in the peripheral immune system in experimental autoimmune encephalomyelitis

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Background: There is evidence of age-related changes in the immune system in experimental autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS) patients, which suggests that immunosenescence could be playing a determinant role in MS immunopathogenesis in elderly patients.
Objectives: To study the transcriptomic profile of the peripheral immune response in experimental autoimmune encephalomyelitis (EAE) in young and aged mice.

Methods: Eight-week-old (young mice) and forty-week-old (aged mice) C57BL/6J mice were immunized with MOG_{35-55}. Spleens from non-immunized mice (basal) and from EAE mice at the inflammatory phase (14 days post-immunization; dpi) and at the chronic phase (28 dpi) of the disease were collected. Total RNA was isolated and its quality was assessed using Bioanalyzer. RNA sequencing was performed by polyA selection and retrotranscription into DNA libraries, before sequencing 150 bp paired end with a coverage of 20 million reads per sample. Statistical analysis was performed to compare gene expression between young and aged mice over EAE time-points, from basal to 14 dpi and from 14 dpi to 28 dpi. Differentially expressed genes (DEGs) with a fold change higher than 1 and an adjusted p value lower than 0.05 were considered to perform gene set enrichment analysis (GSEA) using *Metascape* and *Trrust*.
Results: The hierarchical clustering of the most variable genes showed main differences between EAE time-points, but not between ages. GSEA showed the positive regulation of miRNA transcription from basal to 14 dpi and the adaptive immune system from 14 dpi to 28 dpi as the most enriched pathways in aged mice. In addition, protein interaction analysis revealed interaction networks related to the positive regulation of miRNA transcription, DNA binding and muscle structure development from basal to 14 dpi, whereas from 14 dpi to 28 dpi protein interaction networks involving chromatin organisation, adaptive immune system, spinocerebellar ataxia, cell division, RNA processing, cellular response to DNA damage and inhibition of replication initiation of damaged DNA by RB1/E2F1 were identified. Transcriptional regulation analysis revealed many enriched transcription factors in aged mice from basal to 14 dpi, while Myc was identified as the unique enriched transcription factor from 14 dpi to 28 dpi.
Conclusions: Although these results require validation, our data suggest that ageing influences the immunopathogenesis of MS.

Disclosure
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XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

Pathology and pathogenesis of MS - Microbiology and virology

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COVID-19 course and outcome after three mrna vaccine doses in MS patients treated with high efficacy DMTs

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Background: High-efficacy (HE) disease-modifying therapies (DMTs) for Multiple Sclerosis (MS), such as anti-CD20 monoclonal antibodies - i.e., Ocrelizumab (OCR) and Rituximab - may worsen COVID-19 course. Preliminary data suggest that two doses of mRNA COVID-19 vaccine (RNA-Vax) reduce the risk of breakthrough/severe COVID-19 in patients with MS (pwMS) under treatment with HE-DMTs. Little is known about the protective effect of a third booster dose of RNA-Vax in pwMS treated with most commonly used HE-DMTs, such as Natalizumab (NTZ), Fingolimod (FNG), and OCR.
Aim: To compare COVID-19 course and outcomes in pwMS on NTZ, FNG, and OCR after receiving the third dose of RNA-Vax.
Methods: Inclusion criteria were: >18 years old, being treated with NTZ/OCR/FNG since the first vaccine dose, diagnosis of COVID-19 after a third booster dose of RNA-Vax, not being treated with steroids within the month prior to any vaccine dose or COVID-19.

Results: 232 pwMS (63 NTZ, 106 OCR, 63 FNG) from 17 Italian MS centers were included in the analysis. pwMS on NTZ (37±9) were younger than those on OCR (42±10, p=0.026) and FNG (43±11, p=0.006); EDSS was higher in pwMS on OCR (3.0, IQR=1.5-5.5) than those on FNG (2.0, IQR=1.0-3.0, p=0.017). COVID-19 was diagnosed 65±41 days after receiving the third booster dose.

PwMS on OCR compared with those on NTZ showed more frequently (p<0.02-0.001): fever >38°C (53.8% vs 20.6%), cough (67% vs 36.5%), dyspnea (18.9% vs 3.2%), longer symptoms duration (9.5±8.7 vs 6±4.6 days), use of NSAIDs (74.5% vs 52.4%), oxygen (7.5% vs 0%), antibiotics (45.3% vs 14.3%). PwMS on OCR compared with those on FNG needed more frequently the use of oxygen (7.5% vs 1.6%, p=0.002). PwMS on FNG compared with those on NTZ showed more frequently (p<0.03-0.002): fever >38°C (39.7% vs 20.6%), cough (65.1% vs 36.5%), dyspnea (15.9% vs 3.2%). There were no differences between the 3 groups of pwMS regarding: COVID-19 treatment with steroids or monoclonal antibodies, hospitalization, and full recovery or death (0%).

Discussion and Conclusions: Breakthrough COVID-19 after a third booster dose of RNA-Vax was more symptomatic in pwMS on OCR and FNG than those on NTZ. Nevertheless, no deaths were reported and the Covid-19 course in terms of full recovery and hospitalization rates was not different across different HE-DMTs. These results support the efficacy of a third booster dose of RNA-Vax in preventing severe COVID-19 (with hospitalization/death) in pwMS treated with most common HE-DMTs.

Disclosure

The authors have no competing interests to disclose.

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Risk and severity of SARS-CoV-2 reinfection among patients with multiple sclerosis vs. the general population: a population-based study

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Introduction: Reports of reinfection in immunocompromised patients increased concern regarding multiple sclerosis (MS) patients since they are mostly on immunosuppressant agents.

Objectives: to compare the risk of reinfection between multiple sclerosis (MS) patients and a control group without MS.

Aims: Measure the rate of possible reinfection among MS patients and control, protection against reinfection, odd of reinfection among those who previously tested positive; and effect of rituximab on the protection

Method: In thisretrospective study, data of all SARS-CoV-2 tests (n=793,301) and almost all MS patients (n=10639) in Isfahan province were collected from January 01, 2020 to August 22, 2021. Of the 2196 MS patients and 793,301 persons from the general population who had been tested at least once, 3 control for each MS patient were identified, leaving 1560 MS patients and 4680 controls without MS. We compared the risk of reinfection after 90 days of a primary infection between those with and without a previous positive COVID-19 test.

Results: 736 (48.2%) MS patients and 2013 (43.0%) control individuals had at least one positive test. A total of 17 (2.3%) and 22 (1.1%) possible reinfections in MS and control groups were observed. The adjusted risk ratio (RR) of infection among previously infected patients compared to uninfected persons in all MS patients was 0.318 (95%CI: 0.188, 0.538), MS patients on rituximab was 0.426 (95%CI: 0.169, 1.070), MS patients on DMTs rather than rituximab was 0.280 (95% CI: 146, 0.537), and control individuals was 0.179 (95%CI: 0.115, 0.279). The estimated protection against reinfection in all MS patients, MS patients on rituximab, MS patients on DMTs rather than rituximab, and controls were 68.2% (46.3%, 81.2%), 57.4% (-0.1%, 83.5%), 71.5% (45.5%, 85.2%), and 82.1% (72.1%, 88.5%), respectively. We found no statistically significant difference in estimated protection (p=0.123) and odd of reinfection (adjusted OR: 2.01 [0.98, 4.08]) between all MS patients and control group.Two patients were hospitalized at first infection but none required hospitalization at reinfection event.

Conclusions: Prior SARS-CoV-2 infection is protective against reinfection in MS patients. Those on rituximab may be at a greater risk of reinfection. We found no evidence regrading increased risk of severe reinfection compared to the primary infection Further studies are required to assess the risk of the second reinfection among the MS population.

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SARS-CoV-2 vaccination and COVID-19 infections in people with multiple sclerosis treated with ocrelizumab in the prospective, multicenter, noninterventional MuSicalE and CONFIDENCE studies

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Background: Understanding outcomes of Coronavirus Disease 2019 (COVID-19) and the impact of COVID-19 vaccination deserve significant consideration for people with multiple sclerosis (MS) treated with ocrelizumab (OCR).

Aims: To report the number, characteristics and outcomes of COVID-19 cases in all OCR-treated patients and in those with COVID-19 vaccination (i.e. breakthrough cases) in two real-world cohort studies.

Methods: We analysed data from OCR-treated patients enrolled in ongoing, prospective, noninterventional studies conducted in Germany (CONFIDENCE, EUPAS22951) and in 25 other countries (MuSicalE, NCT03593590). COVID-19 seriousness was assessed per ICH guidelines. Outcomes were captured as recovered, recovered with sequelae, recovering, not recovered or fatal. Vaccine breakthroughs were cases with COVID-19 onset ⩾14 days after completion of the primary immunisation schedule recommended for each COVID-19 vaccine platform. 'Unvaccinated' included patients without COVID-19 vaccination recorded (including the prevaccination era) or with incomplete immunisation scheme.

Results: Analyses included 1,702 OCR-treated patients from MuSicalE (73.1% relapsing-remitting MS, 21.2% primary progressive MS [PPMS], 5.6% relapsing secondary progressive MS) and 2,784 from CONFIDENCE (81.7% relapsing MS, 18.3% PPMS). As of March 2022 (preliminary data), completion of primary immunisation schedule was recorded for 542 (31.8%) and 710 (25.5%) patients in each study, mainly with mRNA vaccines (72.3% and 93.8%). COVID-19 infection was reported in 189 and 122 patients in MuSicalE and CONFIDENCE (11.1% and 4.4% among all patients), mostly reported as nonserious (85.2% and 83.6%), including 71 and 31 vaccine breakthroughs (13.1% and 4.4% among fully vaccinated patients). The following rates were reported in vaccinated and unvaccinated patients in MuSicalE and CONFIDENCE, respectively: (a) hospitalisations, 8.5% (6/71) vs 16.0% (19/118) and 9.7% (3/31) vs 14.3% (13/91); (b) serious cases, 8.5% (6/71) vs 17.8% (21/118) and 9.7% (3/31) vs 18.7% (17/91); (c) fatalities, 1.4% (1/71) vs 2.5% (3/118) and 0 deaths vs 2.2% (2/91). In both studies, the majority of patients had fully recovered (79.9% and 74.6%) or were recovering (11.1% and 7.4%) at last follow-up. Updated vaccination rates will be presented.

Conclusions: Most COVID-19 cases were nonserious in these OCR-treated patient cohorts. Initial data suggest more favourable clinical outcomes associated with COVID-19 vaccination.

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Spike antibody seroconversion and breadth following SARS-CoV-2 vaccination in Australian people with multiple sclerosis

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Background: COVID-19 vaccination induces protective Spike antibodies. Some responses are attenuated in people with multiple sclerosis (MS) on high efficacy disease-modifying therapies (DMT).Whether antibodies afford immunity against emerging SARS-CoV-2 Variants of Concern (VoC) such as Delta and Omicron is unknown.

Aims: To assess the longevity and breadth of Spike antibody in MS patients after COVID-19 vaccination.

Objective: To determine seroconversion and antibody binding toVoC Spike.

Methods: Spike antibodies to Clade A SARS-CoV-2 were assessed in 535 MS sera at baseline (n=292), 1 (n=141) and 6 month (n=67) post-second dose, and 1 month post-third dose (n=35), and 489 health worker controls. When known, COVID-19 vaccines were BNT162b2 (n= 489 controls, n=108 MS patients) and ChAdOx1-S (n=37).Spike antibody binding to VoC Delta and Omicron BA1 was assessed in 68 sera 1 month post-second dose. Demographic and DMT information was available in 269 patients.

Results: 123/141 sera at 1 month post-second dose, 66/67 at 6 months post-second dose, and 26/35 at 1 month post-third dose were positive for Spike antibodies.Patients who did not seroconvert at 1 and 6 month post-second and 1 month post-third dose (n=28) were treated with ocrelizumab (n=22), cladribine (n=1), fingolimod (n=4), and siponimod (n=1). At 1 month post-second dose, the median and IQR Spike antibody levels were 67,224± 101,251 in the seroconverted MS group compared to 145,510± 99,669 in controls (n=489). When patient sera were assessed for binding to Clade A Spike, and VoC Delta and Omicron BA1 Spikes, most sera were able to bind the three different Spike antigens (n=61). However,Spike antibody immunoreactivity was decreased by 70% against Delta Spike and 90% for Omicron BA1 Spike compared to the original clade A Spike.As observed for Clade A Spike antibody, DMTs, such as ocrelizumab, fingolimod, and ofatumumab, decreased the antibody binding to Delta and Omicron Spike. Still, the pattern of antibody recognition was similar between the three Spikes and all DMTs analysed, i.e. alemtuzumab, natalizumab, teriflunomide, and interferons. Our data suggest that,irrespectively of DMTs, antibodies generated after vaccination did not bind Spike from recent VoCs to the same extent as the original Spike used in COVID-19 vaccines.

Conclusions: Some DMTs reduce Spike antibody titres or prevent seroconversion. The sequence of Spike used in the first generation of vaccines may need to be updated for emerging VoC.

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Pathology and pathogenesis of MS - Environmental factors

P565

Multiple sclerosis and molecular mimicry between NS5 Zika virus epitope and PLP autoantigens

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Introduction: Evidences indicate a strong link between Zika virus (ZikV) and neurological complications. Acute myelitis, optic neuritis, polyneuropathy and encephalomyelitis that mimic inflammatory idiopathic demyelination disorders (IIDD) after ZikV infection have been reported in Brazil. Objectives: The present study aims to investigate the possible occurrence of molecular mimicry between ZikV antigens and Multiple Sclerosis (MS) autoantigens, the most frequent IIDD of the central nervous system (CNS).

Methods: A retrospective cohort study with 305 patients admitted due to suspected arbovirus infection in 3 university hospitals in Rio de Janeiro was performed, all patients were submitted to neurological examination and biological sample was collected for serologic and molecular diagnostic. Bioinformatics analysis were used to identify the peptides shared between ZikV antigens and MS autoantigens.

Results: Of 305 patients, twenty-six were positive for ZikV and 4 presented IDD pattern found in MS cases. Sequence homology comparisons by bioinformatics approach between NS5 ZikV and PLP MS protein revealed a homology of 5/6 consecutive amino acids (CSSVPV/CSAVPV) with 83% identity, deducing a molecular mimicry. Analysis of the 3D structures revealed a similar conformation with alpha helix presentation.

Conclusions: Molecular mimicry between NS5 Zika virus antigen and PLP MS autoantigens emerge as a possible mechanism for IDD spectrum in genetically susceptible individuals.

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Laise Carolina França: Nothing to disclose

P566

Differential methylation mediates significant proportions of environmental and lifestyle factors' associations with MS risk: results from the Ausimmune case-control study

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Background: The mechanisms by which modifiable environmental and lifestyle factors, including Epstein-Barr virus (EBV) exposure, sun exposure/vitamin D, and smoking exert their effects on multiple sclerosis (MS) risk are unclear. Here, we explored the extent to which differential DNA methylation mediated the associations of previously reported environmental/lifestyle risk factors for first clinical demyelination (FCD).
Methods: The Ausimmune case-control study was a multicentre study comprising 282 people recruited soon after an FCD referral and 576 matched-controls. Smoking status, glandular fever history, and recent summer and winter sun exposure were queried. Serum samples were analysed for 25-hydroxyvitmain D (25(OH) D) and anti-EBV serology. Whole-blood EWAS measures were measured using Illumina EPIC BeadChip Array. FCD-associated methylation points (CpG, n=2,432) were inputs to weighted gene-correlation network analysis and 10 CpG clusters were identified. Mediation by dimension-reduced CpG cluster scores was assessed using the MedFlex package in R.
Results: Of the 10 CpG clusters, eight were significant mediators of environmental/lifestyle risk factors, indirect effects ranging between 19-34% of EBV, 15-40% of sun exposure, 17-49% of 25(OH)D, and 15-30% of smoking, with some factors acting through common CpG clusters. CpG clusters aligned with pathways involved in signal transduction and transcription regulation, and T-cell activation/proliferation.
Discussion: These results demonstrate for the first time that roughly one-third of the associations seen for EBV exposure, sun exposure, 25(OH)D, and smoking are explicable by differential methylation of loci involved in immune cell regulation, providing biologically plausible mechanisms by which these factors can affect MS risk, and suggesting potential points of intervention.

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P567
Longitudinal trajectories of diet quality and associations with clinical progression over 7.5 years in an international sample of people with MS

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Background: Modifiable factors, including diet, have been implicated in MS progression. However, evidence from large sample, longitudinal cohort studies to substantiate the validity of these relationships are lacking.
Objectives: To assess longitudinal relationships of diet quality with subsequent change in disability, fatigue, and depression in an international cohort of people with established MS.
Methods: Data from the Health Outcomes and Lifestyle In a Sample of people with Multiple sclerosis (HOLISM) cohort were utilised, including baseline, 2.5-, 5-, and 7.5-year timepoints. Diet quality was assessed by modified Diet Habits Questionnaire. Disability was assessed by Patient-determined MS Severity Score (P-MSSS), fatigue by Fatigue Severity Scale, and depression risk by Patient Health Questionnaire 2. Characteristics of outcomes

were assessed by log-binomial, log-multinomial, and linear regression, adjusted for age, sex, MS type, disability, fatigue, comorbidities, antidepressant and antifatigue medication use, and ongoing symptoms due to relapse, as appropriate.
Results: Among 602 participants with data at all four timepoints, baseline DHQ scores in the top quartile (>89%) were associated with 48% lower risk of increasing P-MSSS and 0.44 points lower P-MSSS accrual over follow-up. Participants with decreasing DHQ score over baseline-2.5-year review had 2.8-times greater risk of increasing P-MSSS and had 0.36 higher P-MSSS accrual. Participants consuming meat and dairy at baseline had 2.06- and 2.02-times greater risk of increasing P-MSSS and had 0.28 and 0.43 higher P-MSSS accrual, but no consistent associations of change in meat or dairy consumption with P-MSSS were seen. No consistent associations of baseline or change in diet quality with fatigue or depression outcomes were seen.
Conclusions: These results suggest improving diet quality in people with MS may be a useful point of intervention to reduce disability progression.

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P568

Gene-environment interactions increase the risk of pediatric-onset multiple sclerosis associated with household chemical exposures

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Introduction: We previously reported an association between household chemical exposures and increased risk of pediatric-onset multiple sclerosis (POMS).
Objectives/ aims: To examine potential interactions between household chemical exposures and genetic risk factors for POMS risk.
Methods: Using a case-control pediatric MS study, odds of having POMS were compared according to different genotypes and exposure to household chemicals. Genetic risk factor of interest included the 2 major HLA MS risk factors, *DRB1*15*and absence *A*02*, and MS variants on the metabolic pathways of main household toxic chemicals including*IL-6* SNP (rs2069852, GG genotype), *BCL-2* SNP (rs2187163, GG genotype) and*NFKB1* SNP (rs7665090, GG genotype). Potential interactions between chemical exposures and MS risk variants and odds of POMS were evaluated. Additive and multiplicative interactions were estimated using the logistic regression model. In order to minimize bias due to missing exposure, inverse probability weighting was used.
Results: A total of 490 POMS cases and 716 controls contributed to the analyses.Exposure to insect repellent for tick or mosquitos (OR 1.55, 95% CI 1.11-2.16, P = 0.009), weed control products (OR 2.20, 95% CI 1.54-3.15, P < 0.001) and plant/tree insect or disease control products (OR 3.35, 95% CI 1.98-5.64, P < 001) was associated with increased odds of POMS. There was significant additive interaction between exposure to weed control products and *NFKB1*SNP GG (attributable proportions (AP) 0.48, 95% CI: 0.10–0.87). For exposure to plant/tree insect or disease control products and absence of *HLA-A*02*only an additive interactionwas present (AP 0.56; 95% CI: 0.03-1.08). No interaction was found with*IL-6* and BCL-2 SNP GG genotypes.
Conclusion: The presence of gene-environment interactions with household toxics suggests their possible causal role in POMS.

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P569

Smoking and multiple sclerosis risk in blacks: a nested case-control study

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Background: Over the last five decades, the incidence of multiple sclerosis (MS) has been relatively stable in Whites while recent studies have reported an increased incidence in Blacks. It is unclear what underlies these findings, but the effects of environmental risk factors may vary with race/ethnicity. Smoking is a well-established risk factor for MS in Whites that has not been investigated in Blacks. Therefore, we aimed to evaluate whether smoking was associated with an increased risk of MS in a racially diverse cohort of young adults.
Methods: We conducted a case-control study nested within a cohort comprised of more than 10 million US military personnel with serum samples stored at the Department of Defence Serum Repository. We measured cotinine levels, a marker of tobacco smoke exposure, in 157 Black and 23 White individuals who developed MS during follow-up. Controls were randomly selected and matched to each case by age, sex, race/ethnicity, dates of sample collection, and branch of military service. We defined ever smoking as cotinine levels >25ng/mL in any of the samples, while never smoking was defined as levels <25ng/mL in all samples.The association between smoking and MS was estimated using conditional logistic regression.
Results: Smoking was not associated with an increased risk of MS in Blacks (RR 0.95, 95%CI 0.57-1.61). The results remained similar when we restricted the analyses to smoking status at baseline, using different cut-offs in cotinine to define smoking status, and when comparing persistent smoking over time to never smoking. In Whites, being a smoker was associated with an increased MS risk (RR 1.64, 95%CI 0.62-4.34), although the results did not reach statistical significance.
Conclusions: In this prospective cohort study, smoking was not associated with MS risk in Blacks. The risk estimate in Whites was of similar magnitude to what has previously been reported, but did not reach statistical significance. These results suggest that there are racial differences in how smoking affects MS risk.
Disclaimer: The views expressed in this article are those of the authors and do not reflect official policy or position of the Uniformed Services University of the Health Sciences or the Department of Defence.

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P570

Association between abdominal obesity, adipokines and disease severity in patients with multiple sclerosis

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Introduction: Obesity during adolescence has been identified as a risk factor for MS, but the mechanisms are still unclear. Adipose tissue – especially visceral adipose tissue – is an endocrine organ secreting adipokines with immune regulating functions, however, data on the potential effect of adipokines on MS disease severity are scarce.
Aims and objectives: This study aims to identify potential differences in body composition and levels of the adipokines leptin, adiponectin and resistin between patients with MS and healthy controls (HCs). Furthermore, the potential associations between body composition, circulating levels of the above adipokines and MS disease severity will be explored.
Methods: In this cross-sectional, case-control study, a total of 80 MS patients and 47 HCs were recruited from the Danish Multiple Sclerosis Center (DMSC). Body composition was assessed using body mass index (BMI), waist-to-hip ratio (WHR) and sagittal abdominal diameter (SAD). Serum concentration of the adipokines leptin, adiponectin and resistin were measured by enzyme-linked immunosorbent assay (ELISA). The Multiple Sclerosis Severity Score (EDSS) and yearly relapse rate were calculated based on data from the COMPOS sclerosis register. Finger

dexterity, cognitive function and walking ability were evaluated using the 9-hole-peg-test (9-HPT), symbol digit modalities test (SDMT) and timed 25-foot walk test (T25FWT) respectively.
Results: Adiponectin levels were significantly higher among MS patients (mean=8860 ng/mL, IQR=5802–12430) compared to HCs (mean=7334 ng/mL, IQR=4574–8740), however leptin and adiponectin levels were higher among females compared to males within the same cohort. Among all participants, correlations emerged between leptin and BMI (corr=0.750, $p<0.001$) and SAD (corr=0.759, $p<0.001$), and between adiponectin and all body parameters (BMI: corr=-0.179, $p=0.045$, WHR: corr=-0.315, $p<0.001$, SAD: corr=-0.218, $p=0.014$). MSSS correlated with BMI (corr=0.263, $p=0.018$), WHR (corr=0.231, $p=0.040$), SAD (corr=0.377, $p<0.001$) and leptin (corr=0.291, $p=0.009$). Attack rate correlated with BMI (corr=0.288, $p=0.010$), SAD (corr=0.305, $p=0.006$) and leptin (corr=0.234, $p=0.038$). T25FWT correlated with BMI (corr=0.40, $p=0.035$), SAD (corr=0.45, $p=0.007$) and leptin (corr=0.41, $p=0.027$).
Conclusion: This study provided evidence of correlations between BMI and visceral fat according to adipokines (leptin, adiponectin and resistin) and disease severity.

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P571
Long-term exposure to ambient air pollution is associated with increased neuronal injury in people with multiple sclerosis

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Introduction: Contributors to multiple sclerosis (MS) heterogeneity remain poorly understood. High ambient air pollution exposure has been associated with increases in acute systemic inflammatory responses and neuroinflammation in the general population. However, limited studies have explored whether ambient pollution exposure affects disease outcomes in people with MS (PwMS).
Objective/Aims: To assess whether ambient air pollution exposure is associated with serum neurofilament light chain (sNfL) levels, as a sensitive biomarker of subclinical disease activity in PwMS.
Methods: Annual fine particulate matter of diameter $\leqslant 2.5\mu m$ ($PM_{2.5}$), ozone(O_3) and nitric oxide (NO_2) exposure were estimated from validated models with spatial resolution of 1km. Estimates were linked to geocoded addresses associated with clinical encounters for patients receiving care at the Johns Hopkins MS Center. sNfL was measured using a high-throughput immunoassay (Siemens Healthineers), and age-specific cut-points of sNfL and adjusted Z-scores were derived from a comparable cohort of healthy control participants. We evaluated the association between sNfL and cumulative average of individual pollutants and overall pollutant mixture exposure that were estimated from encounters prior to sNfL-associated blood draw. Statistical analyses were performed using generalized linear models and quantile g-computation (for pollution mixtures analysis). Analyses were adjusted for multiple sociodemographic, neighborhood, comorbid, and MS-related characteristics.
Results: Pollution exposure for the 1113 PwMS (75% female; mean age: 47.2y[SD: 12.3y]; 30% progressive MS) included was estimated for a median 7.1y [IQR: 3.1-12.1y] prior to sNfL blood draw. In multivariable-adjusted models, $PM_{2.5}$and O_3 exposure were associated with higher sNfL Z-scores (per 1SD increase in $PM_{2.5}$: 0.16; 95%CI: 0.08-0.24; $p<0.001$, per 1SD increase in O_3: 0.08; 95%CI: 0.00-0.17; $p=0.05$). $NO_2$was not individually associated with sNfL. In mixture analyses, higher composite pollution exposure was associated with higher sNfL Z-scores (per 1SD increase in pollution mixture: 0.14; 95%CI: 0.02-0.25; p=0.02). Consistent results were observed when we dichotomized sNfL z-scores and when pollutants were modeled using splines.
Conclusions: Higher ambient air pollution was significantly associated with increased subclinical measures of disease activity in PwMS. Future studies are warranted to understand mechanisms underlying this finding.

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Pathology and pathogenesis of MS - Neurobiology

P572

Expansion of chronic active multiple sclerosis lesions is linked to the dysregulation of cholesterol metabolism

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Introduction: Chronic active white matter lesions (CA WML), characterised by a rim of activated microglia/ macrophages, are associated with increased multiple sclerosis (MS) severity. The products of cholesterol oxidation, the oxysterols, are lipid ligands that regulate glial and neuronal cell health, myelination and inflammation.
Aims: We hypothesised that an altered cholesterol homeostasis in MS may promote a damaging inflammatory milieu, contributing to sustained damage at the expanding CA WML edge.
Methods: Post-mortem, snap frozen brain from progressive MS (n=11, male=4, age=49yrs; REC 13/WA/0292) and controls (n=5, male=3, age=61yrs) were stained for anti-MOG; anti-HLA-D & anti-TMEM119; oil red O & perilipin-2 to characterise myelin, microglia/macrophages and lipids (including stored cholesterol and lipid droplets) respectively. Regions of interest, including CA WML centre and edges, and normal appearing white matter (NAWM), were macrodissected, oxysterols extracted, and quantified using liquid chromatography–mass spectrometry.
Results: Key lipid metabolic systems differ between MS and control brain, and within CA WMLs. Cholesterol: 20.8±3.9μg/mg control WM (mean ±standard deviation), 12.7±13.2μg/mg NAWM, 3.9±2.1μg/mg CA WML edge, 2.2±2.4μg/mg CA WML centre. 24S-hydroxycholesterol (24S-HC): 15.1±1.7ng/mg control WM, 7.8±4.9ng/mg NAWM, 3.3±1.3ng/mg CA WML edge, 1.9±1.1ng/mg CA WML centre. Evidence of altered cholesterol homeostasis was supported by the finding of abundant lipid droplet (oil red O, perilipin-2+) positive macrophages at CA WML edge and a 70-fold reduction in*CYP46A1*transcript in the MS brain, whose product metabolises cholesterol to 24S-HC ($p<0.05$). Our cholesterol findings were validated using matrix-assisted laser desorption/ionisation (MALDI), allowing on-tissue imaging and analysis of cholesterol in MS for the first time ($p<0.05$).
Conclusions: Excessive cholesterol build-up in microglia/macrophages in CA WMLs may result in a failure of phagocytes to resolve inflammation. Interventions to restore cholesterol homeostasis, for example by increasing *CYP46A1*, may resolve chronic inflammation and reduce the severity of disease.

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P573

The role of dual immunoglobulin domain containing cell adhesion molecule (DICAM) Expressing myeloid cells in multiple sclerosis lesion formation and disease progression

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Introduction: Multiple sclerosis is characterized by leukocyte infiltration into the central nervous system (CNS), which leads to the blood-brain barrier (BBB) and brain-meningeal barrier (BMB) disruption and lesion formation. Our lab has determined Dual immunoglobulin domain containing cell adhesion molecule (DICAM) expression on $CD14^+$ monocytes and $CD11c^+$ dendritic cells from MS patients, as well as expression of its ligands, αVβ3 and DICAM, on the BBB and BMB.
Objectives: To investigate DICAM expression on myeloid cells and its role in migration into the CNS. To study the effect of blocking DICAM*in vivo* during experimental autoimmune encephalomyelitis (EAE).
Aims: The first aim is to characterize DICAM expression on myeloid cells, namely monocytes and dendritic cells. Furthermore, we aim to explore the role of DICAM in myeloid cell migration across the BBB/BMB *in vitro* and *in vivo*.
Methods: Using flow cytometry and immunohistofluorescence (IHF), we have studied DICAM expression on peripheral blood mononuclear cell (PBMC) derived monocytes and dendritic cells from MS patients as well as healthy subjects. To unravel DICAM's role in human monocyte migration, we performed *in vitro* Boyden migration assays as well as Flow Adhesion assays mimicking the blood flow. Finally, we have used the active MOG_{35-55} EAE mouse model to investigate the effect of blocking DICAM on disease severity.
Results: We found a higher frequency of $DICAM^+$ monocytes in RR (relapsing remitting), SP (secondary progressive) and PP(primary progressive) MS patients when compared to healthy subjects. Strikingly, the frequency of $DICAM^+$ monocytes was significantly higher in MS patients with active disease. Furthermore, SPMS patients have a higher frequency of $DICAM^+$ dendritic cells compared to healthy donors. In vitro flow adhesion assays showed that blocking DICAM reduced monocyte rolling and adhesion on BBB ECs by 33%, whereas migration assays revealed a 30% decrease in monocyte migration after DICAM blockade. Subsequently, when mice affected by active MOG_{35-55}EAE were treated with anti-DICAM antibody, we observed 3 times less infiltration of myeloid cells (F4/80, IBA1) compared to the mice treated with the isotype.
Conclusion: Our results suggests that DICAM plays an important role in myeloid cell migration into the CNS and possibly affects

disease progression. DICAM blockade can reduce myeloid cell transmigration across the brain barriers and could therefore decrease lesion formation.

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P574
Myelin dynamics in the optic nerve during development

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Background: The pattern of myelin internodes plays a crucial role in determining the speed of conduction of electrical signals in the nervous system. Yet, we are still debating whether this process of patterning is stochastic or dynamically responds to extrinsic cues. This project characterizes internodal length during development to assess how it is tuned over time.
Methods: We precisely quantify internodal length in the optic nerve using a novel mouse model, PLP-CreER^T;STARS, of stochastically sparse labeled oligodendrocytes. We administer tamoxifen to these mice at P10, shortly after the initiation of myelination, and collect optic nerves at multiple time points during development (P11 to P60).
Results: Preliminary results from these experiments reveal that each oligodendrocyte has a wide variety of internodal lengths, and that their average length remains constant throughout development. At post-natal day (P)11, internodes reported as mean (min, max) are 113.6 μm (19.5 μm, 238.7 μm) long in the optic nerve of mice (N=3), have a coefficient of variation of 38.5% and are skewed to shorter internodes (Skewness: 0.7). After development at P60 (N=3), internodes are 118.9 μm (45.6 μm, 240.3 μm), have a coefficient of variation of 35.2% and adopt a gaussian distribution (Skewness: 0.49). While internodal length is stable through development, there is a significant increase in the myelinogenic potential of oligodendrocytes: at P11 each oligodendrocyte have 7.8 ± 0.7 internodes and at P60 it reaches 10.5 ± 0.4, with a significant increase at P14.
Conclusion: Overall, the myelin formed in the optic nerve during early development does not significantly change in length, however the myelinogenic potential of oligodendrocytes increases until adulthood. Further experiments to study the impact of extrinsic cues on internodal length are ongoing. These approaches will not only establish that myelination during development is a dynamic process, but will also provide a model for internodal length determination.

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P575
Hyaluronan synthesis and catabolism as therapeutic targets for cognitive disturbances in multiple sclerosis

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Introduction: Patients with multiple sclerosis (MS) experience cognitive dysfunction involving multiple domains, including hippocampus-dependent learning and memory. Patients with early relapsing-remitting MS demonstrate decreased performance in a pattern recognition test, consistent with deficits in the hippocampal dentate gyrus (DG). We findthat mice with experimental autoimmune encephalomyelitis (EAE), a model of MS, also develop hippocampal memory deficits consistent with DG dysfunction before the onset of motor deficits and before demonstrating hippocampal demyelination.
Objectives: This study aims to define the contributions of dynamic changes in the extracellular matrix (ECM) of the DG to cognitive dysfunction in early stages of EAE, and to test how manipulating these changes could improve the cognitive function of MS patients.
Methods and Results: Using biochemical, immunohistochemical, and molecular assays, we found that changes in cognitive function in early stages of EAE are linked to alterations in the hyaluronan (HA)-based ECM of the DG. HA is a glycosaminoglycan synthesized at the cell membrane and serves as the backbone for proteoglycans in perineuronal nets (PNNs) surrounding parvalbumin-positive (PV) interneuronsthat regulate output from the DG. HA is elevated in PNNs in the DG and in thesubgranular zone (SGZ), a neural stem cell (NSC) niche,in mice with early-stage EAE.Despite increases in HA synthesis,the average molecular weight of HA is reduced in DG tissues (<250 kDa) from mice with EAE compared to healthy controls coincident with transcriptional upregulation of the CEMIP hyaluronidase. Changes in HA synthesis and catabolism are accompanied byreduced long-term potentiation (LTP) in the DG, consistent with the memory deficits we observed. Hyaluronidase in the DG induces NSC proliferation and delays neuronal maturation. Disrupting HA signaling causes hippocampal memory deficits, mirroring the phenotypes seen in mice with EAE and patients with MS.Significantly, blocking HA synthesis can reduce PNNs and improve memory in mice.

Conclusions: Altogether, these data support the hypothesis that early hippocampal dysfunction in MS is linked to alterations in HA synthesis and catabolism that impact PV neurons and SGZ neurogenesis, and that HA synthases or CEMIP activity are potential therapeutic targets for at least some of the cognitive deficits experienced by MS patients.

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P576
Spatial gene expression profiling of multiple sclerosis lesion cores and rims predict lesion evolution

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Introduction: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. In MS, different types of lesions are present, ranging from active to inactive, and from demyelinated to remyelinated. To understand the molecular pathways underlying lesion heterogeneity, different gene expression profiling approaches have been used, including bulk, single-cell, and single-nucleus sequencing. However, these techniques lack spatial resolution of the analyzed tissue.
Aim: In this study, we aim to identify unique spatial gene expression profiles between and within different MS lesions.
Methods: Spatial transcriptomics was performed on well-characterized human post-mortem brain tissue from healthy subjects and MS patients to quantitatively define gene expression levels with spatial resolution.
Results: Using unbiased clustering, we identified distinct spatial clusters in active, mixed active/inactive, inactive and remyelinated white matter lesions. Particularly, we discovered unique rim clusters in active MS lesions. In addition, perilesional white matter of all lesion types was transcriptionally distinct from lesion-free normal-appearing white matter. Furthermore, specific signatures for active, mixed active/inactive and remyelinated cores were identified. By constructing pseudotime trajectories, we identified two trajectories with differential involvement of lesion rims and cores, resulting into a proposed model of MS lesion evolution.
Conclusion: Our findings revealed novel and differential spatial gene expression profiles for the distinct lesion types and lesion surroundings, that point to different pathological processes in MS lesion progression. Ultimately, it would be ideal to understand the intermediate phases leading towards detrimental and beneficial endpoints in lesion evolution, to be able to inhibit or promote these routes in the future towards the route ending in remyelination.

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Pathology and pathogenesis of MS - Neurodegeneration

P577
Impact of age in the central nervous system pathogenesis of the in vivo model of multiple sclerosis

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Introduction: Multiple Sclerosis (MS) is a progressive autoimmune disease of the Central Nervous System (CNS) and the major cause of non-traumatic neurological disability in young adults. Over the past years, a few studies have revealed that age of onset has a tremendous impact on disease worsening along with poor response to treatments. We recently describe that in an in vivo model of MS, age is positively correlated with worse disease phenotype. However less is known concerning the influence of age in the interplay between immune system and glial cell response in MS and how it may correlate with disease severity/progression.
Aims: We aimed to evaluate the impact of age in the response of glial cells and associated functional genes expression along disease progression in the in vivo model of MS, the Experimental Autoimmune Encephalomyelitis (EAE).
Methods: We induced EAE in C57BL/6 female mice in 3 groups: 3-, 6- and 12-months-old mice. Mice were induced on day 0 and followed for 23 days. On sacrifice day, mice spinal cords were isolated for immunohistochemistry (IBA1 for microglia/macrophages, and GFAP for astrocytes) and for RealTime-qPCR gene expression.
Results: Our results demonstrated that 12-months-old EAE mice show a significantly increase in the percentage of $IBA1^+$and $GFAP^+$cells in lesion areas compared to 3- and 6-months-old EAE mice ($p<0.05$). Regarding gene profile it was observed that

12-months-old EAE mice present downregulation ($p<0.05$) of genes related to complement system (*C1qA,B*and*C*) and phagocytosis (*TREM2*) in parallel with an upregulation ($p<0.05$) of T cells associated cytokine genes (*IFN-g,IL-17*and*IL-10*) compared to 3- and 6-months-old EAE mice.

Conclusion: Our results demonstrated that age influences EAE course and is accompanied with increased gliosis, with variable expression of inflammatory molecules. Most importantly, aging alters crucial functions of immune response and regenerative microglia phenotype potentially contributing to EAE disease progression.

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P578

Using high-resolution quantitative MRI to discriminate demyelination in postmortem multiple sclerosis spinal cord tissue

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Introduction: Spinal cord involvement in MS is associated with disability accumulation associated with demyelination and neurodegeneration. We previously found T2*-hyperintensity represented a mix of myelinated and demyelinated regions. Here we used 7T MRI to discriminate demyelination from normal appearing white/grey matter (WM/GM) and WM fraction (WMF) with immunohistological validation.

Objectives: To evaluate if 7T MRI can discriminate demyelination in the MS spinal cord.

Aims:1) Determine a threshold of quantitative T2*-relaxation time that discriminates demyelination; 2) evaluate differences in disability and MRI in WMF cord extremes.

Methods: 7T MRI of 2-cm fixed postmortem cervical cord segments of 40 MS cases was performed using T2*-multigradient echo (MGE). 30-micron sections of corresponding MRI-visible lesions were stained for myelin, axons, and activated microglia/macrophages. Regions of interest were identified as a) myelinated WM/GM with MRI T2*-normal appearing intensity; b) demyelinated WM/GM with MRI T2*-hyperintensity; c) myelinated WM/GM with MRI T2*-hyperintensity. Receiver operating characteristic (ROC) analysis was used to determine the accuracy, sensitivity and specificity of T2* in discriminating demyelinated vs myelinated (normal appearing and T2*-hyperintense). WMF was manually segmented and extremes [(30^{th} (median 0.79, IQR 0.06) vs 70^{th} percentile (median 0.88, IQR 0.05)] of WMF were compared (n=9 each) with EDSS and MRI using Wilcoxon rank sum test. Brain T2LV was obtained from postmortem*in situ* MRI

Results: A 7T T2* cutoff of 47.0ms was able to discriminate WM demyelination with an accuracy 89.7%, sensitivity 95.5%, and specificity 87.0%; GM cutoff 44.6ms, with accuracy 84.3%, sensitivity 76.2%, and specificity 90%. In extremes of WMF, EDSS was not different (p=0.07). However, UCCA was lower in subjects with the lowest WMF [median 58.6 (IQR 8.7)] compared to those with highest [81.9cm^2 (24.1); $p = 0.02$]. Brain T2LV was greater in subjects with the lowest WMF [median T2LV 117.5 (IQR 2.5) vs 36.7cm^3 (27.0), $p = 0.02$].

Conclusions: 7T T2* in postmortem fixed spinal cord can discriminate demyelination. Furthermore, spinal cord segments with the lowest WMF, suggestive of cord axonal loss, had the lowest upper cervical cord area and highest brain T2LV in our cohort. These findings merit further investigation using clinical imaging modalities to improve the specificity of evaluating demyelination and axonal loss in MS.

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P579

Myelinated axon degeneration associated with periventricular T2 hyperintensities

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Introduction: Myelocortical multiple sclerosis (MCMS) is characterized by paucity of cerebral white matter demyelination and

abundant spinal cord and cortical demyelination. Despite the lack of cerebral white matter demyelination, T2-weighted hyperintensities appeared similar to those detected in postmortem MS brains with cerebral white matter demyelination.

Objectives/Aims: To establish the 3D distribution of T2-weighted (T2W) hyperintensities and T1-weighted (T1W) hypointensities in MCMS and typical MS brains (TMS) and to develop imaging protocols that identifies postmortem MCMS cases. To characterize pathological changes associated with periventricular T2W hyperintensities in MCMS.

Methods: We examined the 3D distribution of T2W hyperintensities and T1W hypointensities in postmortem MCMS and TMS brains. We investigated whether specific T1W thresholds could distinguish pathologically confirmed myelinated and demyelinated T2W hyperintensities in MCMS and identify additional MCMS cases in our autopsy cohort. Periventricular white matter regions with T2W hyperintensities were co-registered on fixed brain slices and examined for myelin and axonal pathology.

Results: Based upon 3-D reconstructions of postmortem brain MRI, myelinated T2W hyperintensities in MCMS brains have a periventricular distribution that is most prominent at the anterior and posterior poles of the lateral ventricle. Using MRI sequences from pathologically confirmed MCMS and TMS brains we developed a decision tree that reliably distinguished myelinated and demyelinated T2W hyperintensities. When applied to 55 additional postmortem cases, this decision tree, which thresholds T1W hypointensities identified 9 potential MCMS cases (16%), out of which 8 cases were found to have a paucity of cerebral white matter demyelination on pathology. Myelinated axonal loss, myelinated axonal swelling and Wallerian degeneration were prominent at the ventricular surface and decreased with distance from the ventricle.

Conclusions: Myelinated T2W hyperintensities in MCMS are confluent, periventricular and can be identified by thresholding T1W hypointensities. Pathological correlates of periventricular myelinated T2W hyperintensities in MCMS support a possible CSF-associated mechanism of myelinated axonal thinning and Wallerian degeneration that is independent of demyelination.

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Pathology and pathogenesis of MS - Repair mechanisms

P580

Transcranial direct current stimulation applied to prevent optic nerve damage and to promote remyelination in the experimental autoimmune encephalomyelitis mouse model

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Introduction: Altered nerve conduction can be modulated by transcranial direct current stimulation (tDCS) which is a non-invasive brain stimulation that has promising clinical outcomes in multiple sclerosis. TDCS induces polarity-dependent changes in membrane excitability by depolarizing (anodal tDCS) and hyperpolarizing (cathodal tDCS) neurons under the stimulated areas. TDCS application on animal models appears fundamental to understand and validate its treatment efficiency. Chronic Experimental Autoimmune Encephalomyelitis (EAE) is characterized by optic nerve abnormalities, consisting of demyelination/axonal loss, and retinal thinning.

Objective and Aim: to test multisession tDCS to restore visual function in EAE pre-motor onset phase.

Methods: Optic nerve functional alterations were investigated using non-invasive visual evoked potentials (VEPs), before immunization and 24 hours after last session treatment, and histology to confirm *in vivo* results.

Results: Cathodal stimulation significantly decreased VEP latency delay compared to EAE-Sham and EAE-Anodal groups. Immunohistochemistry on optic nerves, showed a significant decrease in microglia/macrophage cells density and axonal loss in EAE-Cathodal mice compared to EAE-Sham and -Anodal, while the percentage of demyelination was comparable between EAE groups. Considering this last result, immunofluorescence staining to investigate the node of the Ranvier structure was performed. The node length did not show a significant difference between groups, while the paranode length was significantly increased in EAE-Anodal mice. Moreover, in EAE-Cathodal mice, a significantly higher number of paranode domains was found than EAE-Sham and EAE-Anodal groups. These results were reflected by the negative correlation with VEP latency change. Finally, the number of the single paranode was significantly decreased in EAE-Cathodal compared to EAE-Sham.

Conclusion: cathodal stimulation was able to reduce the visual damage in the pre-motor onset EAE phase, while anodal stimulation seems to have no positive effect.

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P581

Low serum n-acetylglucosamine levels are associated with serum neurofilament light chain increase after 12 months

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Background: N-glycan branching regulates immune cell activity and differentiation of oligodendrocyte progenitor cells towards myelin producing oligodendrocytes. N-acetylglucosamine (GlcNAc) is a rate limiting metabolite required for N-glycan branching. We have previously shown that patients with primary and secondary progressive multiple sclerosis (MS) display markedly reduced serum GlcNAc, which implicates that N-glycan branching and GlcNAc may be relevant for disease progression in MS.
Objective/Aims: To investigate if serum GlcNAc levels predict disease progression in MS, assessed as change in serum neurofilament light chain (NfL) concentration, an emerging biomarker of neuroaxonal damage.
Methods: Retrospective analysis of data from 180 MS patients. We analyzed serum NfL in 103 MS patients (age 44±10 years, 64/39 women/men) with available serum samples at baseline and at 12-month follow-up. Sixty-eight patients had a relapsing-remitting phenotype, 35 patients a primary or secondary progressive phenotype. Serum GlcNAc was measured using targeted tandem mass-spectroscopy at baseline. We used a previously established cutoff of 514nM GlcNAc serum concentration to separate patients with decreased and normal serum GlcNAc levels. Serum NfL was measured using a Simoa assay at baseline and 12-month follow-up.
Results: Patients with low GlcNAc levels had 12.7±7.1pg/mL serum NfL, whereas patients with high/normal GlcNAc levels had 10.5±6.2pg/mL serum NfL, but this difference was not significant when correcting for age (B=1.4, 95%-C=-1.4–4.2, p=0.318). Compared to patients with normal GlcNAc, patients with decreased GlcNAc levels showed a greater increase in serum NFL at 12-month follow-up (Est=2.8, 95%-CI=0.2 - 5.3, p=0.034, corrected for age).
Conclusions: Our study supports that low serum GlcNAc is associated with worse disease progression in patients with MS in the following 12 months. Further studies are needed to investigate non-linear age effects and differences in patients with active vs. inactive disease.

Disclosure

A.U. Brandt is cofounder and holds shares of medical technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patents and patent applications describing methods for retinal image analyses, motor function analysis, multiple sclerosis serum biomarkers and myelination therapies utilizing N-glycosylation modification. He is cofounder, member of the board and currently elected Secretary/Treasurer of IMSVISUAL.
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Z. Yu reports no disclosures.
J. Dennis reports holding a patent for PCT/US16/15807 N-Acetyl Glucosamine as a Biomarker of MS Disease Course and being an inventor on this patent, a patent on methods and compositions for preventing and treating a disease related to glycan dysregulation issued toWellsley Therapeutics, and a patent on Analogs of N-acetylglucosamine pending; and being a cofounder of and holding shares in Glixis Therapeutics LLC.
M. Demetriou reports having a patent for US9775859B2 issued, a patent for US10495646B2 issued, and a patent for US20170042919A1; and being a cofounder and shareholder of Glixis Therapeutics.
F. Paul served on the scientific advisory boards of Novartis and MedImmune; received travel funding and/or speaker honoraria from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is an associate editor of Neurology: Neuroimmunology & Neuroinflammation; is an academic editor of PLoS ONE; consulted for Sanofi Genzyme, Biogen, MedImmune, Shire, and Alexion; received research support from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Geynzme, Alexion, and Merck Serono; and received research support from the German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy-Jackson Charitable Foundation, and NMSS.

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Characterization of galectin-1 and galectin-4 expression levels in Sera of multiple sclerosis patients and their effect on oligodendrocyte precursor cells differentiation and inflammation

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Background: Oligodendrocyte precursor cells (OPCs) are present in MS lesions. However, remyelination by mature oligodendrocytes is usually inadequate, particularly in progressive MS.Galectins-1-4 are master regulators of immune cell response, and are players in remyelination. However, their precise role in MS pathology remains obscure.

Objective: To investigate levels of galectin-1-4 in sera of MS patients, and study their effect on OPCs differentiation, and on macrophages M1/M2 phenotype.
Methods: Sera of 153 MS patients and 64 aged matched healthy controls were analyzed for galectin-1, -4 levels using ELISA. Rat OPCs were treated with recombinant human galectin-1, -4 to study their effect on oligodendrocytes differentiation*in-vitro*. Monocytes isolated from MS patients and healthy individuals were subjected to differentiation, treated with M-CSF and galectin-1, stained for macrophage markers and analyzed by flow cytometry for M1/M2 distribution.
Results: Galectin-1 serum levels were significantly reduced in both SP-MS (n=30; 13,870±3,706 pg/mL) and PP-MS patients (n=20; 4,977±1,574pg/mL) compared to RR-MS (n=103; 47,601±13,677 pg/mL; p=0.016, p=0.002, respectively), and to healthy control (HC) (n=64; 55,343±17,098; p=0.02, p=0.005, respectively).Galectin-4 serum levels were significantly reduced in SP-MS (1,147±314 pg/mL) and PP-MS patients (758±183 pg/mL) compared to RR-MS (2,696±485 pg/mL; p=0.008, $p<0.001$, respectively) and to HC (2,911±576 pg/mL, $p=0.008$, $p<0.001$, respectively). Furthermore, galectin-1 (500 ng/ml) increased OPCs differentiation to mature oligodendrocytes by 3-fold (p=0.04), galectin-4 (18 ng/ml) generated similar results. Galectin-1 increased %M2 macrophages differentiated from monocytes of healthy individuals by 20%, compared to untreated cells. However, this effect was not seen with monocytes of MS patients.
Conclusions: Low levels of galectin-1 in sera of MS patients and particularly PP-MS patients may be related to insufficient OPCs differentiation, and to reduced M2 macrophages immune-regulatory activity. These results support the possibility that galactin-1and -4 have a dual role in the regeneration of oligodendrocytes and in the reduction of inflammation in MS.

Disclosure
Nothing to disclose

P583
Neuregulin-1 enhances oligodendrocyte maturation and remyelination through microglia dependent mechanisms

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Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS) that eventually leads to progressive neurodegeneration. Remyelination is a critical repair process in these lesions that occurs completely or partially at early stages of the disease. However, remyelination declines with progression of the disease. Thus, uncovering the underlying mechanisms of remyelination is necessary to allow for development of effective reparative treatments for progressive MS. The pro-inflammatory CNS resident microglia and infiltrating macrophages contribute to the destruction of myelin sheath during demyelination. However, these cells can also acquire disease-resolving phenotypes required for remyelination. Pro-regenerative microglia and macrophages exhibit a higher phagocytosis capacity for cholesterol-rich myelin debris in MS lesions, and augmenting the reparative potential of these cells can be of paramount importance for remyelination.
We previously reported that Neuregulin-1 (Nrg-1), a key signaling protein for CNS myelination, is significantly reduced in MS lesions. We showed that restoring Nrg-1 levels in lysolecithin-induced focal acute demyelinating lesions can promote remyelination and foster pro-regenerative phenotypes in microglia and macrophages. Thus, we hypothesize that Nrg-1 bioavailability can promote maturation of oligodendrocyte progenitor cells (OPCs) into myelinating oligodendrocytes in demyelinating lesions by enhancing the ability of microglia and macrophages for myelin phagocytosis and cholesterol biosynthesis.
Aim: To evaluate whether Nrg-1 promotes oligodendrocyte maturation and myelination by regulating microglia myelin phagocytosis and cholesterol biosynthesis.
Using primary cultures of microglia and bone marrow-derived macrophages (BMDMs), we found that Nrg-1 promotes phagocytosis of myelin debris in both microglia and BMDM populations in a time-dependent manner. Moreover, Nrg-1 elevates the cellular levels of esterified and free cholesterol in microglia following myelin phagocytosis resulting in an increase in efflux of cholesterol from these cells through upregulation of cholesterol efflux transporter ABCA1. Exposure of OPCs to conditioned media from activated microglia treated with Nrg-1 promoted maturation of OPCs into myelinating oligodendrocytes.
These findings introduce the potential of Nrg-1 in enhancing myelin repair in chronic MS lesions where microglia and macrophages are abundantly present.

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P584
Targeting GPR183/oxysterol signalling in remyelination

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Introduction: The GPR183 (aka EBI2) is one of the key regulators of the innate immune system. It is upregulated in MS plaques and in natalizumab treated MS patients. We showed before that myelination is delayed in EBI2 knock-out (KO) mice during postnatal days. Similarly, in the organotypic cerebellar slice model persistent and long-term inhibition of GPR183 with an antagonist, resulted in a less efficient spontaneous remyelination after lysophosphatidylcholine (LPC)-induced demyelination. In the cuprizone model, EBI2 KO mice remyelinated less efficiently than the wild-type mice indicating the significance of GPR183 signalling in normal myelination and during remyelination. Interestingly, persistent activation of GPR183 with oxysterol 7α,25OHC in LPC-demyelinated cerebellar slices did not enhance spontaneous remyelination beyond the levels observed in

non-treated slices. Moreover, long-term activation of GPR183 during myelin development in cerebellar slices resulted in decreased myelination. We speculated that these inhibitory effects are a consequence of receptor downregulation after continuous agonist binding and an overall decrease in GPR183 signalling. Indeed, long-term pharmacological inhibition of GPR183 signalling with an antagonist also resulted in less efficient myelination.
Objectives & Aims: To test if pharmacological inhibition of agonist-induced internalisation retains GPR183 at the cell membrane and allows for repeated agonist-induced receptor signalling. Examine whether persistent agonist-induced GPR183 signalling enhances remyelination in LPC-demyelinated organotypic cerebellar slices.
Methods: Human monocytes were treated with 7α,25OHC with or without barbadin and changes in calcium mobilisation were recorded using a confocal microscope. Organotypic cerebellar slices were demyelinated with LPC and allowed to remyelinate for 20 days with or without 7α,25OHC and barbadin.
Results: Barbadin, a selective β-arrestin/β2-adaptin interaction inhibitor, prevented agonist-induced GPR183 internalisation in U937 monocytes. Upon agonist stimulation of barbadin-treated cells, GPR183 remained functional and continued to signal intracellularly, as shown by agonist-induced calcium release in barbadin-treated cells. Finally, pharmacological inhibition of GPR183 internalisation in organotypic cerebellar slices affected remyelination.
Conclusions: Pharmacological modulation of GPR183 signalling is a druggable target for remyelination therapy.

Disclosure
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Imaging and non-imaging biomarkers - MRI & PET

P585
Characteristics of the diffusion-based brain connectivity among multiple sclerosis phenotypes

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Introduction: Diffusion-based structural connectivity is disrupted in patients with MS (pwMS) but it is unknown if different phenotypes possess specific connectivity abnormalities.
Objectives and aims: We aimed to define brain network changes across MS phenotypes.
Methods: We collected clinical and MRIs data of 823 pwMS from seven MAGNIMS centers [mean (standard deviation) age: 45.5 (11.7) years; disease duration: 12.4 (9.5) years; median (range) EDSS: 2.5 (0-8.5)] and 221 healthy controls (HC) [age: 40.5 (11.6) years]. The cohort included 74 clinically isolated syndromes (CIS), 571 relapsing-remitting (RR), 121 secondary-progressive (SP) and 57 primary-progressive (PP) pwMS. We used advanced tractography processing pipelines to reconstruct 2850 fiber pathways, and obtained age and sex corrected fractional anisotropy (FA) weighted connectivity matrices. Differences in whole brain graph theory metrics and FA connections between phenotypes were explored with analysis of variance or Kruskal–Wallis H test with Tukey HSD or Dunn's test after ComBat harmonization. Finally, we used the Receiver Operating Characteristic to assess model performance in classifying MS phenotypes.

Results: We found significant differences between pwMS and HC and among MS phenotypes in local and global efficiency (corrected $p<0.05$). Almost all connections showed significant reductions in FA in CIS and RR compared with HC, while CIS and RR pwMS did not show differences. Compared with CIS and RR combined (n=645), SP pwMS showed a reduction in 1511 (83.4%) connections involving bilateral areas of the frontal, parietal and temporal cortex. PP pwMS had reduced FA compared with CIS and RR in 140 (7.7%) connections including bilateral frontal and right parietal lobes, whilst they showed higher FA in 13 (0.7%) connections mainly within deep grey matter (dGM). Compared with PP, SP pwMS displayed decreased FA in 790 (43.6%) connections in bilateral parietal cortex and dGM. The classification performance reached a mean area under the curve of 0.75 (0.05), 0.79 (0.09), 0.80 (0.05), when comparing the FA matrices from CIS and RR to SP, CIS and RR to PP and SP to PP, respectively.

Conclusions: Brain structural connectivity is globally disrupted in pwMS. Results identify different patterns of regional connectivity impairment among MS phenotypes, being most prominent in the secondary progressive form. Such characteristics contribute to classify the course of MS.

Disclosure

The authors declare the following potential conflicts of interest: E.Martinez-Heras, F.Vivó, S.Alba-Arbalat, E.Strijbis, S.Groppa, V.Fleischer, R.Dineen, D.Pareto, S.Collorone and F.Prados have nothing to disclose; E.Solana and E.Lopez-Soley received travel reimbursement from Sanofi and ECTRIMS; A.Saiz received compensation for consulting services and speaker honoraria from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, TEVA, Novartis and Roche; Y.Blanco received speaking honoraria from Biogen, Novartis and Genzyme; S.Llufriu received compensation for consulting services and speaker honoraria from Biogen Idec, Novartis, TEVA, Genzyme, Sanofi and Merck.

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A. Rovira serves on scientific advisory boards for Novartis, Sanofi-Genzyme, Synthetic MR, TensorMedical, Roche, Biogen, and OLEA Medical, and has received speaker honoraria from Bayer, Sanofi-Genzyme, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis, Roche, Bristol-Myers and Biogen.

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The predictive value of the multilayer graph properties on clinical status in patients with multiple sclerosis

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Background: We recently demonstrated the usefulness of the multilayer network combining different network modalities to describe brain damage in patients with multiple sclerosis (pwMS). However, their predictive value in the longitudinal clinical status needs to be elucidated.
Objectives and aims: To assess the association of multilayer network graph metrics with current disability, and their predictive value on longitudinal clinical status at long-term in pwMS.
Methods: We studied 114 pwMS with available clinical assessment at follow-up [baseline age 47.7±9.8 years, disease duration 15.7±9 years, and median EDSS 2.0 (range 0-7.5)]. Patients were divided in two groups regarding disease duration, MS1 (⩽10 years, n=34, EDSS 1.5, range 0-6.0) and MS2 (>10 years, n=80, EDSS 2.0, range 1.0-7.5). Anatomical 3D-T1, 3D-FLAIR, diffusion-weighted imaging and resting-state functional MRI were acquired at baseline to compute the multilayer network properties. We calculated node strength, closeness centrality and local efficiency of the multilayer network, and these were used as features in the machine learning analysis to identify the measures best related with baseline and follow-up EDSS.
Results: At baseline, node strength (R2= 0.28 and 0.05 for MS1 and MS2, respectively) and local efficiency (R2= 0.20 and 0.17) were related to EDSS, mainly in the group with lower disease duration. After a mean follow-up of 3.9 years, the median EDSS was 2.0 (range 0-8.0) and 16% of patients showed a clinical significant decline (defined as a change of 1.0 point or more at EDSS levels <5.5, or 0.5 or more at EDSS >5.5), 1.5 (0-6.5) in MS1 and 2.0 (0-8.0) in MS2. In MS1, the predictive value for the EDSS at follow-up reached an R2= 0.27 using node strength and R2= 0.44 with local efficiency. Strength information, mainly from deep grey matter and parietal cortex and local efficiency from the frontal and temporal lobes, were the areas with the highest relevance in each model. Instead, no predictive value was found in the MS2 group. Closeness centrality was not significantly associated with EDSS in any group.
Conclusions: Multilayer graph network properties, which integrate morphological, structural and functional features of the brain connectivity, are related to ongoing and future disability, especially in the first decade of disease. The characteristics of brain connectivity may be useful for predicting clinical status in pwMS, monitor disease evolution and efficient stratification in clinical trials.

Disclosure:
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Regional altered diffusion in lesional and normal-appearing cortex is linked to cognitive impairment in multiple sclerosis

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Introduction: Multiple sclerosis (MS) commonly features cortical lesions (CL) and pathological microstructural changes to normal appearing grey matter (NAGM), both of which can impact cognitive functioning. However, it is unknown whether grey matter (GM) microstructural integrity in regions with CL relates to cognition similarly to NAGM integrity, and how do integrity changes in NAGM and CL spatially behave across functional networks.
Aims: To evaluate which regions and networks are most severely affected by integrity changes, and to assess which integrity changes in CL and NAGM most strongly relate to cognitive impairment.
Methods: 176 MS patients and 48 healthy controls (HC) underwent MRI (3D-FLAIR, 3D-T1, double inversion recovery and diffusion) and neuropsychological assessment (expanded Brief Repeatable Battery of Neuropsychological Tests). GM integrity was assessed within CL and NAGM, based on fractional anisotropy (FA) and mean diffusivity (MD). Cortical GM regions were spatially divided into seven networks of functionally related regions using the Yeo atlas. Integrity was compared between cognitive groups: cognitively preserved (CP), mildly cognitively impaired (MCI; ⩾2 domains at $Z<-1.5$ below controls), or cognitively impaired (CI; ⩾2 domains at$Z<-2$ below controls).
Results: Mean cortical MD was increased in MS versus HC ($p<0.001$), and mean FA decreased ($p=0.004$). Within-subject analyses showed higher FA in CL versus NAGM in the overall MS cohort, and specifically in CP and CI ($p<0.001$), but not in MCI. CI showed higher cortical MD compared to CP in both CL and NAGM ($p=0.003$ and$p=0.008$, respectively), whereas FA showed no significant differences and was not explored further. Within networks, an increased MD was mostly driven by NAGM changes and seen in CI compared to CP in ventral attention, visual, sensorimotor and default-mode networks (*p-range*=0.012-0.037), with largest effect sizes in sensorimotor and default-mode networks. CI-related MD changes in CL were only seen in the default-mode network.
Conclusions: Cortical diffusion changes were most pronounced in cognitively impaired MS patients. Whereas FA was able

to differentiate CL and NAGM, MD seemed more relevant for distinguishing cognitive phenotypes, especially in NAGM. GM integrity was most severely reduced in the default-mode and sensorimotor networks, which could indicate a preferential susceptibility for cortical pathology in these networks.

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Cortical lesions in functional networks are related to cortical atrophy, but only in normal-appearing grey matter

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Introduction: Multiple sclerosis (MS) frequently features cortical lesions (CL) and cortical atrophy, which both occur largely non-uniformly across the brain and affect cognitive functioning. How CL and cortical atrophy are related, however, remains unclear, as well as how this relation differs between regions.

Aim: To investigate whether the relationship between CL and cortical atrophy varies across functionally related areas, i.e. functional brain networks, and if so, how this relates to cognitive functioning.

Methods: 176 MS patients and 48 healthy controls (HC) underwent structural 3T MRI (3D-FLAIR, 3D-T1 and double inversion recovery) and neuropsychological assessment (expanded Brief Repeatable Battery of Neuropsychological Tests). We parcellated the brain in 212 regions of interest (ROI), which were then spatially divided into seven networks of functionally related regions using the Yeo atlas. Cortical volume was calculated of each ROIs, which were classified as either having CL or normal-appearing grey matter (NAGM). Individual volumes were then Z-transformed based on HC, averaged within functional networks and then compared between cognitive groups: cognitively preserved (CP), mildly cognitively impaired (MCI; $\geqslant$2 domains at $Z<$-1.5 below controls), or cognitively impaired (CI; $\geqslant$2 domains at $Z<$-2).

Results: The cortex as a whole showed significant more atrophy in MS compared to HC ($p<0.001$), which was negatively correlated with total CL volume (r=-0.222,p=0.003). CI showed more atrophy compared to CP across the brain (p=0.010), which was driven by atrophy in NAGM (p=0.018) instead of atrophy in ROI with CL (not significant) based on logistic regression analysis. Within functional networks, MS patients had significant atrophy only in the default mode network (DMN) compared to HC (p=0.033), where CL fraction of the DMN was related most strongly to NAGM volume (r=-0.304,$p<0.001$), with a lower correlation for volumes of CL ROIs (r=-0.220,p=0.026). For the DMN, CI showed more atrophy compared to CP (p=0.002). Logistic regression analysis showed this effect was driven by atrophy in NAGM ROIs (p=0.021) but not ROIs with CL.

Conclusion: This study indicates that atrophy, particularly in the DMN, is worst in CI patients, but mostly in NAGM areas and not in areas with CL. The association between CL fraction and NAGM atrophy could indicate a CL-induced disconnection between cortical areas driving neurodegeneration, which warrants further study at higher resolutions.

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Multiparametric quantitative MRI for Brain microstructural tissue characterization in multiple sclerosis

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Introduction: Quantitative magnetic resonance imaging (MRI) involves mapping microstructure in standardized units sensitive to histological tissue properties.

Objectives: Multi-parameter mapping (MPM) is a novel MRI sequence providing quantitative maps of magnetization transfer saturation (MT), proton density (PD), longitudinal relaxation rate (R1), and transverse relaxation rate (R2*) after reconstruction.

Aims: This cross-sectional study aims to investigate microstructural differences in brain tissues between multiple sclerosis (MS) patients and healthy controls (HC) using MPM.

Methods: 110 MS patients (80 females, age 20–68 years), including 79 relapsing-remitting MS (RRMS), 7 secondary progressive MS (SPMS), 24 clinically isolated syndrome (CIS) patients, and 14 HC (13 females, age 21–67 years) were scanned at 3.0T. All participants underwent MPM at 1.6mm isotropic voxel resolution, with Gibbs ringing correction and bias field correction using B1+ maps, and fluid-attenuated inversion recovery (FLAIR) MRI at 0.8mm isotropic resolution. Each mean MPM metric was extracted from normal appearing white matter (NAWM), normal appearing cortical grey matter (NACGM), and normal appearing deep grey matter (NADGM). Analysis of variance (ANOVA) and linear regression models, adjusted for age and sex, were used to evaluate i) effect sizes between the 3 disease groups and HC, as well as ii) parameter association to clinical disability measured by the expanded disability status scale (EDSS), in each tissue class.

Results: Largest effect sizes for the difference between MS and HC were observed for PD in NAWM, or PD-NAWM (eta^2 =0.4, $p<0.001$), with a decreasing trend in MS groups ($F=18.9$, $p<0.001$), followed by a decrease in R1-NACGM ($eta^2=0.12$, $p<0.001$) in MS ($F=4.2$, $p<0.01$). Both RRMS and SPMS relatively to CIS ($F=6.4$, $p<0.001$) presented a greater decrease in MT-NACGM ($eta^2=0.18$, $p<0.001$). SPMS relatively to i) HC ($F=3.2$, $p<0.01$) had lower R1-NAWM ($eta^2=0.09$, $p=0.01$) and ii) to other groups ($F=3.5$, $p=0.005$) showed reduced R1-NADGM ($eta^2=0.09$, $p=0.003$).

EDSS associated with PD-NADGM ($F=9.9$, $p=0.002$), MT-NADGM ($F=12.6$, $p<0.001$), MT-NAWM ($F=10.49$ $p=0.002$), MT-NACGM ($F=12.5$, $p<0.001$) and R1-NAWM ($F=4.37$, $p=0.04$).

Conclusions: Tissue class alterations in MPM suggest diffuse microstructural differences between MS types and compared to HC. An association with disability suggests disease-relevance and warrants further exploration of MPM for translational and clinical research in MS.

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A.U. Brandt: is cofounder and holds shares of medical technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patents and patent applications describing methods for retinal image analyses, motor function analysis, multiple sclerosis serum biomarkers and myelination therapies utilizing N-glycosylation modification. He is cofounder, member of the board and currently elected Secretary/Treasurer of IMSVISUAL.

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Using spinal cord atrophy as a progressive marker without dedicated scanning

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Introduction: Spinal cord (SC) atrophy has been established as an important marker of disability progression but is infrequently used as a quantitative measure in clinical trials of people with MS, as high-quality, high-resolution MRI of the SC is not routinely acquired. High quality T1-weighted (T1w) brain imaging, however, is a key part of standard of care imaging in MS. It has been recently proposed that T1w brain images with sufficient SC

coverage could substitute for dedicated SC imaging in analysis of SC atrophy. Use of these images would allow SC atrophy to be used as a marker in larger populations with longer follow-up than is currently feasible.

Objective/Aims: To determine if SC cross-sectional area (CSA) measurements in T1w brain images can be used as a marker for disability similarly to dedicated T2-weighted (T2w) SC images.

Methods: Sagittal 3D T1w MPRAGE or Multi-Echo MPRAGE brain images and T2w SC images were acquired on people with MS as a part of an ongoing, prospective study (progressive: n=70, relapsing: n=111) using two different 3T scanners. The Spinal Cord Toolbox was used to automatically label the vertebral regions. CSA was averaged over the C2-C3 region. To account for different scanners, ComBat was used to harmonize the data. Spearman rank correlation and corrected correlations with multivariate linear regression models were used for statistical analysis.

Results: Included participants were on average aged 55.3yr (SD: 8.7yr) and were 71% female. CSA measurements from T1w brain and T2w SC images were highly correlated (r=0.92, $p<0.0001$). CSA from both image types showed a significant difference between relapsing and progressive subjects after adjusting for age and sex (T1w: $p<0.0001$, T2w: $p<0.0001$). CSA from T2w SC images was significantly correlated with EDSS (r=-0.28, p=0.0002), timed 25ft walk (T25W) (r=-0.29, p=0.0005), and 9-hole peg test (9HPT) (r=-0.38, $p<0.0001$). CSA from T1w brain images was similarly correlated (EDSS: r=-0.34, $p<0.0001$, T25W: r=-0.38, $p<0.0001$, 9HPT: r=-0.44, $p<0.0001$). After correction for age and sex, however, CSA from either image type was no longer significantly correlated with T25W.

Conclusions: SC CSA measurements from T1w brain and T2w SC images show strong correlation to each other as well as to mobility-related disability scores. Results suggest routinely acquired T1w brain images may enrich clinical trial datasets targeting progression, which may or may not include dedicated SC imaging.

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Microglial activation in multiple sclerosis patients treated with current high-efficacy disease modifying treatments: Individualized [F-18]PBR06-PET analysis

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Introduction: Cortical grey (CoGM) and white matter (WM) microglial activation (MA) is involved in the pathogenesis of multiple sclerosis (MS). [F-18]PBR06 positron emission tomography (PET) targeting 18kilodalton-translocator protein (TSPO) can detect abnormal MA in MS.

Aims and Objectives: The goal of this study is to determine the effect of DMT efficacy on modulating the extent and clinical and radiological correlates of MA in MS patients.

Methods: Thirty [F-18]PBR06 PET scans were performed in 22 MS patients (13 RR, 9 SP, mean age 46±14 years, 15 females, median EDSS 3.5, mean T25FW 7.2±4.6s) and 8 healthy controls (HC). Individualized z-score maps of brain parenchymal MA were generated by voxel-by-voxel comparison between each subject's PET SUVR images and a HC dataset. Logarithmically transformed 'Glial activity load on PET' scores (calculated as the sum of voxel-by-voxel z-scores ⩾4 in CoGM and WM regions), 'lnGALP', were compared between MS subjects on disease modifying treatment (DMT) with high efficacy (HT; including rituximab, ocrelizumab, natalizumab and fingolimod, n=13) versus those on no or lower efficacy treatment (LT; including glatiramer acetate and interferons), and correlated with clinical measures and cortical thickness (measured using FreeSurfer). $p<0.05$ was considered statistically significant.

Results: CoGM and WM lnGALP scores were higher in MS vs. HCs (10.0±1.5 vs. 7.5±1.5 and 9.8±1.5 vs. 6.6±2.4, both $p<0.01$) and were inversely correlated with global cortical thickness across groups (r=-0.44 and -0.48, both $p<0.05$, n=30). In HT-MS group, CoGM and WM lnGALP was significantly lower as compared to LT-MS group (9.1±1.0 vs. 11.3±1.1 and 9.1±1.3 vs. 10.8±1.4, p=0.000075 and 0.006) but remained abnormally higher than in HC group (p=0.006 and 0.02, respectively). Within HT-MS patients, CoGM lnGALP scores were higher in SP vs. RR subgroups (p=0.008), correlated positively with EDSS, T25FW and fatigue scores (r=0.65,0.79 and 0.75, all $p<0.05$), and inversely with cortical thickness (r=-0.66,p=0.01).

Conclusions: Current high-efficacy DMTs decrease, but do not normalize, CoGM and WM MA in MS patients. Such "residual" MA in CoGM is associated with clinical disability, symptom severity and cortical degeneration. Individualized mapping of TSPO-PET using [F-18]PBR06 can potentially serve as an imaging biomarker for evaluating emerging therapies targeting MA in MS patients who are worsening despite currently available high-efficacy DMTs.

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Subpial lesions with juxta-cortical rims of increased susceptibility in multiple sclerosis: characteristics and clinical relevance

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Background: Cortical lesions (CL) in multiple sclerosis (MS) are associated with increased physical and cognitive disability. Subpial CL are the most prevalent type of focal cortical damage in MS and specific to this disease; some of them present a juxta-cortical hyperintense rim (jxc-rims) on quantitative susceptibility mapping (QSM).
Objectives: (i) To characterize subpial lesions with jxc-rims histologically; and (ii) to assess their frequency and clinical relevance in in-vivo MS patients.
Methods: Five brains of deceased MS patients were imaged on a 3T MR-scanner using 3D EPI for QSM reconstruction and CL detection. Jxc-rims were then analyzed histologically.
We also screened QSM maps and MP2RAGE from 166 MS in-vivo patients (102 relapsing-remitting -RRMS- and 64 progressive -PMS-; mean age: 46y; males = 65; median Expanded Disability Status Scale (EDSS) = 3) to assess the presence of jxc-rims and CL. We compared demographics, disease duration, clinical phenotype and EDSS, as well as the presence of focal cortical pathology between MS patients with and without jxc-rim by means of Mann-Whitney or chi-square tests.
Results: We observed 20 jxc-rims in one postmortem brain and obtained the histology of 6 of them, which corresponded to iron-laden microglia and macrophages. Those rims were underlying areas of subpial cortical demyelination in all cases.
16/166 (10%) MS patients presented ⩾1 jxc-rims; we identified a total of 26 jxc-rims and 15/26 (58%) were associated with a detectable CL on MP2RAGE. The group of patients with jxc-rims did not show any significant differences in demographics, disease duration and EDSS compared to those without jxc-rims. Patients with jxc-rims were tendentially more often RRMS than PMS (80% vs. 60%) and showed tendentially more CL evident on MP2RAGE (87% vs. 70%).
Conclusions: Some subpial lesions exhibit a juxta-cortical rim of increased susceptibility, representing activated phagocytes. This feature was detectable in 10% of patients in vivo and more frequently in RRMS patients. Juxta-cortical rims may represent an initial stage of subpial demyelination and help in MS differential diagnosis, as they underlie subpial CL.

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Impact of natalizumab on chronic active lesions

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Introduction: Increased innate immune cell activation in the normal appearing white matter has been associated with multiple sclerosis (MS) progression and development of neurodegeneration. We have demonstrated a reduction in innate immune cell activation in this region after natalizumab treatment. Later, an automated method for phenotyping of chronic T1 lesions into chronic active, overall-active and inactive lesion based on TSPO-PET-measurable microglial activation in lesion core and rim was developed. The impact of high-efficacy MS-treatments on microglial activation at the edge of chronic active lesions is not yet known.
Objectives: To evaluate how one-year treatment of natalizumab impacts chronic lesion subtype distribution.
Methods: In this study, 10 MS patients [age 49.15 (± 9.33) years] underwent PET imaging using ^{11}C-PK11195 radioligand and conventional MR imaging before and after 1-year treatment with natalizumab. For comparison, 11 MS patients [age 47.88 (± 10.23) years] with no disease modifying therapy were scanned similarly with a one-year-interval. T1-hypointense lesions were identified from the MR images at both time points and lesions were phenotyped based on the proportion of highly active PET-voxels at the lesion rim and in the lesion core. Disability assessment using Expanded Disability Status Scale was performed at the time of PET imaging.
Results: Patients treated with natalizumab had a total of 175 chronic T1-lesions at baseline [rim-active 29, (17 %), overall-active 80 (46 %), inactive 66 (38 %)]. In the untreated cohort, the total number of lesions was 245 [rim-active 36, (15 %), overall-active 142 (58 %) and inactive 67 (27 %)]. The proportions of lesion types was unaltered in both groups during one-year follow-up. However, in rim-active lesions, the proportion of active voxels at the rim reduced significantly in natalizumab-treated patients but not in untreated patients [median change -7.7 % (IQR -11.2– -4.5) vs. +0.2 % (-2.1– 1.4), p = 0.008, Wilcoxon]. Similar change was observed in overall-active lesions [-3.8 % (-5.9– -1.6) vs. +0.8 % (-1.3– 2.6), p = 0.004].
Conclusions: TSPO-PET-imaging enables longitudinal evaluation of smoldering inflammation associated with chronic MS lesions. One-year treatment with natalizumab reduced the inflammatory burden at the active rim of chronic MS lesions but did not impact the proportions of the chronic lesion subtypes.

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A comparison in performance of an automated Central Vein Sign (CVS) Detection method, select-6* counts, and CVS+ proportions for the diagnosis of multiple sclerosis – a multicenter study

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Background: The central vein sign (CVS) is a potential imaging biomarker for multiple sclerosis (MS). The proportion of white matter lesions exhibiting the CVS is higher in MS compared to radiological mimics. Several simplified measures have been proposed to facilitate CVS adjudication in practice. These measures include manual identification of CVS+ lesions or a subset thereof, an approach that is time-consuming and has variable inter-rater reliability.

Objective: To compare the performance of a previously published automated CVS detection method with visually assessed select-6* lesion counts and manual subject-level CVS+ proportion as approaches for MS diagnosis.

Methods: 3T MRI, including 3D T_1-weighted MPRAGE (T1 MPRAGE), T_2-weighted fluid attenuated inversion recovery (FLAIR), and high-isotropic-resolution T2*-weighted segmented echo-planar imaging post gadolinium injection (T2*-EPI GAD) sequences were acquired from 97 participants in a 10-site multicenter study using two MRI vendors. Data from 9 sites were included, with exclusion of one site due to differences in imaging protocols and 8 subjects due to image processing failures. Of the 79 participants included in the initial analysis, MS diagnosis was ascertained in 41 based on 2017 McDonald Criteria. An automated CVS detection method was employed using T1 MPRAGE, FLAIR, and T2*-EPI GAD images, and resulting measurements were analyzed in comparison to CVS+ proportions and select-6* counts, in which local raters identified up to 6 CVS+ lesions on FLAIR* (voxels-wise product of FLAIR and T2*-EPI GAD).

Results: The automated CVS approach discriminated between participants with and without MS, with area under the receiver-operator characteristic curve (AUC) of 0.79 (95% confidence interval: [0.68,0.89]). There was no apparent difference in AUC compared to select-6*(0.80 [0.70,0.90]) or CVS+ proportion (0.86 [0.77,0.95]). In a sensitivity analysis, after exclusion of 11 participants due to motion, the AUC for the automated method was 0.81 [0.71,0.92], comparable to that for select-6* (0.79 [0.68,0.90]) and proportion CVS+ (0.88 [0.80,0.97]).

Conclusion: These results demonstrate the promise of CVS approaches that avoid complete manual lesion assessment. Large prospective multicenter studies that include the breadth of disorders referred for suspect MS are needed to determine optimal approaches utilizing CVS as a diagnostic biomarker for MS.

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An in vivo study of microglial activation and astrocyte reactivity in MS brain by PET-imaging and concurrent use of two radioligands

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Introduction: Adenosine 2a receptors (A2AR) are G-protein coupled transmembrane receptors. A2AR expression has been described on astrocytes and is upregulated upon CNS injury. We have previously demonstrated upregulation of A2AR in secondary progressive MS brain using positron emission tomography (PET)-imaging and the radioligand^{11}C-TMSX.
Objectives: To explore the association of astrocytic A2AR expression (^{11}C-TMSX binding) with microglial activation, measured with translocator protein (TSPO)-binding radioligand^{11}C-PK11195.
Methods: 41 MS patients (age 44.7, SD 10.1) underwent brain PET/MRI-imaging with radioligands^{11}C-TMSX and^{11}C-PK11195. MS lesions were defined automatically followed by manual slice by slice correction. Chronic lesions were segmented based on their^{11}C-PK11195 binding to inactive, overall-active, and rim-active lesions.^{11}C-TMSX and^{11}C-PK11195 specific binding (distribution volume ratio, DVR) was calculated in the deep normal-appearing white matter (deepNAWM). Associations between^{11}C-TMSX and^{11}C-PK11195 DVRs were explored in these regions of interests.
Results: Higher^{11}C-TMSX binding in the deepNAWM correlated significantly with increased expanded disability status scale score (R= 0.46,p=0.0026) and with increased T2 lesion load (R=0.44,p=0.0047). The number of large lesions (lesion size above the 80th percentile in the studied population, >242 voxels) correlated significantly with deepNAWM^{11}C-TMSX binding (R=0.46,p=0.0027). Interestingly, a strong correlation was found between deepNAWM^{11}C-TMSX and^{11}C-PK11195 binding (R=0.67,$p<0.0001$). Moreover, the number of the TSPO-segmented rim- and overall active lesions correlated significantly with deepNAWM^{11}C-TMSX binding (R=0.59,$p<0.0001$ and R=0.36,p=0.02, respectively). In the 3-6mm perilesional area,^{11}C-TMSX binding (median[IQR]) was significantly higher in rim-active (0.84[0.79-0.89]) and overall-active (0.83[0.78-0.88]) lesions compared to inactive lesions (0.75[0.70-0.82]) ($p<0.0001$).
Conclusions: A2AR expression is increased in the deepNAWM of MS patients with high clinical and MRI-measurable disease burden. PET-imaging-detectable A2AR colocalization with TSPO implies a detrimental interaction between astrocyte reactivity and microglial activation in MS. PET-imaging enables quantification of MS progression-related compartmentalized inflammation *in vivo*.

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SyMRI quantification of gray and white matter alterations in patients with MOG antibody-associated disease: associations with disability measures

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Introduction: Myelin Oligodendrocyte Glycoprotein antibody-associated disease(MOGAD) is an immune-mediated demyelinating disease of the central nervous system. Besides white matter demyelination, recent studies indicate gray matter(GM) involvement in MOGAD. Synthetic MRI(SyMRI) is suited for fast and robust brain volumetry and myelin quantification based on relaxometry parameters.

Objectives and Aims: To investigate patterns of brain tissue alterations in MOGAD and relapsing remitting multiple sclerosis(RRMS) patients compared to controls, and to study their associations with clinical disability(EDSS).

Methods: SyMRI using a multiecho, saturation recovery pulse sequence(QRAPMASTER), provides automatic brain tissue and myelin volumetry based on R1 and R2 relaxation rates and proton density quantification. 17 MOGAD patients and age and sex matched RRMS(N=69) and healthy controls(HC, N=56) received QRAPMASTER at 1.5Tesla.

SyMRI quantified intracranial(ICV), brain parenchymal (BPV), myelin(MY), gray and white matter(GM, WM) volumes, longitudinal(R1), and transverse(R2) relaxation rates. All brain volumes were standardized as fractions of ICV. We assessed group differences using a general linear model(multivariate ANOVA). Partial correlations were performed between SyMRI-derived values and EDSS(disease duration or age as covariates).

Results: Median and interquartile range values of clinical parameters in MOGAD/RRMS were: EDSS 2.5[2.5]/2.0[2.0], disease duration(years) 4.0[12.0]/3.0[4.0].ICV fractions of WM, GM, MY and BPF, mean relaxation rates(R1, R2) of the WM and mean R2 of the GM were significantly lower in MOGAD and in RRMS compared with HC, but MOGAD patients exhibited no significant differences compared to the RRMS group (means of HC/MOGAD/RRMS: WM 34.2/32,7/32.8%; GM 51.5/49.3/50%, MY 10.3/9.7/9.8%; BPF 86.8/83.2/84.1%; WM_R1 1.44/1.40/1.41s^{-1}; WM_R2 13.3/13.0/13.1s^{-1}; GM_R1 0.80/0.79/0.79s^{-1}; GM_R2 10.7/10.5/10.5s^{-1}). EDSS was inverse correlated with MY intracranial fraction in the RRMS group, while in the MOGAD group GM intracranial fraction exhibited a significant negative association with EDSS (Pearson's correlation coefficient(r): -0.512, p=0.043).

Conclusion: SyMRI showed GM and WM atrophy, myelin reduction and significant alterations of R1 and R2 in MOGAD, similar to RRMS. The EDSS was associated with GM loss in the MOGAD group and with myelin metrics in RRMS. Our study provides new MRI evidence of GM involvement in the pathophysiology of MOGAD.

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Soma and neurite density imaging (SANDI) as a novel diffusion model to better characterize multiple sclerosis brain neuroaxonal damage in vivo

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Introduction: Soma and neurite density imaging (SANDI) is a new biophysical model that incorporates soma in addition to neurite density, thus possibly providing more specific information about the complex pathological processes of multiple sclerosis (MS).

Objectives: To investigate SANDI feasibility on a clinical 3T scanner; to assess its ability to detect white matter (WM) and gray matter (GM) microstructural pathology in MS patients and to evaluate the associations between SANDI-derived measures and clinical disability as well as conventional MRI variables.

Methods: We applied SANDI to 3T brain MRI diffusion data to evaluate the fractions of neurite ($f_{neurite}$) and soma (f_{soma}) in 23 MS patients (11 relapsing-remitting [RR], 12 progressive [P]) vs 20 healthy controls (HC).

Results: $F_{neurite}$ was lower in MS normal-appearing (NA) white matter (WM) vs HCs' WM (p=0.009), whereas MS WM lesions showed lower $f_{neurite}$and f_{soma} compared to both MS NAWM and HCs' WM ($p<0.001$). Cortical $f_{neurite}$ and f_{soma} were lower in MS vs HC ($p\leqslant0.007$). Compared to PMS, RRMS patients had lower $f_{neurite}$ in NAWM and cortex ($p\leqslant0.031$) and lower cortical f_{soma} (p=0.004). $F_{neurite}$and f_{soma} in the different brain compartments were correlated with disease duration, disability, brain T2-hyperintense WM lesion volumes, normalized brain, cortical and WM volumes (r from -0.761 to 0.821, $p\leqslant0.033$).
Conclusions: SANDI may be a clinically feasible and relevant model to better characterize the complex pathological substrates of MS, including neuro-axonal loss and astrogliosis.

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MAGNON – implementation and contribution of lublin criteria and quantitative mri-analysis for daily clinical routine of MS patients

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Introduction: Revised Lublin criteria, which provide a definition of remitting and progressing Multiple Sclerosis to classify disease activity of patients with Secondary Progressive Multiple Sclerosis (SPMS) as well as quantitative and standardized MRI analyses are only rarely used in clinical practice.
Aims: MAGNON aims to evaluate if standardized quantification of MRI data and assessment of MS patients based on the Lublin criteria provide benefits for neurologists working in day-to-day MS patient management.
Methods: Approximately 680 MRI scans of patients with SPMS or suspected SPMS have been provided by 50 centers in Germany. The analysis of standardized MRI data comprises a volumetric quantification of brain and thalamic volumes as well as T2-lesion-volume and number using a centralised automatic processing pipeline (Biometrica MS®, jung diagnostics GmbH). Percentage brain volume change is computed when follow-up scans are available. The value of standardized MRI analysis and the impact on patient assessment, including potential changes in Lublin classification, is evaluated.
Results: Interim analysis data show that for more than 45% of patients with suspected SPMS, already a single standardized MRI scan provided additional information that patients are transitioning to SPMS. According to the treating physicians, for about 30% of patients with suspected SPMS, the quantitative MRI further suggested a change in MS treatment. Within the following year, 18% of patients with suggested treatment change actually switched their therapies. Further findings with regards to the correlation of quantitative MRI parameters and clinical observations will be presented.
Conclusion: MAGNON interim results indicate that individual assessment of disease activity and progression of MS patients according to the Lublin criteria can be facilitated by routinely performed quantitative standardized MRI analyses, which can thus enhance individualized patient care.

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Hippocampal atrophy in patients with early multiple sclerosis and its correlation to memory impairment

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Introduction: Hippocampal atrophy represents a relevant measure in multiple sclerosis (MS), particularly in association with memory impairment. Studies on the structural and functional correlates of hippocampal damage and its subfields in the early disease course are lacking.
Aims: To assess regional hippocampal atrophy in a large multicenter dataset of early MS and to investigate the association of hippocampal abnormalities with memory impairment using a voxel-based approach.
Methods: From the Italian Neuroimaging Network Initiative (INNI) dataset, we selected volumetric 3D-T1W brain images acquired at 3T on i) 219 early (disease duration <5y) Relapsing-Remitting (RR) MS patients (150F, 34y+10, EDSS: 1.5 [1-2]) who underwent Selective Reminding Test (SRT) and Spatial Recall Test (SPART) and ii) 246 age and sex-matched healthy controls (HC) (133F, 34y+9). Left and right hippocampal binarized masks were obtained following the EADC-ADNI protocol. Voxel-based analysis (VBM) was performed to select regionally atrophied hippocampal areas in RRMS and to select, within the regional areas significantly atrophied in RRMS, the voxels correlating with clinical scores. Finally in a post-hoc analysis projecting back hippocampal clinically significant regions in the native space, the correlations between volumes stratified for subfields (as obtained by using FreeSurfer) and clinical scores was further evaluated. Significant results ($p<0.05$, in VBM corrected for multiple comparisons) are reported.
Results: Early RRMS showed lower volumes in the whole, right and left ($p<0.001$ for all) hippocampi compared to HC. In RRMS, lower volume of the right hippocampus correlated with SRT and SPART performance ($p<0,01$, corrected). Spearman analysis demonstrated a selective involvement of right hippocampal subfields. Specifically, atrophy of rightcornus ammonis (CA1) and tailcorrelated with SRT impairment (r= 0.28 for both). CA1 atrophy also correlated with SPART (r=0.27) (p=0.01l). No correlation was found between memory impairment with other subfields of right hyppocampus and with left hippocampal subfields.
Conclusions: Hippocampal atrophy represents an early event in RRMS.The relationship betweenatrophy of the right hippocampal subfields (mostly CA1) and impairment of verbal and spatial processing tests suggests that deficits in the memory processes are relevant since the early phase of the MS.

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P600
Accounting for label uncertainty in training a machine learning model to predict new disease activity using MRI after a first clinical demyelinating event

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Introduction: Machine learning (ML) is a computational approach that can identify patterns in health data to predict disease outcomes. Missing data due to subject withdrawal or loss to follow-up is a common challenge in training ML algorithms with clinical trial data. Prior evidence suggests that samples with unknown outcomes can still be useful for training ML models, especially in smaller datasets. We hypothesized that MRIs with uncertain labels can help an ML model predict new disease activity within 2 years of a first clinical demyelinating event in multiple sclerosis (MS).
Objective: Compare two closely related ML models, one trained using data with only confirmed outcomes (labels), the other using 30% additional data with unknown labels, to determine whether unknown labels can improve predictions.
Methods: Baseline 3D T1-weighted MRIs of 140 subjects from a completed placebo-controlled trial of minocycline were used as training data, with the trial outcome (2005 McDonald criteria for MS based on clinical relapses and/or new MRI lesion activity) used to assign labels. Within 2 years, 80 subjects had new disease activity, 28 were stable, and 32 withdrew early while stable (unknown outcome). Advanced Normalization Tools were used to segment the thalami, putamina, globi pallidi, and caudate nuclei.

A semi-automated algorithm was used to create white matter lesion masks [1]. The ML models were trained using deep grey matter volume, lesion volume, and treatment group as input variables, and new disease activity or not as binary outcome labels.
A random forest (RF) and a probabilistic RF (PRF, a variation of RF that can incorporate probabilistic values to model uncertainty in labels) were trained and evaluated using nested and stratified 7-fold cross-validation. RF was trained using subjects with known labels only (n=108). For training PRF, the entire dataset was used (n=140). Subjects with unknown labels (n=32) were given a stable class label, but with only 50% probability, while all confirmed labels were assigned 100% probability. The test set in each fold included only subjects with known labels.
Results: PRF outperformed RF with higher F1-score (89.6%, SD=4.9 vs. 83.8%, SD=2.8), AUC (78.0%, SD=1.4 vs. 73.0%, SD=1.7), recall (94.8%, SD=6.6% vs. 89.9%, SD=3.3) and precision (85.7%, SD=8.6 vs. 79.0%, SD=6.5).
Conclusion: Including training data with unknown outcomes in ML algorithms capable of modelling label uncertainty can improve predictive performance.

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The association between age and inflammatory disease activity on MRI in relapse onset multiple sclerosis

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Introduction: There is some evidence for a decrease in inflammatory disease activity with higher age in multiple sclerosis. Previous work has shown lower prevalence of contrast-enhancing lesions (CELs) with higher age. Those studies have mainly focused on cross-sectional data, and less is known about the relation between age and the long-term development of new T2-lesions in MS patients.
Aim: To investigate if age is associated with the presence of inflammatory disease activity on baseline MRI, and with the development of new inflammatory MRI activity during long-term follow-up, in a large real-world cohort of MS patients.
Methods: Data of relapse onset MS patients were collected from the ongoing observational Amsterdam MS cohort study of patients that visited the MS Center Amsterdam. Collected data were standard clinical and MRI parameters at baseline and during regular clinical follow-up. MRI parameters were collected from clinical MRI reports, and included presence of CELs and development of new T2-lesions during follow-up. Longitudinal analyses were performed with logistic and negative binomial generalized estimating equations (GEE) models. Analyses were corrected for sex and use of disease-modifying therapy (DMT).
Results: 1,089 patients were included in the analyses, for whom a total of 10,729 MRI-scans were available. Median follow-up duration from baseline until last MRI-scan was 119 months (IQR 59-166). Mean age at baseline was 34.9 years (SD 10.2). Higher age of the patient was significantly associated with a lower risk of CELs on baseline MRI (45-55 years vs. $<$45 years: OR=0.620, p=0.027, $>$55 years vs. $<$45 years: OR=0.488, p=0.127). In addition, higher age was associated with a lower occurrence of MRI activity, i.e. either new T2-lesions or CELs, during follow-up (45-55 years vs. $<$45 years: OR=0.486, p$<$0.0001, $>$55 years vs. $<$45 years: OR=0.301, p$<$0.0001), and with the development of a lower number of new T2-lesions during follow-up (45-55 years vs. $<$45 years: rate ratio (RR)=0.583, p$<$0.0001, $>$55 years vs. $<$45 years: RR=0.427, p$<$0.0001).
Conclusion: Our results indicate that higher age is associated with a lower risk of inflammatory MRI activity at baseline, a lower risk of development of new inflammatory MRI activity during follow-up, and a lower level of new inflammatory MRI activity during follow-up.

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Assessment of brain volume loss by age in ponesimod relative to teriflunomide treated patients in the optimum phase 3 study

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Introduction: Multiple Sclerosis (MS) is an inflammatory and neurodegenerative disease with changes in brain volume often occurring early in the disease process. The phase 3 OPTIMUM study in relapsing multiple sclerosis (RMS) evaluated brain volume loss (BVL) as an exploratory endpoint. As brain volume loss occurs early in the disease and is a leading indicator of future disability, it is important to understand brain volume changes among patients in different age groups.
Objectives: To evaluate brain volume loss by age for ponesimod relative to teriflunomide from the Phase 3 OPTIMUM study
Methods: Brain volume was analyzed between baseline and week 60, and week 108, using the Structural Image Evaluation, using Normalization, of Atrophy (SIENA) methodology in the OPTIMUM study. In the full analysis, ponesimod demonstrated a significant reduction of brain volume loss relative to teriflunomide −0.91% vs −1.25% (mean difference, 0.34 [95% CL, 0.17-0.50] percentage points; $P < .001$).In this post-hoc analysis, we evaluate BVL by age subgroups: 18-30 years old (n=119, ponesimod; n=116 teriflunomide), 31-40 (n=169, ponesimod; n=167 teriflunomide), 41-55 (n=148, ponesimod; n=151 teriflunomide). A mixed effects repeated measures model with factors: baseline EDSS, prior DMT use, Gd+ T1 lesions, baseline brain volume (covariate), and visit along with random subject intercept was used to evaluate BVL for ponesimod patients versus teriflunomide at week 108.
Results: For the 18-30 and 31-40 age groups ponesimod demonstrated a significantreduction inBVL at week 108: −1.18% vs −1.57% (mean difference, 0.39 [95% CL, 0.1-0.77] percentage points; $P = .04$), and −0.85% vs −1.28% (mean difference, 0.43 [95% CL, 0.17-0.69] percentage points; $P = .001$), respectively. However, for the 41-55 age group, while lower BVL was observed with ponesimod than teriflunomide, the findings were not statistically significant:-0.78% vs −0.93% (mean difference, 0.16 [95% CL, -0.08-0.40] percentage points; P=NS).
Conclusion: Ponesimod demonstrates a numerical benefit in brain volume preservation relative to teriflunomide for all age groups and is significantly superior in age 18-40. In this study, BVL was more pronounced in younger patients. Given BVL can occur early in the disease process and strongly correlates with physical and cognitive disability, preservation of BVL should be an important consideration in selecting an appropriate disease modifying treatment for MS patients.

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Choroid plexus volume is enlarged in clinically isolated syndrome patients with optic neuritis

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Introduction: Recent reports demonstrated that people with Multiple Sclerosis (MS) have larger choroid plexus (CP) volume than normal controls. However, it is not evident how early in the course of the disease the CP volume increases.
Objective: To evaluate the CP volume in early MS we quantitatively assessed brain MRI scans in patients presenting with optic neuritis as a clinically isolated syndrome (CIS); a cohort with established Relapsing Remitting Multiple Sclerosis (RRMS); and normal controls.
Methods: The CP volume was annotated on 3D-T1 images using Jim v9 by a skilled operator. SienaX scaling was used to correct for inter-subject variability of head size.
Results: We included 41 ON CIS subjects, 40 healthy controls and 40 RRMS patients. All groups had similar age and sex composition. There was a significant difference in scaled CP volume between groups ($p<0.001$, one-way ANOVA). Post-hoc analysis revealed significantly larger scaled CP volume in both RRMS

(2227+/-683mm^3) and CIS (2260+/-534 mm^3) groups compared to normal controls (1761+/-343mm^3, p<0.001 for both). There was, however, no difference in CP volume between CIS and RRMS patients (p=0.9).
Of the twenty-one CIS patients who did not have brain MS lesions on the baseline scan, 16 were clinically followed for 10 years. Eight patients who converted to CDMS during follow-up period and had an increased baseline CP volume compared to normal controls (2191+/- 300mm^3, p=0.002). The CP volume of the 8 patients who did not convert to CDMS remained similar to the control group (1976+/-255mm^3, p=0.1).
Conclusion: This study demonstrated a significantly enlarged CP volume in CIS and RRMS patients compared to controls. CP volume is increased at the time of the first clinical attack (ON) suggesting its early involvement in MS. Furthermore, increased CP volume in CIS patients without baseline MRI T2 lesions is associated with an increased risk of conversion to CDMS.

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Pattern of thalamic nuclei atrophy in early relapse-onset multiple sclerosis

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Introduction: Thalamic atrophy is prominent in MS; however, the thalamus is not a unitary structure; it consists of discrete nuclei with diverse neural connections and functions. Little is known about differential vulnerability to MS-related change across thalamic nuclei, especially very early in disease. Characterization of thalamic subfield volumes may inform hypotheses about early MS-related pathological processes.
Aims: To determine which thalamic nuclei (a) differ between patients with early MS versus healthy controls, (b) are most related to T2 lesion volume as a quantitative radiologic measure of MS neuropathology, and (c) are linked to future disability progression.
Methods: Persons with early MS (n=182; diagnosed ⩽5.0 years) and healthy controls (n=35) received high-resolution 3.0T MPRAGE scans analyzed with FreeSurfer 6.0 to derive 25 thalamic subfield volumes. These were parcellated into six superordinate subfields (anteroventral, lateral posterior, ventral, intralaminar, medial, posterior) and 15 subordinate nuclei based on established anatomical maps. Independent t-tests assessed differences between patients and controls across thalamic subfield volumes, with adjustment for multiple comparisons ($p<0.0026$). Pearson correlations assessed links between thalamic subfield volumes and (a) T2 lesion volumes and (b) clinically-meaningful change in EDSS over three years.
Results: Individuals with MS had lower volumes of anteroventral, lateral posterior, and posterior subfields versus controls ($d$range 0.59 to 0.73); there were no differences in ventral or medial subfields (d range 0.03 to 0.08). Higher T2 lesion volume was more related to lower volume of the posterior subfield (R^2=0.42) than to all other subfields (R^2 range 0.14 to 0.24). Of subfields, lower posterior volume was the best predictor of EDSS change over three years (d=0.69).
Conclusions: We found a pattern of lower anterior, posterior, and lateral posterior thalamic nuclei volumes and preservation of medial and ventral nuclei. Findings were strongest for posterior nuclei (i.e., pulvinar). In addition to research on neuroimaging and functional outcomes, results may inform hypotheses about neuropathology in early MS. For instance, toxic CSF-mediated processes may help explain findings, as the pattern of volume loss corresponds to thalamic regions that are adjacent to the ventricle, whereas relatively spared regions (e.g., medial and ventral nuclei) have little exposure to the ventricle.

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P605
Differentiating MS lesions with or without paramagnetic rim with advanced MRI

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Introduction: In MS, paramagnetic rim lesions (PRLs) are thought to reflect chronic active inflammation mediated by microglia which may lead to a progressive neuronal damage and peripheral iron accumulation. PRLs microstructural characterization by advanced MRI techniques may help to clarify their role in MS pathophysiology.
Objectives: To investigate if there are differences in microstructure between PRLs and no-PRL MS lesions detectable via diffusion MRI and/or quantitative susceptibility mapping (QSM).
Methods: 78 RRMS patients were prospectively enrolled. WM lesions were stratified as PRLs and no-PRLs by visual inspection on GRE-phase images and QSM maps. Both PRLs and no-PRLs were further subdivided in two groups: FLAIR hyperintense/T1 isointense (isoT1) and FLAIR hyperintense / T1 hypointense (hypoT1) lesions. Within the lesions groups, differences in microstructure were studied with diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) while intensity of paramagnetic signal was extrapolated from QSM. All measures were compared with Kruskal-Wallis and then Mann-Whitney Test accounting for age, sex, and lesion volume.
Results: out of 2819 lesions identified, 125 (4.4%) were PRLs. While all PRLs resulted hypoT1, 432 (15.3%) no-PRLs were isoT1 and 2262 (80.2%) were hypoT1. All DTI and NODDI parameters except for NODDI-isotropic volume fraction were significantly different between PRLs and isoT1 no-PRLs, and between no-PRLs hypoT1 and isoT1 ($p<0.001$ for all parameters). Statistically significant lower FA (p:0.005) and higher MD (p:0.034) and RD (p:0.005) together with higher ICVF (p:0.013) were found in PRLs compared to hypoT1 no-PRLs. Paramagnetic signal was significantly higher in PRLs than in both hypoT1 and isoT1 no-PRLs ($p: <0.001$ for both groups).
Conclusions: Microstructural analysis with DTI and NODDI and paramagnetic signal quantification with QSM were able to distinguish PRLs from no-PRLs. Particularly, PRLs showed higher degree of axonal damage and increased paramagnetic signal in comparison not only with isoT1 but also with hypoT1-noPRL. Therefore, PRLs seemed to show a more destructive behaviour which may contribute to explain their association with disability accrual in MS.

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P606
Application of generalised boundary shift integral to measure longitudinal atrophy in brain structures

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Background: Change in brain volume as a result of progression of neurodegenerative disease is an important biomarker for measuring therapeutic response. Considering this, accuracy in measuring brain volume changes is clinically important. Generalised Boundary Shift Integral (gBSI), a probabilistic registration-based method for accurate estimation of longitudinal volume changes, has been successfully applied in the past on the spinal cord and the whole brain for multiple sclerosis (MS). Methods for accurately determining change in deep grey matter (DGM) structures are scarce.
Aims and Objectives: To assess the feasibility of using registration-based techniques to accurately capture longitudinal tissue changes within DGM structures.
Methods: 20 randomly selected subjects from the MSSTAT2 study with secondary progressive MS were subjected to the gBSI processing pipeline, using 3T MRI scans at timepoints month 0 and month 12. The 3DT1 images were subjected to bias field correction. Subsequent tissue parcellation involved lesion filling and using Geodesic Information Flows (GIF). This was followed by registration to half-way space to reduce asymmetric bias using an affine registration. Lastly, differential bias correction was performed for intensity harmonisation between time points.
Two BSI implementations were used depending on the brain structure: (ii) single window BSI for structures surrounded by only one tissue type, such as the whole brain encompassed by the CSF only, or the pallidum only by WM; (ii) double-intensity window BSI to accommodate boundaries between GM-CSF and GM-WM.
Results: The percentage change in volume (PCV) for each of the brain regions under study, except for the pons, was calculated by hemisphere. The mean PCV (PCV%) was -0.39% for the whole brain, with a standard deviation (SD) of 0.77. For the left and right thalamus, the mean PCV was -0.63% and -0.79%, with a SD of 2.56 and 2.11 respectively. The left and right hippocampus had a mean PCV of 0.39% and -1.1%, with a SD of 3.89 and 3.67 respectively.

Conclusions: We have shown that gBSI can be used to study the longitudinal tissue volume changes in other relevant brain structures. Future work will analyse the sensitivity and specificity of GBSI against other well established techniques for specific brain areas like deep grey matter.

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The predictive value of diffusion tensor imaging on clinical, physical and cognitive disability in multiple sclerosis

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Background: Diffuse damage is present in both white (WM) and grey matter (GM), however the contribution of microstructural abnormalities on physical and cognitive disability in patients with multiple sclerosis (MS) is poorly understood.
Objectives and aims: To explore the associative value that exists between the microstructural properties of WM and GM at baseline and the physical and cognitive disability in patients with MS.
Methods: Longitudinal study with 185 patients [age: 43±9.7 years and disease duration: 10.6 (range: 0.1-41.7) years] who underwent Expanded Disability Status Scale (EDSS) rating, timed 25-foot walk (T25FW), 9-hole peg test (9HPT), and the Symbol Digit Modalities Test (SDMT) at two time points (4.1 years apart). Baseline diffusion tensor imaging (DTI) was analysed using the standard preprocessing steps to compute fractional anisotropy (FA) and mean diffusivity (MD) maps. A total of 42 WM bundles and 76 GM areas from different atlases (XTRACT and Desikan–Killiany cortical parcellation with FSL-FIRST subcortical GM segmentation) were registered to DTI space to obtain the mean FA and MD values of each region of interest. Prediction models were generated by Lasso penalized regression to identify which WM tracts and GM regions at baseline are associated with each outcome at follow-up.
Results: At follow-up, the median (IQR) score for the EDSS was 2.0 (range: 0-7.0); T25FW= 4.20sec (3.61-5.18); 9HPT=20.17sec (18.6-22.8) and SDMT score=52 (45-61). Both WM and GM diffusion, mainly from the frontal and temporal cortex were able to predict EDSS score (RMSE=0.76 and R2=0.44, RMSE=0.88 and R2=0.28, respectively). Lower T25FW performance was mainly predicted by the FA decrease in longitudinal fasciculus tracts (RMSE=0.42 and R2=0.23) while SDMT was associated with temporal and frontal MD (RMSE=0.86 and R2=0.22). The 9HPT was related to FA metrics, including frontal connectivity (RMSE=0.44 and R2=0.33).
Conclusions: These results highlight the differential contributions of WM and GM integrity in each outcome. The EDSS score at follow-up was predicted by microstructural parameters that involve both tissues. Motor performance was mainly related to FA, and cognition to cortical MD measures, especially affecting the rostral multimodal cortex.

Disclosure:
The authors declare the following potential conflicts of interest: EM-H, AS, JR, FV, FP and SA-A have nothing to disclose; EL-S and ES received travel reimbursement from Sanofi and ECTRIMS; MS received speaker honoraria from Roche and Biogen; YB received speaker honoraria from Merck, Biogen, Sanofi, Roche and Brystol Myers; JM-C received speaker honoraria from Sanfi, PV is a shareholder and has received consultancy fees from Accure Therapeutics SL, Attunne Neurosciences Inc, QMenta Inc, Spiral Therapeutix Inc, CLight Inc, Adhera Health Inc and NeuroPrex Inc, as well as having held grants from the Instituto de Salud Carlos III and the European Commissions; AS received compensation for consulting services and speaker honoraria from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, TEVA, Novartis and Roche; SL received compensation for consulting services and speaker honoraria from Biogen Idec, Novartis, TEVA, Genzyme, Sanofi and Merck.

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Cognitive function and imaging correlates in MOGAD: a comparison with MS and NMOSD-AQP4

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Introduction: Cognitive impairment (CI) has been largely studied in Multiple Sclerosis (MS) and associated with grey matter pathology. In neuromyelitis-optica associated with aquaporin-4 antibodies (NMOSD-AQP4), it is not clear whether CI is limited to those with brain disease. In myelin-oligodendrocyte-glycoprotein antibody-associated disease (MOGAD), studies assessing the cognitive function using standardized cognitive batteries for demyelinating disease, are lacking.
Objectives: To compare the CI across MS, NMOSD-AQP4, MOGAD and healthy controls (HC) and to describe the association with MRI findings.
Aims: To describe different patterns of CI and their imaging markers.
Methods: The Rao's Brief Repeatable Battery of neuropsychological test scores were available for 71 subjects (18 MS, 17 NMOSD-AQP4, 19 MOGAD, and 17 HC). The global cognitive index (GC) was calculated by averaging the z-score for each test. Linear regression models were fitted in each disease group, using the GC as the independent variable and the deep grey matter volume (DGMV), cortical volume (CV), and thickness (CT) as the dependent variables.
Results: The most affected cognitive domains in the cognitively impaired participants were visual memory in both MOGAD and NMOSD-AQP4 and learning and verbal memory in MS. In addition, MOGAD participants also presented executive function impairment. In MOGAD the DGMV showed a significant association with the GC (R2=0.248, p=0.026). In the NMOSD-AQP4 group, the GC was significantly associated with the CV (R2=0.261, p=0.036). In the MS group, the GC was significantly associated with the DGMV (R2=0.221, p=0.049). The remaining associations were not significant.
Conclusions: Cognition is associated with deep grey matter volume loss in MOGAD and MS, while is mainly driven by cortical volume loss in NMOSD-AQP4. Our findings suggest that cognition can be affected in MOGAD and NMOSD-AQP4 patients with brain involvement and should be assessed by clinicians even when not reported by patients.

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Roca-Fernandez A has nothing to disclose
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Jenkinson M has nothing to disclose
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Investigating the relationship between white matter tracts and cognitive impairment in relapsing-remitting multiple sclerosis patients

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Introduction: The role of white matter tracts in cognitive impairment among relapsing remitting multiple sclerosis (RRMS) patients is still unclear.
Objectives: To examine the relationship between region based diffusion tensor imaging(DTI) tractography (usingfractional anisotropy(FA) andmean diffusivity(MD) measures in white matter(WM) tracts) and cognition measured by 3-seconds-inter-stimulus interval paced auditory serial addition test(PASAT-3) and symbol digit modalities test(SDMT) among RRMS patients.
Aims: The contribution of the white matter to cognitive impairment in MS
Methods: Thirty RRMS patients underwent PASAT-3 and SDMT at clinic visit.All patients underwent whole brain MRI scans on a SIEMENS 3 Tesla Verio scanner.DTI metrics includingFA and MDwere measured in 37 WM regions selected from association pathways, projection pathways, commissural pathway, by applyingHuman Connectome Project(HCP)842 tractography atlas after DTI data reconstruction and registration to HCP1065 diffusion template were performedin DSI Studio (version March 2021). Spearman's rank correlation analysis was performed to investigate the relationship between DTI WM tracts and cognitive scores in SPSS v26.
Results: Mean PASAT-3 and SDMT scores were31.5±12.8 and46.9±16.7 respectively.Higher FA values were associated with better cognitive function, while higher MD values were associated with worse cognitive function.

FA values in left acoustic radiation (AR_L) and Right Medial Lemniscus (ML_R) were positively correlated with PASAT-3 and SDMT scores ($p<0.05$), while MD values were negatively correlated with both PASAT-3 and SDMT scores in six regions: Left Arcuate Fasciculus (AF_L),Right Arcuate Fasciculus (AF_R),Right Cingulum (C_R),right Inferior Longitudinal Fasciculus (ILF_R),Left Corticothalamic Pathway (CT_L) and-Right Corticothalamic Pathway (CT_R)($p<0.05$).
Conclusions: Region-based DTI tractography may serve as a biomarker of cognitive impairment in RRMS. FA and MD values in specific WM tractsmay have a follow up utility of cognitive impairment among RRMS patients.Large sample of studies are needed for further investigation.

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P610
Implementation of standardized MRI finding report form for daily neurological practice in Germany

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Introduction: In the last decades MRI emerged as the most relevant paraclinical tool for both the diagnosis and treatment monitoring of MS. In real world setting, there is a wide variation regarding the quality of MRI acquisition but also regarding the image interpretation and reporting with clinically relevant consequences for the neurologist particularly with respect to the clinical decision making.
Objective/Aims: To design and implement a standardized MRI finding report form for routine neurological practice purposes in multiple sclerosis (MS) patients facilitating a more precise and faster clinical decision making compared to the conventional non-standardized MR reporting procedure.
Design/Methods: In 101 MS patients, one conventional MRI report (continuous text) and one standardized MRI report in tabular fashion according to the 2021 MAGNIMS-CMSC-NAIMS, was generated for every individual patient between 2021 and 2022 as part of routine MRI scanning for diagnostic and monitoring purposes. The radiologists generated either the conventional or standardized tabular MRI report. The neurologists treating the patients in private practices filled out a questionnaire to assess which of the two approaches was most useful and time efficient in the clinical practice setting.
Results: According to the evaluating neurologists, the use of the standardized tabular reporting form was more time efficient compared to that using the conventional report in text format (1min and less 68,3% vs. 7,9%, 2min and less 99,0% vs.63,4%, $p<0,01$). In addition, the trust in the content was higher in the tabular form (97% vs. 3%). The involved neurologists felt that the time commitment in the tabular form was more appropriate in relation to the content than the report in the conventional text format (Numeric Ranking Scale (NRS; 0-10) (interval 7 up to 10 96% vs. 9,9%).There were more queries about the findings in the conventional report than in the tabular form (100,0% vs. 46,5%).
Conclusions: A standardized tabular MRI report form is more time efficient and can be helpful in everyday neurological practice. It is a possible way to combine the highest possible quality of a MS-oriented finding report with the shortest possible time needed for evaluation from a neurological point of view, to be able to make therapeutic decisions in a sufficiently timely manner and to have confidence in the contents of the report.
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P611
Myelin content is different in the normal appearing white matter from multiple sclerosis brains with and without slowly evolving lesions

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Introduction: Slowly evolving lesions (SELs) are defined as contiguous regions of pre-existing T2 lesions with constant and concentric local expansion on serial conventional MRIs. Previous studies have shown that the presence of SELs may indicate ongoing inflammatory activity which leads to a worse prognosis. Myelin water fraction (MWF), magnetization transfer ratio (MTR) and quantitative T1 (QT1) can be used to quantify changes affecting myelin in multiple sclerosis (MS). Along with lesions, normal appearing white matter (NAWM) also shows variable axonal loss and demyelination which impacts disability and progression.
Objectives: To compare z-scores from myelin-related MR measures within NAWM in relapsing MS (RMS) participants with and without SELs over 192 weeks.

Methods: Forty-nine patients with RMS (31 females; mean age: 38±10 y; median EDSS: 2.0) participating in a substudy of OPERA II (NCT01412333) had 3T imaging at baseline, week 24, 48, 96 (double blind period), 144 and 192 (open label extension). 23 healthy controls (HC; 15 females; mean age 37±11 y) underwent the same imaging protocol. From the myelin imaging, MWF, MTR and QT1 maps were obtained. SELs were derived from T1- and T2-weighted images using timepoints up to week 96. Non-SELs were defined as all pre-existing T2 lesions not identified as SELs. NAWM masks were created by segmentation and removal of lesions. Baseline HC maps were registered to a common template and averaged into an atlas. Z-score maps were derived for each MS participant by comparing their myelin imaging map to the control atlas. The number of abnormal voxels (defined as z-score>4 or <-4) was calculated at each timepoint. Comparison between the number of abnormal voxels in NAWM from participants with SELs (SEL+) and without SELs (SEL-) was tested using a linear mixed-effects model.

Results: SELs were found in 33 out of 49 participants. Although not different at week 0, by week 192 NAWM for SEL+ participants had a larger fraction of low z-score voxels for MWF (1.0 vs 0.2%, p=0.04) and MTR (1.7 vs 0.6%, p=0.05), and high z-score voxels for QT1 (3.5 vs 1.1%, p=0.03) compared to SEL- participants. The number of abnormal NAWM voxels was not correlated with lesion volumes.

Conclusions: Participants with SELs showed more accumulation of abnormal voxels in the NAWM compared to participants without SELs. Further understanding of the linkage between the pathogenesis of SELs and NAWM changes may elucidate mechanisms of progression in MS.

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I Vavasour has nothing to disclose

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D Clayton is an employee and shareholder of F. Hoffmann-La Roche Ltd

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U Bonati is an employee and shareholder of F. Hoffmann-La Roche Ltd

C Bernasconi is an employee and shareholder of F. Hoffmann-La Roche Ltd.

L Gaetano is an employee of Novartis Pharma AG and shareholder of F. Hoffmann-La Roche Ltd.

A Traboulsee has received research support from Sanofi Genzyme and Roche; has received consulting fees from Sanofi Genzyme, Roche, Teva Neuroscience, Novartis, Biogen and EMD Serono; and has received honoraria for his involvement in speaker bureau activities for Sanofi Genzyme and Roche.

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TSPO-PET-measurable microglial activation is higher among males compared to females both in people with multiple sclerosis and healthy individuals

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Introduction: More robust adaptive immune responses in females explain the higher incidence of multiple sclerosis (MS) in women. On the other hand, men often end up with a progressive disease course with more severe disability. One potential factor that might contribute to greater likelihood of disease progression among men could be more prominent microglial activation in male sex compared to female sex.

Objectives: To explore, using translocator protein (TSPO) -targeting positron emission tomography (PET), whether there is evidence for a sex difference in microglial activation both in people with MS and healthy individuals.

Methods: The study cohort consisted of 94 MS-patients with mean (SD) age of 45.1 (9.8) years and median disease duration of 12.1 (range 0.2-33.1) years. Most patients had relapsing remitting MS (76%) and were females (74%). Microglial activation was measured using TSPO-binding radioligand 11C-PK11195 and PET. Age-and sex-matched healthy individuals (n=34) were imaged for comparison. Specific TSPO-binding was determined as distribution volume ratio (DVR) in several brain regions of interests (ROI). Wilcoxon rank-sum test was used for group comparisons.

Results: Compared to healthy controls, MS-patients had higher DVR values in the normal appearing white matter (NAWM) (1.18±0.05 vs. 1.22±0.05, p=0.005), whole brain (1.19±0.03 vs. 1.20±0.03, p=0.003) and thalamus (1.29±0.06 vs. 1.33±0.08, p=0.015). Men with MS had higher DVR compared to females in the NAWM (1.24±0.06vs.1.21±0.05, p=0.006), whole brain (1.22±0.04vs.1.20±0.02, p=0.008) and thalamus (1.36±0.08 vs.1.33±0.08, p=0.004). Healthy men had similarly higher DVR in the NAWM (1.22±0.05 vs. 1.17±0.04) and the whole brain (1.21±0.03 vs. 1.18±0.02) compared to women (p=0.02 and p=0.01; respectively). Microglial activation in lesion-associated ROIs such as T1 lesion core or T1 lesion rim was not statistically significantly different between male and female MS-patients. Of all the studied subgroups, secondary progressive male MS-patients had highest DVRs in all ROIs while female controls had the lowest DVRs.

Conclusions: We observed higher microglial activation in the NAWM and whole brain in males compared to females both among people with MS and in healthy individuals. This sex-driven inherent variability in microglial activation may predispose male MS-patients to greater likelihood of disease progression.

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Attention-based deep learning with relevance distribution identifies regions on quantitative MR contrasts related to patient disability

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Background: Quantitative MRI (qMRI) is sensitive to microstructural changes of focal and diffuse brain pathology relevant to disability in multiple sclerosis (MS) patients.
Objective: To assess which brain regions on qMRI maps determine the classification of patients with mild vs severe disability, we proposed a deep learning method based on (i) gated attention and Dense Convolutional Network (aDN) and (ii) modified Layer-wise Relevance Propagation (LRP).
Methods: 100 relapsing-remitting and 69 progressive MS patients (median EDSS=2.5) underwent 3T MRI acquisition to obtain quantitative measures (qMs) of T1 relaxation times (qT1,1x1x1 mm^3), neural density index (NDI,1.8x1.8x1.8 mm^3) myelin water fraction (MWF,1.25x1.25x5 mm^3). 69 patients had atwo-year follow-up acquisition. 40/169 patients had EDSS $\geqslant$5 (severe disability group) and 129/169 had mild disability ($<$5). 21/169 patients were in the independent test dataset. Stratified three-fold cross-validation was used.
A multi-path aDN was built to classify patients having severe or mild disability and generate attention weights (AWs) quantifying relative importance of qMs. Patients' ages were part of the hidden feature. To reflect the heterogeneity within the groups, the closeness between EDSS=5 and patients' EDSS was considered in the training loss. The evaluation metric was the area under the receiver operating characteristic curve (AUC).
Modified LRP considered the contribution of the gated-attention part of aDN and generated the relevance maps based on AWs from the best AUC model. A map containing joint qMs information for each patient was obtained by combining the relevance maps and qMs. The combined map was binarized with a median threshold as important. To assess if the mean qMRs on the map correlated with EDSS, Spearman's correlation (ρ) with two-sided 20,000 permutation tests was performed.
Results: The mean validation AUC and test AUC were respectively 0.86 and 0.89 indicating aDN learned the right pattern to classify patients. The most important qMs based on AWs were qT1 (0.47) followed by NDI (0.37) and MWF (0.16). The mean qMRs within important regions had mild correlation with EDSS (qT1: ρ=-0.37, $p<0.001$; NDI: ρ=0.43, $p<0.001$).
Conclusion: By performing aDN and LRP for EDSS, we obtained maps of potential regions related to patients' disability. qT1 and NDI appeared to capture best clinically relevant pathology.

Disclosure

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Commercial automated MRI reporting tools in multiple sclerosis: a systematic review of the evidence

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Background: Magnetic Resonance Imaging (MRI) is integral to the diagnostic workup of Multiple Sclerosis (MS) and is important for clinical prognostication. Quantitative volumetric reporting tools (QReports) can improve the accuracy and objectivity of MRI-based clinical assessment. Several QReports are commercially available, however, validation and in-use evaluation can be difficult to establish and does not currently follow a common, structured pathway.
Methods: With the aim of aiding evidence-based clinical decision-making, we performed a systematic review of commercial QReports for use in MS, including technical details, and their published validation and in-use evaluation. We categorise studies into three types of testing: technical validation of tool performance, for example, comparison to manual segmentation, clinical validation by clinicians or interpretation of results alongside clinician-rated variables, and in-use evaluation, such as health economic assessment.
Results: We identify 10 companies that offer QReports for MS, which provide lesion and brain segmentation and volume quantification, and 38 relevant validation/evaluation studies. Tools received regulatory approval between 2006 and 2020, and all provide contextualisation of results to a normative reference population, ranging from 620 to 8000 subjects, requiring both T1- and T2-FLAIR-weighted input sequences for longitudinal assessment of whole brain volume and lesions. Seven QReports have evidence of technical validation in an MS population, 3 companies have also conducted clinical validation by correlating results with clinical variables, only 1 has tested their QReport by clinician end-users investigating reporting time, intra/inter-observer variability, and diagnostic accuracy, and 1 has performed a simulated in-use socioeconomic evaluation.
Conclusion: We conclude that despite the range of commercial MS QReports available, there is limited evidence in the literature regarding their clinical validation and in-use evaluation. There is a particular lack of clinician end-user testing. Our systematic review provides clinicians and institutions with the available evidence when considering adoption of a quantitative reporting tool.

Disclosure
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P615
Quantifying white matter lesions in multiple sclerosis: a multiple technique comparison

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Introduction: Volumetric measurement of white matter (WM) lesions is important in the diagnosis and treatment of multiple sclerosis (MS). Manual delineation is time consuming and demonstrates operator dependant variability. Semi and fully automated methods have been developed and widely used in research, but direct comparisons are limited.
Objectives: To directly compare several WM quantification techniques in an MS cohort.
Aims: To quantify variability across WM lesion volumes from two semi-automated software packages JIM 7.0 (Xinapse Systems, Northants, UK) and 3D Slicer, and one fully-automated FDA-cleared and CE-marked method QyScore®
Method: Total lesion volume was calculated for 44 MS research patients (mean age=53 (range 36-65), 16M/28F, 16 Primary Progressive/28 Secondary Progressive) using JIM, 3D Slicer, and QyScore®
Comparisons were performed by calculating linear regression with the agreement between the different software packages assessed using the Bland-Altman method.
Visual assessment of the results from a subset of the cases was conducted by experienced image analysts to identify sources of discrepancy with neuroradiologist review pending.
Results: Mean (sd) lesion volumes were 13.3 (7.74), 21.45 (12.11), and 31.44 (18.86) ml for 3D Slicer, QyScore® and JIM respectively.
Correlation coefficients were calculated with greater similarity found between 3D Slicer and QyScore® in determining relative lesion volume compared to JIM.
Bland-Altman analysis indicated significant discrepancy between all three methods with a percentage bias of +39% (153% CI) between JIM and QyScore®, -47% (61% CI) between 3D Slicer and QyScore®, and +80% (139% CI) between JIM and 3D Slicer. The difference between regression and bias results highlights the challenges in delineating WM lesions across a typical pathological range.
Visual assessment suggests this is largely driven by erroneous grey matter inclusion using JIM and under sampling of lesions with 3D Slicer. In the most discrepant cases QyScore® produced the most representative WM segmentations. An additional consideration with semi-automated software is user dependency.

Average user-input time (minutes) was <2 for QyScore® and >30 for both JIM and 3D Slicer.
Conclusions: QyScore® produces fast, accurate and reproducible quantification of MS lesions. Choice of method significantly impacts lesion volumes and ongoing work to better characterise this variability is key for precision and efficacy in MS clinical decision making.

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P616
7T imaging of multiple sclerosis: evidence for a diffusible agent with "surface in" cortical lesions

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Introduction: Pathogenesis of generalized cortical disease and focal cortical lesions in Multiple Sclerosis appears to involve pathologic phenomena at variance with those typically associated with classic acute white matter lesions. Furthermore, surface pial and thalamic changes have provided evidence that a CSF borne agent or trigger may be involved in inducing non-inflammatory demyelination and neuronal loss in superficial brain regions.
Objectives: To identify the nature of focal cortical lesions on 7T MRI in a group of adult MS patient.
Methods: 20 adult patients with diagnoses of Multiple sclerosis, including relapsing remitting, primary progressive, and secondary progressive disease were scanned in a Siemens 7T scanner using standardized T2, DIR, SWI, and MPRAGE sequences. Imaging was performed with patient consent under IRB approval and supervision. Images were reviewed for detectability of superficial cortical focal lesions. Comparison of identified lesions between imaging series and correlation with disease duration and clinical status was pursued.
Results: High resolution T2 with 2mm slice thickness proved consistently to be the most sensitive to the presence of intracortical and superfical subpial disease. A particular subtype of superficial cortical lesion was found in patients with disease of longer duration whereby the lesion configuration suggested a base along the pial surface and T2 signal emanating deeply from this base in an approximately circular configuration consistent with diffusion of an agent from the pial base. In 25% of patients, lesions of this nature were identified in close proximity on opposite sides of a sulcus, adding to the perception of an incitement of pathologic change spreading from the CSF inwards. Cortical lesions of this configuration showed interruption of the linear pattern of cortical iron on SWI, possibly indicating an MRI finding of focal cellular loss in these lesions.
Conclusion: 7T T2 weighted imaging with high resolution proved more sensitive to superficial cortical lesion detection than other sequences. The configuration of many focal lesions in a high proportion of patients provides an argument for diffusion of a neurotoxic agent into the cortex in a "Surface In" direction of propagation. Such an agent could be leaking from overlying pial lymphoid follicles or from another superficial source.

Disclosure
None

P617
Assessing heterogeneity of multiple sclerosis lesions in susceptibility-weighted MRI: a cross-sectional and longitudinal study

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Background and Aims: Imaging protocols encompassing susceptibility-weighted imaging (SWI) are increasingly used to diagnose and monitor multiple sclerosis (MS), owing to its ability to demonstrate white matter lesions (WMLs) with paramagnetic rim (PRLs) and central vein sign (CVS). Yet, MS WML heterogeneity in SWI is not well understood.
Objectives: i, to study *in vivo*characteristics and ii, longitudinal evolution of MS WMLs in SWI.
Methods: Forty-three MS patients (35RRMS/8PMS; 23F/20M; age 57±9.5y) underwent T1 MPRAGE (Magnetization Prepared Rapid Acquisition with Gradient Echoes), FLAIR (Fluid-attenuated inversion recovery), SWI, diffusion-weighted MRI with apparent diffusion coefficient (ADC) mapping at 3T MRI. We retrospectively identified examinations, for which a follow-up examination after 18±6 months was available. WMLs (n=1750) were segmented automatically and manually corrected on FLAIR. Brain mask, normal-appearing WM (NAWM) extraction and MRI registrations were performed in FreeSurfer and FSL. WMLs were classified into 3 groups according to their appearance on SWI: (i) isointense; (ii) hypointense (iii); hyperintense. PRL and CVS lesions were visually identified on phase and magnitude MRI, respectively. Mann-Whitney and Kruskal-Wallis test with Dunn's correction for multiple comparisons were used to compare lesion types with each other and NAWM. Correlation studies with whole-brain volume (WBV) were performed using a general linear regression model (GLM) with age, sex, and disease duration as covariates.
Results: Of 37 new lesions on follow-up MRI (none of those showed Gd-enhancement on post-contrast T1), 21.6% hyper-and 78.4% iso-intense (50% and 41.3% CVS+ respectively) lesions were detected. None of the new lesions appeared PRL+ in phase MRI. In cross-sectional analysis: 77.7% hyper-, 21.4% iso- and 0.8% hypo-intense WMLs were detected.
All lesion types exhibited higher ADC value compared to NAWM (all P<0.0001). There was a trend towards increase in ADC value

in hyperintense vs isointense, in PRL+ vs PRL-, in CVS+ vs CVS- WMLs (not statistically significant; P>0.05). Except from age (P<0.0001), other parameters including number and volume of SWI WML types did not show any correlation with WBV (all P>0.05).

Conclusion: New WMLs mainly appear isointense in SWI and tend to evolve towards a hyperintense appearance over time, which might be due to iron deposition and demyelination. Although MS WML in all types showed higher ADC value than NAWM suggestive of tissue destruction, microstructural damage measured by ADC was quite similar among all lesion types.

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P618

Assessment of candidate MRI biomarkers of ongoing MS disease in the absence of acute inflammation

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Introduction: Treatments are needed that target MS disease processes continuing in the absence of acute inflammatory activity. A key limitation is the lack of MRI biomarker endpoints of such processes suitable for short-term trials.

Objectives: To identify MRI measures with the highest sensitivity to change due to MS during periods free from acute clinical and radiological inflammatory activity.

Methods: Patients included were consented in MS PATHS, had ⩾2 standardized MRIs over ⩾1 year without change in treatment, and had no relapses nor new/newly enlarging T2 lesions in the follow-up window. MRI volumetric and lesion-based measures were assessed in this selected MS cohort, as well as in smaller cohorts participating in MS PATHS sub-studies to assess scan-rescan variability (n=30 MS patients) and longitudinal changes in age- and gender-matched healthy controls (HC, n=220). Signal to noise was assessed as: mean annual change/ standard deviation (SD) of annual change (SNR1); and mean annual change in the full cohort of MS patients/mean absolute differences in the scan-rescan cohort (SNR2). Effect size (of mean annual change) compared to HC was assessed by Cohen's D.

Results: Analyses included 1419 patients (mean age 44 years; 388 male) with mean (SD) of 1.34 (0.73) years follow-up. Mean (SD) annualized changes were brain parenchymal fraction (BPF): -0.19% (0.55), log of T1 lesion volume in chronic T2 lesions (T1LV): 0.13 (0.44), grey matter fraction (GMF): -0.40% (1.9), mean normalized T1 intensity in chronic T2 lesions (nT1I) -0.02 (0.08), T1 lesion volume as a proportion of chronic T2 lesion volume (T1LP): 0.01 (0.07), log of T2 lesion volume (T2LV): -0.02 (0.17), cortical grey matter fraction (cGMF) -0.32% (3.59), thalamic volume fraction (TF): 0.01% (2.68). The best MRI metrics in terms of SNR1 were BPF: 0.35, T1LV: 0.30, GMF: 0.21, nT1I: 0.18, and T1LP: 0.17. The best metrics in terms of SNR2 were T1LP: 1.21, BPF: 1.18, T1LV: 1.10, GMF: 0.59, nT1I: 0.59. Effect sizes were BPF: 0.18, GMF: 0.07, TF: 0.06, and cGMF: 0.04. Effect sizes were not calculated for lesion metrics due to lack of lesions in HC.

Conclusions: Whole brain atrophy and T1 metrics in chronic lesion had the highest sensitivity to change in MS patients over time in treatment-stable periods of no inflammatory activity. Future work will assess relationships between these measures and disability progression and define predictors of larger rates of change.

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AR serves on scientific advisory boards for Novartis, Sanofi-Genzyme, Synthetic MR, TensorMedical, Roche, Biogen, and OLEA Medical, and has received speaker honoraria from Bayer, Sanofi-Genzyme, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis, Roche and Biogen.
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P619

Neural network-based classification of remyelinated white matter lesions on quantitative susceptibility maps

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Introduction: In multiple sclerosis (MS) patients, white matter lesion types are heterogeneous and may be classified histopathologically based on cellular composition as well as axonal and myelin content. Recently, an in vivo classification of MS lesion types has been proposed on Quantitative Susceptibility Mapping (QSM) images in patients. Interestingly, QSM appears to be highly sensitive and specific to identifying fully remyelinated (RM) lesions, which appear hypo- and isointense, and demyelinating (DM) lesions. We propose an automatic neural network classifier for RM MS lesions.p
Aims: Automatic differentiation of RM QSM lesions from other lesion types in MS patients.
Objectives: To develop an automatic classifier that would provide the remyelination status of a lesion based on its MRI data patches.
Methods: We enrolled 91 MS patients who underwent 3T MRI including 3D FLAIR 1mm isotropic, MP2RAGE 1mm isotropic, and 3D EPI 0.67mm isotropic for Quantitative Susceptibility Mapping. Automatic lesion segmentation was performed on FLAIR and MP2RAGE images, followed by manual correction. Masks were co-registered to 3D EPI. 65% of the lesions were not included due to image artifacts or impossibility of classification. The remaining lesions, used for training and testing, were manually classified into either RM or DM categories on QSM images. For each lesion, a patch with FLAIR, QSM, and lesion mask channels was created. The obtained dataset was split into training and testing sets using a 70/30 ratio. The training set was extensively augmented and balanced by rotating and flipping the patches. Several neural network architectures were tested, with the finally selected optimal one consisting of 3 convolutional and one fully connected layer.
Results: Overall accuracy for binary classification of RM vs. DM lesions was 88.9%. The true positive (TP) rate for the RM class was 0.89, the true negative (TN) rate was 0.88, while false positive (FP) and false-negative (FN) rates were 0.11 and 0.12 respectively.
Conclusions: The selected architecture was a compromise between risks of model overfitting and insufficient model adaptability, indicating an extended training dataset could improve results further. The results, together with future work of addressing ways to discard lesions not able to be classified, may facilitate translation of these novel biomarkers of remyelination into clinical practice and alleviate the need for tedious manual identification.

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P620

Multiparametric quantitative MRI reveals progressive cortical damage over time in relapsing-remitting MS

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Introduction: In relapsing-remitting Multiple Sclerosis (RRMS), there is emerging evidence that two processes coexist: focal inflammation resulting in relapses and global/diffuse inflammation, which can hardly be quantified with conventional MRI techniques.
Objective: It was aimed to assess diffuse microstructural damage to the cerebral cortex over time in patients with RRMS. To this end, we used multiparametric, surface-based quantitative MR imaging (qMRI) techniques including T1, T2 relaxation time and proton density (PD) mapping.
Methods: Quantitative T1, T2 and PD mapping was performed on 40 patients with RRMS and 33 age and gender matched

healthy control subjects at baseline and follow-up after 2 years. Cortical qMRI parameter values were extracted using a surface-based approach with Freesurfer. QMRI parameter values, EDSS and relapse rate were compared between time-points via t-tests.

Results: T1 (t_0: 1524.41 ± 37.29 ms, t_1: 1550.39 ± 32.09 ms, p⩽0.001), PD (t_0: 80.89 ± 1.48 percent units (pu, with 100 pu corresponding to CSF), t_1: 81.95 ± 1.66 pu, p⩽0.001) and T2 (t_0: 83.49 ± 3.58 ms, t_1: 84.48 ± 4.51 ms, p=0.005) - with mean ± SD listed for all parameters and both time points t_0 and t_1- values significantly increased over two years in the patient group. In the control group, no significant changes were observed for T1 (p=0.53), PD (p=0.15) and T2 (p=0.54). EDSS values did not change over time (t_0: 2.49 ± 1.13, t_1: 2.53 ± 1.26 p=0.827) and the relapse rate decreased (t_0: 0.718 ± 0.70 relapses per year, t_1: 0.321 ± 0.52 relapses per year, p=0.001).

Conclusion: EDSS and relapse rate indicated clinical stability. Still, cortical T1, T2 and PD values increased over time, indicating progressive cortical demyelination and increasing water content. QMRI therefore has the potential to provide surrogate parameters for diffuse inflammatory cortical processes beyond relapse activity for future clinical studies.

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P621

First evidence on the utility of T_1 mapping of the optic nerve to investigate differences between MS and NMOSD

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Introduction: Multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) are characterized by optic neuritis, transverse myelitis and/or brainstem attacks, therefore exhibiting possible overlap between paraclinical and radiological features. Hence, new radiological biomarkers are desirable to enable an accurate diagnosis.

Aims: Here, we study the anatomical distribution and extent of T_1 abnormalities in the optic nerve for different subtypes of NMOSD and MOGAD compared to early MS.

Methods: Ninety-two healthy controls (60 females, age=[21-59] y/o), 16 NMOSD (12 females, age=[22-57]y/o, 13 with aquaporin-4 antibodies (+AQP4), and 3 seronegative), 3 with MOGAD (1 female, age [19-37]y/o) and 6 early MS patients (3 females, age=[19-32]y/o) were scanned at 3T (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) using MP2RAGE. All patients had experienced at least one episode of optic neuritis. Healthy subject datasets were co-registered in a study-specific template space, and a reference voxel-wise T_1 atlas was established using a linear model with age and gender as covariates. The chiasm, anterior and posterior parts of the optic nerve were manually segmented in the template. For each patient, voxel-wise deviations from the T_1 atlas (in unit #std difference) were determined, yielding z-score maps. Volumes of voxels with |z-score|>2 were extracted and a laterality index (LI=|L-R|/(L+R)) was computed for the anterior and posterior segments.

Results: The results are reported as median and interquartile ranges. Volumes of |z-scores|>2 were lower for MS patients in all optic nerve segments. The largest difference was observed in the chiasm, between seronegative NMOSD (85.0[40.5]) and MS patients (24.0[30.7]), confirming the clinical expectation. MS patients had a higher laterality index in both anterior (MS=0.48[0.56], +AQP4=0.17[0.19], MOGAD=0.19[0.18], seronegative NMOSD=0.29[0.11]) and posterior segments (MS=0.23[0.07], +AQP4=0.08[0.16], MOGAD=0.09[0.09], seronegative NMOSD=0.07[0.05]).

Conclusions: These preliminary results show the potential of using T_1 z-score mapping in the optic nerve to differentiate between early MS and NMOSD patients with optic neuritis, both in terms of abnormality extent and laterality index. However, the size of the dataset did not allow for statistical assessment and future work should focus on validating these findings on larger patient cohorts.

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P622
Age-related decline in cerebral oxygen consumption in relapsing-remitting multiple sclerosis

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Introduction: Despite disease modifying treatments relapsing-remitting multiple sclerosis patients (RRMS) experience disease progression and cerebral atrophy. Inflammation impacts cerebral energy metabolism, and there is increasing evidence of mitochondrial damage in RRMS.
Objectives: To determine the cerebral oxygen consumption in RRMS patients and its correlation with age and cerebral atrophy.
Aims: To investigate dysfunctional cerebral energy metabolism as a contributing factor in disease progression in multiple sclerosis.
Methods: Patients with RRMS (N = 44) and healthy age-matched controls (HC) (N = 36) were scanned on a 3T MRI scanner to measure the cerebral metabolic rate of oxygen consumption by susceptibility mapping, cerebral blood flow by phase contrast mapping, cerebral volumes by a high-resolution 3D T1-weighted sequence, and lesion load by delineation on a T2 FLAIR weighted sequence. Brain parenchymal fraction was determined by automatic segmentation in FreeSurfer and EDSS scores were collected from medical records. Statistics were calculated in R, using Welch t tests and general linear models with interaction between age and disease status.
Results: The cerebral metabolic rate of oxygen consumption was lower in patients than controls (patients: 121.2 μmol/100g/min, controls: 143.2, difference: 21.9, 95% CI: 7.8 to 36.1, p = 0.002) and decreased with age in patients relative to the controls (beta = -1.35, p = 0.036). The lower rate of oxygen consumption was explained by a lower oxygen extraction fraction (p = 0.007) because the cerebral blood flow was not reduced in patients (p = 0.69). The patients did not have a significantly higher degree of cerebral atrophy, measured as the brain parenchymal fraction, than the controls. The cerebral metabolic rate of oxygen consumption was neither correlated with EDSS score (median 2, range 0 – 5) nor lesion volume (median 7.69 ml, IQR 3.37 – 15.25).
Conclusion: We observe a decreased cerebral rate of oxygen consumption before the appearance of significant cerebral atrophy in RRMS patients. This supports the evidence of mitochondrial dysfunction as a potential pathogenic mechanism in RRMS. Whether reduced cerebral oxygen consumption reflects future atrophy and can be used as an early biomarker for this will require further studies to be elucidated.

Disclosure
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P623
Higher mean intensities in the lateral ventricular region of FLAIR MRI may indicate higher disease activity in early RRMS

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Introduction: Inflammatory infiltrates are produced in the choroid plexus (CP), possibly entering the brain via the lateral ventricles (LV) in MS patients. Disease activity is often characterised by clinical relapses and/or MRI activity, visualised with contrast agents.
Objectives: Investigate if the LV and the region surrounding it, in raw T2-weighted non-contrast enhanced MRIs, can be used in machine learning (ML) methods to predict disease activity in early relapsing-remitting (RR)MS patients.
Aims: Evaluate predictability of RRMS patients with high versus low disease activity (HDA vs. LDA) using clinical data and MRIs cropped around the LV.
Methods: Isotropic 3D T2-weighted fluid attenuated inversion recovery (FLAIR) cerebral 3 Tesla MRIs were collected from 148 patients with early RRMS. FLAIRs were centred on the CP, and cropped to contain the whole LV (dimensions=60x54x2mm). Annualised No Evidence of Disease Activity (NEDA-3) was calculated and binarised to indicate patients with HDA (>1 annualised NEDA-3 score) vs. LDA. Baseline mean intensities of cropped FLAIRs from LDA (N=67) were compared to HDA (N=81) patients using a 2-sample t-test. Age, disease duration, Expanded Disability Status Scale (EDSS), and sex were included as ML clinical variables. Ten repetitions of 5-fold nested cross validation using logistic regression modelling (LRM) and random forest classification (RFC) were performed to predict HDA vs. LDA using clinical variables, cropped FLAIRs, and combined clinical and cropped FLAIR data.
Results: Median baseline characteristics: disease duration=4 months (HDA=4.7 months, LDA=5 months), EDSS=1.5 (in both groups), N follow-up visits=4 (HDA=4, LDA=5), and N T2-brain lesions (HDA=11, LDA=9). Patients with HDA showed higher mean intensities of cropped FLAIRs at baseline than those with LDA ($t=-64.1$, $p=<2.2x10^{-16}$). LRM and RFC were not successful in predicting disease activity groups, where all mean areas under the curve and balanced accuracies were below 0.56, except for RFC including cropped FLAIR data had slightly higher mean balanced accuracies (0.61 ± 0.04).
Conclusions: FLAIR MRIs in and around the LV region have higher mean intensities at baseline in patients with HDA vs. LDA. Although simple ML methods did not successfully predict disease activity using clinical and/or cropped FLAIR data, our findings suggest raw T2-weighted, fluid attenuated MRIs may be useful in the prediction of disease activity in RRMS using more advanced methods.

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M.S., F.E., K.R. declare that they have no conflicts of interest.

P624
Towards better characterization of spinal cord pathology in early stages of multiple sclerosis using T1 mapping

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Introduction: Assessment of focal and diffuse changes in the spinal cord (SC) is to some extent subjective and hindered by image artifacts. T1 relaxometry can provide quantitative information about tissue damage severity and help to identify SC pathology on a single-subject basis.
Objectives: To quantify microstructural SC involvement using T1 values; to determine whether T1 mapping improves the detection of SC pathology when compared to manual assessment on conventional MRI (cMRI); to determine whether diffuse changes and focal lesions can be distinguished objectively.
Methods: Ninety-two healthy controls (HC) and 46 patients with the first clinical symptoms of multiple sclerosis (MS) (mean disease duration 4.7 ± 5.5 months) were scanned at 3T (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany)

with the MP2RAGE sequence for T1 mapping and automated SC segmentation (C1-C5). The neuroradiologist and neurologist only used fat-saturated T2w and PDw in the sagittal plane to qualitatively evaluate SC pathology (focal lesion (F), diffuse changes (D), probable F and D (PF, PD) or normal (N)) for each segment. After scaling with their median, distributions of T1 values in each SC segment were assessed for each MS patient and compared to HC using the Kolmogorov-Smirnov (KS) test (α=0.05).

Results: Overall, 186 SC segments were assessed. Segments manually labeled as N had significantly lower KS values (0.04 ± 0.02) than other groups (F, D, PF, PD; $p<0.001$). Especially segments that were labeled as D (0.16 ± 0.07; $p<0.001$) and F (0.12 ± 0.06; $p<0.001$) had significantly higher KS values. On cMRI, SC pathology (F/PF/D/PD) was described in 79 segments (13-C1, 19-C2, 22-C3, 19-C4 and 6-C5). Area under the curve of the receiver operating characteristic (AUC) was 0.80 to discriminate SC pathology. For only D or F, the AUC was 0.91.

Conclusions: Our preliminary data shows that T1 mapping might serve as an objective measure for SC pathology. Subjective assessment is prone to artifact-driven misinterpretation often resulting in an overestimation of diffuse changes. Some SC pathological changes, although in a restricted number of patients, were detected using T1 mapping while subjectively assessed as normal at disease onset. Validating our results in other cohorts and correlating with disability will be the next steps to better characterize SC pathology in MS.

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P625

Assessment of intrinsic bundle myelination: exploratory analysis for future application in MS

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Introduction: Myelin degeneration in multiple sclerosis (MS) affects the integrity of individual bundles as well as the organization of whole-brain networks. To date, no imaging method exists to properly characterize the role of myelin damage in brain connectivity disruption in MS patients. An open question is also the contribution of aging to this process.

Aims: In this work, we aimed to characterize age-related changes in brain networks obtained using bundle-specific myelination measures in a group of healthy subjects (HS), with the purpose of subsequently investigating alterations in MS patients.

Methods: We constructed myelin-weighted connectomes of 85 HS (46f, 18-69 y.o.) using diffusion MRI tractography filtered for false positives and we segmented grey matter in 84 regions on T1 images. To obtain the connectivity strength, we used both *myelin streamline decomposition* (MySD) and *tractometry* approaches. From each connectome, 3 network metrics were extracted: Global Efficiency (information exchange); Modularity (network segregation); Mean strength (connections strength).

We tested possible associations between age, age^2, and network metrics alterations considering gender and white-matter volume as covariates. The same model was also employed to predict aging effects using leave-one-out cross-validation.

Results: Global efficiency *(MySD: Age^2 $p=0.03$,$R2=0.61$; tractometry: Age^2 $p=0.04$, $R^2=0.26$)* and mean strength *(MySD: Age^2 $p=0.01$, Age $p=0.02$, $R^2=0.78$;tractometry: Age^2 $p=0.01$, Age $p=0.02$, $R^2=0.39$)* changed with age, reaching their maximum peak around 35/40 years. Both MySD and tractometry were

sensitive to these changes, but data calculated using MySD reported higher adjusted R^2 as well as considerably lower errors in age prediction *(0.44; 0.89 respectively for global efficiency and 0.25; 0.77 respectively for mean strength)*. However, in both cases, this quadratic model was not suitable to explain changes in network modularity.
Conclusion: MySD appeared to be sensitive to assessing age-related brain network changes in a way that is superior to conventional tractometry. Future work aims at investigating whether MS accelerates those brain network changes or provokes more focal network disruptions.

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P626
Brain MRI versus spinal cord MRI in measuring cervical spinal cord atrophy

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Introduction: Cord atrophy is a critical imaging biomarker in MS, which correlates with transition to the progressive phase. Measurements optimally must be obtained from dedicated cord MRIs, which provide quantification of the entire cord. However, brain MRIs are often used for cord measurements, which can only acquire quantification of the upper cervical cord (UCC).
Objectives: Investigate the agreement between cord measurements from brain MRIs by an automated method and from cord MRIs by a manual method.
Aims: Analyze associations between 1) cord measurements from brain and cord MRIs 2) cord measurements and age
Methods: 89 consecutive patients with MS (F:M=63/26; 72 relapsing, 17 progressive) from a single center were prospectively enrolled. 130 brain and spinal cord MRI pairs attained within 10 days were included. A previously published and established manual method was used to measure each cervical cord area from C2-7 (mC2, mC3, mC4, mC5, mC6, mC7) and averaged to calculate cervical average segmental area (mCASA) of the entire cervical cord from cord MRIs. A novel automated method was used to measure UCC volumes at different levels (cervicomedullary junction (aCMJ), aC1, aC2, aC3) from brain MRIs: Advanced Normalization Tools nonlinear registration was used to propagate a mask of UCC regions from the atlas template space to each T1-weighted brain MRI and volumes were calculated as the sum of voxels in masks, multiplied by the image voxel volume.
Results: Age (mean±SD) at MRI was 46.0±12.3 years. Manual mC2 and mC3 from cord MRIs correlated with corresponding automated aC2 and aC3 from brain MRIs (C2 $r=0.54$ $p<0.001$; C3 $r=0.36$ $p<0.001$). mCASA correlated with each automated volume from aCMJ to aC3 regardless of the level, but the strongest correlation was with aC2 ($r=0.59$ $p<0.001$). mCASA also correlated with average automated volume from CMJ to C2 level ($r=0.55$ $p<0.001$). Manual mC2 ($r=-0.31$ $p<0.001$), mC3 ($r=-0.41$, $p<0.001$) and automated UCC volumes (aC2 $r=-0.33$ $p<0.001$; aC3 $r=-0.36$ $p<0.001$) all decreased with age.
Conclusion: Cord atrophy is a predictor of subclinical MS progression and analyzing the entire cervical cord from cord MRIs increases sensitivity of the evaluation by reflecting the craniocaudal atrophy, which is more prominent in progressive MS. However, automated and semi-automated methods using brain imaging seem to be a good alternative of dedicated cord MRIs by providing reasonable approximations from existing scans, saving acquisition time.

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P627
Increase in neuronal local connectivity following cortical demyelination prevents cognitive impairment in multiple sclerosis

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Background: The interplay between cortical demyelination, remyelination and neuronal connectivity, as well as the impact of these processes on cognitive impairment in people with MS (PwMS) remain unclear.
Aims: In this study, we aim to assess changes in local functional connectivity density (lFCD) following cortical demyelination/remyelination and to evaluate their impact on cognitive impairment.

Methods: Forty-eight PwMS and 28 healthy controls underwent a neuropsychological assessment and a full MRI protocol at 3T including resting functional MRI (rfMRI) and magnetization transfer (MT) imaging at baseline and at 12 months. lFCD, a data-driven index of local centrality within a brain network, was derived from rfMRI, while MT images were compared between patients and controls to generate cortical maps of baseline demyelination and dynamic demyelination/remyelination. Demyelinated voxels were clustered in each patient to generate cortical parcellations which were classified as mildly, moderately or severely demyelinated. ANOVA, uni- and multi-modal voxel-wise analyses were employed to assess group differences in MRI-derived metrics and to investigate the spatial association between cortical demyelination and lFCD.
Results: In PwMS, lower cortical MT ratio, reflecting decreased myelin content, was associated with higher lFCD, reflecting enhanced neuronal local connectivity, throughout the cortex. Cognitive impaired (CI) PwMS had lower cortical MT ratio than cognitive preserved (CP) PwMS ($p=0.049$). For the same extent of cortical demyelination, lFCD enhancement was very heterogenous among patients, with CP-PwMS showing a significantly higher lFCD than CI-PwMS ($p<0.001$, Partial-Eta-Squared=0.47). CP-PwMS with high lFCD were younger and had a lower white matter lesion burden than CI-PwMS with lower lFCD.Over 12 months, neuronal connectivity enhancement was shown to fade off in the presence of excessive dynamic cortical demyelination (>12%). Conversely, greater cortical remyelination was associated by higher lFCD enhancement ($p<0.001$,Partial-Eta-Squared=0.19).
Conclusion: Cortical demyelination appears to trigger a compensatory increase in neuronal local connectivity, which was highly heterogenous among PwMS. When adequately enhanced, this mechanism, which is modulated by the extent of cortical remyelination, is effective in preventing cognitive impairment in MS.

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P628
Spinal cord reserve and disability worsening over time in patients with multiple sclerosis

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Background: Spinal cord volume is a strong predictor of physical impairment and progression over time in Multiple Sclerosis (MS). Mirroring the concept of "brain reserve", spinal cord reserve has been recently found to be associated with perceived disability, but its value in predicting clinical worsening has not been explored yet.
Objectives and Aims: To evaluate how (i) spinal cord reserve is related to measures of objective disability and (i) how it impacts on disability worsening over time, in patients with MS (PwMS).
Methods: As a part of an ongoing study, we collected clinical [9-hole peg test (9HPT), 25-foot walking test (25FWT), Expanded Disability Status Scale (EDSS)] and Magnetic Resonance Imaging (MRI) data (3D T1W Brain scan covering C2-C3) of 100 PwMS [F: 74; mean age 36.7 ± 8.3; EDSS 2. 0 (range: 0-6.0)] at baseline. Of them, 92 underwent clinical follow-up (FU) (median: 3 years). Clinical worsening at FU was defined according to the EDSS-Plus. A cohort of 41 matched healthy controls (HC) [F:28; mean age 32.8 ± 6.5] underwent the same MRI protocol.Spinal cord and canal areas (SCA and SCaA) were obtained with Jim 7 software at C2/C3 level. Spinal cord parenchymal fraction (SCPF) was computed as SCA/SCaA. Differences between groups were investigated controlling for age and sex via ANCOVA. Linear and binary logistic regression were used to test (i) the association of spinal cord reserve with clinical measures at baseline (adjusted for SCPF, age and sex) and (ii) its value in predicting disability worsening at FU (further adjusted for FU duration, relapse rate and baseline EDSS), respectively.
Results: PwMS showed lower SCA and SCPF compared to HC (SCA: 59.65 ± 9.3 vs 66.5 ± 5.7 mm^2, $p=0.001$; SCPF: 0.31 ± 0.5 vs 0.34 ±0.3, $p=0.004$), while no differences in SCaA were detected (191.0 ± 32.6 vs 194.6 ± 26.35, $p=0.9$). At baseline, SCaA was associated with EDSS (ß=-0.29, $p=0.01$; adj R^2= 0.235, $F=8.2$, $p<0.001$) and 9HPT (ß=-0.37, $p<0.01$; adj R^2= 0.201, $F=7.3$, $p<0.001$). Approximately 39% of patients showed disability worsening at FU. PwMS showing a higher SCaA at baseline had a lower probability of developing future clinical worsening (OR=0.97, 95% CI 0.96-0.99, $p=0.01$).
Conclusions: A larger spinal canal area, as proxy of higher spinal cord reserve, might extert a protective effect against the expression and short-term evolution of motor disability in MS. Further studies with longer follow-up and larger sample are needed to better explore this new concept.

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P629

Infratentorial lesions can predict conversion to clinically definite multiple sclerosis

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Introduction: Abnormalities on baseline brain magnetic resonance imaging(MRI) in patients with initial findings suggestive of multiple sclerosis(MS) are known to predict conversion to Clinically Definite MS(CDMS).
Objectives: To assess the long-term predictive value of baseline MRI infratentorial lesions in patients with initial diagnosis of Clinically Isolated Syndrome(CIS) for conversion to CDMS.
Methods: Patients enrolled fulfilled these inclusion criteria: 1) Age 15-60years; 2)Diagnosis of CIS after first episode of neurologic dysfunction suggestive of MS; 3)Baseline MRI performed in first 6 months with only one relapse; 4)Minimum follow-up 24 months or progression to CDMS.
Results: 316 patients were enrolled, 220(69.6%) women. At initial examination, mean age was 34.22±9.89years. Mean duration follow-up was 70.97±41.3months. Conversion to CDMS occurred in 162(51.3%) patients and 233(73.8%) were diagnosed MS according to 2017-McDonald criteria. Baseline MRI showed infratentorial lesions in 136(43%) patients, asymptomatic infratentorial lesions in 84(26.6%).Grouped by number of lesions, 89(28.2%) patients had 1 and 47(14.9%) had ⩾2 infratentorial lesions.Patients showing evidence of dissemination in space(DIS) in baseline MRI were 216(68.4%). If infratentorial lesions were not included, only 194(61.4%) demonstrated DIS. Conversion to CDMS was found to be significantly related to presence of infratentorial lesions(hazard-ratio:2.3, $p<0.001$) andasymptomatic infratentorial lesions(hazard-ratio:2.33, $p<0.001$). Compared to their absence, existence of⩾1(hazard-ratio:1.97, $p<0.001$) and ⩾2 (hazard-ratio:3.2, $p<0.001$) infratentorial lesions showed significant relationship with development of CDMS.
Conclusions: Infratentorial lesions can predict conversion to CDMS and help in early detection of patients at risk, specially when asymptomatic or when they are found in greater number.

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P630

Improved assessment of leptomeningeal contrast enhancement via 3-Tesla 3D real inversion recovery MRI in multiple sclerosis

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Introduction: Leptomeningeal inflammation is an important feature of multiple sclerosis (MS). Leptomeningeal contrast enhancement (LME) is a candidate marker for leptomeningeal inflammation that can be visualized on contrast-enhanced (CE) T2-FLAIR MRI. Sensitivity of T2-FLAIR to LME varies across studies with different sample sizes and magnetic field strengths. Most studies highlight a need for improved visualization of LME. CE 3D real inversion recovery (IR) is a relatively new technique that is sensitive to low concentrations of gadolinium-based contrast agent (GBCA).
Objectives: To evaluate the sensitivity of 3D real-IR for LME, compared to conventional T2-FLAIR, in a 3T scanner. To assess the relationships between LME, clinical, and radiological outcomes.
Aim: To assess LME with a relatively new 3T technique (3D real-IR) that is sensitive to low concentrations of GBCA.
Methods: 168 scans from 145 patients (124 with MS spectrum disorders, 21 with other neurological and/or inflammatory disorders) were evaluated by a neuroradiologist and a neurologist with expertise in MS imaging. All scans were performed in the same 3T scanner (Siemens, Skyra). FLAIR and real-IR images were both acquired pre- and post- standard dose gadobutrol (0.1 mmol/kg). Grey matter, white matter, cerebrospinal fluid and white matter lesion (WML) volumes were segmented using Classification using Derivative-based Features (C-DEF), a machine-learning algorithm. We calculated contrast-to-noise ratios (CNR) of 20 LME foci on both modalities. We assessed paramagnetic rim lesions (PRL) at 3T (101 MS cases). Clinical and demographic data were obtained.

Results: Mean age (±SD) was 48 (±12), 98/145 female.The total number of LME foci detected in T2-FLAIR and 3D real-IR were 114 and 428, respectively. Prevalence of LME on CE T2-FLAIR and CE 3D real-IR was 34% and 74%, respectively. 3D-real IR detected all LME foci seen on T2-FLAIR. On a patient level, compared to 3D real-FLAIR, T2-FLAIR has 46% sensitivity and 100% specificity. CNR of LME foci on 3D real-IR and T2-FLAIR were 103±33 and 40±24, respectively. Total number of PRL was correlated with the number of LME foci only by 3D real-IR (ρ=0.32, p=0.001) whereas WML volume was not correlated with LME. In multivariable modeling, the major determinant of LME status was age.
Conclusion: The higher visibility of LME on real-IR and its availability on 3T scanners highlights its promise as a tool to detect and characterize LME in MS.

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P631
Leveraging MRI biomarkers and neurobiological underpinnings of de-/re-myelination for translational drug research

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Introduction: Novel classes of therapeutic approaches for multiple sclerosis (MS) aim at restoring myelination by enhancing oligodendrocyte number and function and reinstating the compact multilamellar organization of myelin as an essential component for insulating, supporting and protecting axons. Magnetic resonance imaging (MRI) has been playing a key role in the diagnosis of MS and monitoring of standard-of-care treatments. However, current MRI modalities have limited specificity and sensitivity to myelin quality with a yet to be established quantitative relationship.
Aim: The goal of the present work is to close these gaps for translational drug research by combining in vivo MRI and histology in the genetically inducible MyRF (myelin regulatory factor) mouse model of de-/re-myelination.
Methods: We performed 3 longitudinal preclinical studies in a total of 50+ MyRF mice, each study covering 7-9 visits of the animals over a period of 20 weeks, representing mechanistically and temporally distinct phases of de-myelination and subsequent partial re-myelination. As indicators of myelination and of confounding processes such as neuroinflammation and gliosis, we consistently tracked translational MRI-derived parameters (T2 relaxation time, magnetization transfer ratio, fractional anisotropy, mean kurtosis) as well as various ex-vivo histological readouts (BlackGold, GFAP, Iba1, CD68) in a subset of the animals.
Results: The MyRF model as such produced significant changes in all readouts, and particularly huge effect sizes in the MRI-derived parameters, with time courses highly reproducible across study cohorts. Multivariate analyses were performed to link MRI and histological readouts obtained from the very same individuals (25+ animals). These analyses revealed that individual MRI parameters were correlated with different yet specific subsets of histological readouts.
Conclusion: The present work is a step forward towards unravelling the microstructural and cellular correlates of pertinent MRI modalities, thus affording a key element in establishing an unprecedented quantitative link between the neurobiological underpinnings of de-/re-myelination, neuroinflammation and MRI-based translational biomarkers.

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P632
Linking cortical demyelination to changes in brain metabolism in multiple sclerosis: a 7T MR spectroscopy study

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Introduction: Multiple Sclerosis (MS) alters brain metabolism, but it is unclear how cortical lesions may affect regional metabolite concentrations.
Objectives: To characterize the metabolite profile of the left and right cortical sensorimotor hand area (SM1-HAND) in patients with MS.
Aims: To test whether regional metabolic changes are associated with local cortical demyelination and pathway specific changes in functional integrity.

Methods: 47 MS patients (34 relapsing-remitting (RR), 13 secondary-progressive (SP)) and 23 healthy controls (HC) underwent single-voxel 7T magnetic resonance spectroscopy (MRS) to characterize the metabolite profile of the left and right SM1-HAND. We also acquired structural 7T MRI to measure white matter and cortical lesion load within the MRS voxel and of the corticospinal tract. 20 HCs, 26 RRMS and 11 SPMS patients also underwent transcranial magnetic stimulation (TMS) to investigate corticospinal excitability and integrity. Statistical analyses were done using mixed linear models corrected for age and sex.
Results: We found a gradual decrease in regional N-acetylaspartate (NAA) concentration from HCs to RRMS ($p=0.003$) to SPMS patients ($p=0.039$). Glutamate concentration was also decreased but only in SPMS patients ($p<0.003$). There were no group differences in myo-inositol or GABA. In MS patients, larger cortical lesion volumes within the MRS voxel were associated with an increase in glutamate ($p=0.009$) and a decrease in GABA ($p=0.012$) concentrations, as well as with an increase in myo-inositol ($p=0.04$) and a decrease in NAA ($p=0.029$). When assessing the total lesion volume of the MRS voxel (i.e. including white matter lesion volume) only NAA and myo-inositol were associated. Lastly, TMS over the SM1-HAND revealed that lower NAA was strongly associated with a decrease in conduction speed of the corticospinal tract ($p<0.001$) and that higher glutamate concentration was associated with an increased resting motor threshold ($p=0.024$).
Conclusions: The neuro-metabolic profile of the SM1-HAND is altered in MS, particularly in patients with SPMS. Our results suggest that local cortical demyelination may alter the excitation-inhibition balance of the affected cortex, and confirm previous findings that the balance between NAA and myo-inositol is affected by MS lesions. Lastly, we showed that these changes were associated with functional measures of corticospinal excitability and integrity.

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P633
Relationship between upper cervical cord atrophy and brain metrics of disease activity in MS

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Introduction: Upper cervical cord (UCC) atrophy measured from brain MRI is commonly used as an imaging biomarker in MS, given its higher availability than cord MRIs. Although it is not as sensitive as the measurements from the entire cervical cord, it seems to correlate well with MS disability metrics. Besides its correlation with disease course, it may also be associated with other imaging metrics of disease activity in MS.
Objectives: Analyze the relationship between UCC volume with common brain metrics of MS disease activity and progression.
Aims: Study associations of UCC volume with 1) whole brain 2) thalamus 3) total brain lesion volumes
Methods: 130 brain MRIs from 89 consecutive patients with MS (63F, 26M) were prospectively enrolled from a single center. A novel automated method was used to evaluate lower brainstem and UCC volumes (medulla, cervicomedullary junction (CMJ), C1, C2): Advanced Normalization Tools nonlinear registration was used to propagate a mask of lower brainstem and UCC regions from the atlas template space to each T1-weighted brain MRI and volumes were calculated as the sum of voxels in the propagated masks, multiplied by the image's voxel volume. Automated measurements from each anatomical level (a-Medulla, a-CMJ, a-C1, a-C2) and total volumes from the medulla to C2 (a-Medulla+UCC) and from CMJ to C2 (a-UCC) were identified. Automated Lesion Quant (Cortechs Labs) was used for brain structure and lesion volume analyses.
Results: There were 72 patients in the relapsing and 17 patients in the progressive phase, reflecting the disease continuum. Age at MRI was 46.0 ± 12.3 years. Individual a-CMJ, a-C1 and a-C2 volumes and total volumes (a-Medulla+UCC and a-UCC) significantly correlated with the whole brain and thalamus volumes ($p<0.05$), but associations of a-Medulla with whole brain (unadjusted $r=0.67$ $p<0.001$; adjusted for age & sex $r=0.59$ $p<0.001$) and thalamus volumes (unadjusted $r=0.53$ $p<0.001$; adjusted for age & sex $r=0.46$ $p<0.001$) were the strongest. No associations were found between total brain lesion volume and lower brainstem or UCC volumes ($p>0.05$).

Conclusion: In addition to whole brain and thalamus volumes, brain imaging is also utilized to investigate UCC atrophy in MS. Although these imaging metrics are usually treated as independent variables, they also appear to interact with each other. Hence, a potential composite metric accounting for these metrics, particularly thalamus and UCC volumes, could serve as a stronger and complementary imaging outcome in MS trials.

Disclosure

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P634

Validation of a semi-automated method to quantify lesion volume changes in multiple sclerosis on 2D proton density-weighted images using subtraction imaging

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Introduction: Detection and quantification of brain white matter lesions is important to monitor treatment effects in patients with multiple sclerosis (MS). Automated methods are needed that provide insight in all changes, both positive activity (new and enlarging lesions) and negative activity (disappearing and shrinking lesions), especially for legacy data from large clinical trials where 3D FLAIR imaging is unavailable.

Objectives: To develop and validate a semi-automated method to quantify lesion volume changes on the basis of proton density (PD)-weighted images and subtraction imaging.

Methods: Yearly brain scans from the REFLEX/REFLEXION studies (NCT00404352/NCT00813709) were used. Two normalized, registered, and intensity matched PD images were subtracted. Within manual lesion masks, lesion change was quantified using a subtraction intensity threshold, and total lesion volume change (TLVC) was calculated. Reproducibility was measured by assessing transitivity, specifically both the intraclass correlation coefficient for absolute agreement (ICC_{trans}) and the difference (Δ_{trans}) between the direct (one-step) and indirect (multi-step) measurement of TLVC between two visits. Accuracy was assessed through both the ICC for absolute agreement (ICC_{acc}) and the difference (Δ_{acc}) between automated and manually measured T2 lesion volume change between two visits. Spearman's correlations (ρ) were used to assess the relation of global and central atrophy, T2 lesion load, and lesion volume change with the method's performance as reflected by the difference measures Δ_{trans} and Δ_{acc}; $p<0.05$ was considered significant.

Results: Reproducibility was excellent, with ICC_{trans} values ranging from 0.900 to 0.968. The accuracy was good to excellent, with ICC_{acc} ranging from 0.671 to 0.925. Faster global and central atrophy had a significant negative impact on performance (Δ_{trans}: ρ=0.19-0.34; Δ_{acc}: ρ=0.16-0.33). Higher T2 lesion load was significantly associated with poorer reproducibility (Δ_{trans}: ρ=0.56-0.62) and accuracy (Δ_{acc}: ρ=0.69-0.70), and higher lesion volume change with poorer reproducibility only (Δ_{trans}: ρ=0.22).

Conclusions: The semi-automated method to quantify lesion volume changes has excellent reproducibility and overall good accuracy. It is therefore a valid semi-automatic method that allows reliable quantitative investigation of lesion volume changes over time in (early) MS for follow-up periods up to 5 years in legacy datasets with PD-weighted images.

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P635

Venular distribution of MS cortical lesions with ultra-high field post-mortem MRI

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Introduction: Cortical lesions (CLs) are prevalent in MS and are associated with disability. In vivo 3 tesla(T) MRI is insensitive to CLs, especially subpial (SP), whereas 7T MRI is more sensitive to CLs. White matter (WM), intracortical (IC) and leukocortical (LC) lesions are thought to develop around central veins (CVs), but subpial (SP) are associated with overlying meningeal inflammation and usually lack a CV on pathology. 7T MRI allows for more comprehensive assessment of the relationship between CLs and vessels, but veins are difficult to visualize within CLs in vivo.

Objective: To compare the sensitivity of in vivo vs postmortem 7T MRI for CLs and to assess the relation of CLs to vascular structures.

Aim: To assess relationship between CLs and veins.
Methods: A 69yo woman with PPMS underwent in vivo 7T MRI (MP2RAGE, T2*-w, 0.5mm isometric) in 2017. In 2021 she died due to systemic infection, autopsy was performed, and the formalin-fixed left hemisphere was scanned at 7T (MP2RAGE, CISS, and T2*w, 0.1-0.5mm in-plane). CLs were manually identified and segmented independently on in vivo (left hemisphere)and postmortem images. CLs were classified as LC (involving cortex and WM, not touching pial surface), IC (cortical only, not touching pial surface), SP (cortical only, touching the pial surface), and SPWM (extending from pial surface to WM). CLs were assessed for a CV on postmortem T2*w images (hypointense dot or line surrounded by hyperintense signal).
Results: 51 CLs (1529 μL) were identified in vivo (16 LC, 1 IC, 17 SP, 5 SPWM) vs 145 (3188 μL) postmortem (42 LC, 22 IC, 55 SP, 16 SPWM). 42% of LC lesions had a CV, compared to 38% of IC lesions, 16% of SP lesions, and 8% of SPWM. 42% of SPWM lesions had a vein that was centrally located within the WM portion of the lesion but did not extend into the cortex.
Discussion: In vivo, many CLs may be undetected even on 7T MRI. In this case, IC and LC lesions were more likely to have a CV than SP lesions, in agreement with prior histopathology results. The presence of a CV only in the WM portion of SPWM lesions suggests that these lesions may begin in the WM, around a WM vein, and then spread through the cortex. Alternatively, as perivascular spaces are continuous with the subarachnoid space, there may be simultaneous inflammation coming from a parenchymal vein and the nearby meninges. Future work will include analysis of venular distribution of CLs in additional cases as well as histological correlation.

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P636
7 tesla magnetic resonance imaging has superior sensitivity for enlarged perivascular spaces compared to 3 tesla in multiple sclerosis

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Introduction: Enlarged perivascular spaces (EPVS) on brain magnetic resonance imaging (MRI) have been associated with neurodegeneration and neuroinflammation. However, the clinical relevance of EPVS is not well understood. In addition, no studies have systematically compared sensitivity of ultra-high-field MRI with conventional MRI field strengths to detect EPVS.
Objectives: To investigate the clinical relevance of EPVS in multiple sclerosis (MS) and to compare the sensitivity of 7 tesla (T) MRI with 3T MRI.
Methods: 64 individuals with MS (45 relapsing remitting, 19 progressive) were included, all with a baseline 7T MRI that included 0.5mm isometric MP2RAGE and a 3T MRI that included 0.7mm isometric MP2RAGE. T1w scans had similar acquisition times of around 10 minutes. 57 patients had at least one follow-up MRI, resulting in 165 total scans (101 patient-years). EPVS were manually segmented on both 7T and 3T MP2RAGE T1w baseline scans.
Results: 7T had superior sensitivity for EPVS compared to 3T, including in the centrum semiovale (median EPVS volume on 7T images [interquartile range, IQR]: 1369 [988] μl vs. 3T: 155 [328] μl, $p < 0.001$, Wilcoxon signed rank rest; EPVS count: 31 [26] vs. 7 [10] EPVS, $p < 0.001$) and in the basal ganglia (median EPVS volume 7T [IQR]: 76 [53] μl vs. 3T: 25 [13] μl, $p < 0.001$; EPVS count: 7 [7] vs. 2 [4] EPVS, $p < 0.001$). In multiple linear regression models, male sex and higher age were associated with higher EPVS volume in the centrum semiovale ($\beta = 466 \pm 188$ μl, $p = 0.02$ and $\beta = 5 \pm 8$ μl, $p = 0.02$, respectively).
Conclusions: 7T T1w MRI scans have a substantially higher sensitivity to detect EPVS compared to 3T T1w MRI scans. Male sex and higher age were associated with higher EPVS burden. Ongoing analyses are assessing the association of EPVS with clinical parameters and the temporal evolution of EPVS in MS at 7T.

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P637
Robust marker for whole brain atrophy from multimodal MRI in MS

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Introduction: Brain atrophy in multiple sclerosis (MS) can be identified as an increase in cerebrospinal fluid (CSF) volume. It

can be directly derived from a brain-free water image (BFWI), a high-resolution heavily T2-weighted image, overcoming processing steps that are prone to errors. However, BFWI is an additional 6-min sequence that would need to be acquired on patients.
Objectives: To develop an algorithm that can derive atrophy markers from routinely acquired MRI scans using deep learning models and compare the results with existing CSF-segmentation techniques.
Methods: CSF-deep learning segmentation (CDS) models were trained and validated on participants clinically diagnosed with MS who underwent routine clinical 3T MRI including a 3D FLAIR (SPACE, TR/TE/TI 4800/352/1800 ms, 1 mmisotropic resolution), 3D T_1-weighted MPRAGE or MP2RAGE (TFL, TR/TE/TI 5000/2.9/700 and 2500 ms, 1 mm isotropic resolution), PD and T_2(dual-echo 2D-FSE, TR/TE=5000/18 and 82 ms, resolution of 0.9x0.9x3 mm) and BFWI (3D SPACE, TR/TE=4800/749 ms, 0.65 mm isotropic resolution) after coregistration using AFNI tools. Images were acquired on 3T (Siemens, Skyra) with a 20- or 32-channel head coil. CSF volumes were compared with those derived from Statistical Parametric Mapping (SPM) and a previously published atlas-free brain Classification using DErivative-based Features (C-DEF) technique.
Results: Images from 92 participants (age 50±12 years, 62 women) were randomly divided into 60 training and 32 testing cases. CDS model had mean AUC, accuracy, and specificity all >0.99, while the sensitivity was 0.8±0.1 with respect to BFWI. Bland-Altman analysis with BFWI mask showed that CSF volume percentage difference was lowest in CDS model (bias: 6.8, 95% CI: [-7.6, 21.22]) followed by CDEF (2.9, [-52.57, 58.28]) and SPM (64.54, [-29.02, 100.1]). All CSF volumes derived herein showed significant correlations ($p<<0.05$) with those derived from BFWI, with CDS being most correlated (slope: 1.14), followed by SPM (slope: 0.93), and CDEF (slope: 0.2). CDS model had a faster inference time of ~10 seconds per subject, compared to ~8 minutes for SPM and~58 minutes for CDEF.
Conclusions: We employed a deep learning-based method for segmentation of whole brain CSF in MS patients, which incorporates skull-stripping and bias correction, providing a window for clinicians and scientists to perform rapid assessment of CSF volume in the clinical practice.

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Imaging and non-imaging biomarkers - OCT

P638
Association of the retinal vasculature and disease course in patients with relapsing remitting multiple sclerosis

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Introduction: Optical coherence tomography angiography (OCT-A) is a novel technique that allows non-invasive assessment of the retinal vasculature. Retinal vessel loss of the superficial vascular complex (SVC) but not the deep vascular complex (DVC) occurs in patients with relapsing remitting multiple sclerosis (RRMS) in eyes with and without a history of optic neuritis (ON).
Objectives: To assess whether retinal vessel densities are associated with future disease course and disability in patients with RRMS.
Aim: To integrate retinal vessel pathology into the clinical management of patients with RRMS.
Methods: Prospective observational cohort study involving patients with clinically isolated syndrome and RRMS from a German academic MS center. All patients underwent clinical examination, retinal OCT-A (Heidelberg Engineering) with evaluation of vessel densities of the SVC and DVC and cerebral magnetic resonance imaging (MRI) at baseline and during annual follow-up visits. We excluded eyes with previous ON from the OCT-A analysis. Cox proportional hazards model adjusted for age, sex and immunotherapy were used to assess the predictive capacity of retinal vessel densities on future disease activity as defined by the no evidence of disease activity (NEDA-3) criteria and disability worsening as measured by the expanded disability status scale (EDSS).
Results: We included 86 patients (58% females) aged 34 years (25%-75% interquartile range [IQR] 26-41) with a median disease duration of 5 (IQR 2-8) months and a median EDSS of 1 (IQR 0-2). The median follow-up duration was 17 (12-24) months. A total of 53/86 presented with ongoing disease activity by failing the NEDA-3 criteria and 9/86 patients suffered from sustained disability worsening. Thinning of the SVC (hazard ratio HR 1.5, 95% confidence interval CI 1.1–2.0 for a 1%-point decrease in vessel density, p=0.01) and the DVC (HR 1.5, 95% CI 1.0–2.3 for a 1%-point decrease in vessel density, p=0.05) were associated with higher hazards for disability worsening. We did not detect an influence of SVC or DVC measures on the NEDA-3 status.
Conclusions: ON-independent retinal vessel loss might add to the prediction of future and early disability worsening in patients with RRMS.

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Christian Mardinserves as medical advisor at Heidelberg Engineering.
Bernhard Hemmer is associated with DIFUTURE (Data Integration for Future Medicine) [BMBF 01ZZ1804[A-I]]. Bernhard Hemmer received funding from theDeutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology [EXC 2145 SyNergy – ID 390857198] and theEuropean Union's Horizon 2020 Research and Innovation Program [grant MultipleMS, EU RIA 733161].He has served on scientific advisory boards for Novartis; he has served as DMSC member for AllergyCare, Sandoz, Polpharma and TG therapeutics; he or his institution have received speaker honoraria from Desitin; his institution received research grants from Regeneron formultiple sclerosisresearch. He holds part of two patents; one for the detection of antibodies against KIR4.1 in a subpopulation of patients withmultiple sclerosisand one for genetic determinants of neutralizing antibodies to interferon. All conflicts are not relevant to the topic of the study.
Benjamin Knier is funded by the Else Kröner-Fresenius-Stiftung (Else Kröner-Fresenius Exzellenzstipendium), the Gemeinnützige Hertie Foundation (medMS program) and received a research award from Novartis (Oppenheim award 2020). He received travel support and a research grant from Novartis.

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Retinal ganglion cell loss is associated with future disability worsening in early relapsing remitting multiple sclerosis

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Background: Atrophy of the combined ganglion cell and inner plexiform layer (GCIP) as measured by optical coherence tomography (OCT) is a frequent finding in patients with multiple sclerosis (MS), both in eyes with and without a history of optic neuritis (ON).
Aim: To integrate retinal OCT into the clinical management of patients with early RRMS.
Objectives: To assess the potential of a single retinal OCT for the prognosis of future disease activity and to evaluate the association of longitudinal OCT measures and disability worsening in patients with newly diagnosed clinical isolated syndrome (CIS) and relapsing-remitting MS (RRMS).
Methods: We included mostly treatment naive patients from two academic MS centers in Germany (Berlin and Munich) with newly diagnosed CIS or RRMS (disease duration maximum 6 months) into a prospective observational cohort study. Follow-up visits involving neurological examination, magnetic resonance imaging and retinal OCT were performed annually. Eyes with previous ON were excluded from the OCT analysis. A multivariable Cox proportional hazards model including age, sex, center, disease duration and disease modifying therapy (DMT) was used to assess the predictive performance of OCT on future disease activity and accumulated disability.
Results: A total of 201 patients with a median disease duration of 2.0 months (interquartile range (IQR) 1.5 – 4.0) and a median follow-up of 59 (IQR 43 – 71) months were enrolled into the study. 82% of patients showed signs of disease activity throughout the observation period by failing the no evidence of disease activity (NEDA-3) criteria and 19% revealed confirmed disability worsening. A GCIP thickness lower than 77 µm at baseline was associated with higher hazards for NEDA-3 failure (hazard ratio HR 1.6 [95% confidence interval (CI) 1.1 - 2.6], p=0.03) and a GCIP thickness lower than 69 µm was linked to an increased risk of disability worsening (HR 2.2 [95% CI 1.2 - 4.3], p=0.01). Furthermore, the extent of annual GCIP loss correlated with the risk of subsequent disability worsening in patients with early MS and CIS (HR 2.5 per 1 µm/year increase of GCIP loss, p=0.03).
Conclusion: Ganglion cell loss as measured by OCT allows for risk stratification of future disease activity in patients with early MS and CIS.

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Alexander U Brandt is cofounder and hold shares of medical technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on multiple patents and patent applications describing retinal image analysis methods, multiple sclerosis serum biomarkers, motor function analysis using 3D pose estimation, and myelinating treatments using modulation of N-glycosylation.
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Bernhard Hemmer has served on scientific advisory boards for Novartis; he has served as DMSC member for AllergyCare, Sandoz, Polpharma and TG therapeutics; he or his institution have received speaker honoraria from Desitin; his institution received research grants from Regeneron formultiple sclerosis-research. He holds part of two patents; one for the detection of antibodies against KIR4.1 in a subpopulation of patients withmultiple sclerosisand one for genetic determinants of neutralizing antibodies to interferon. All conflicts are not relevant to the topic of the study.
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Benjamin Knier is funded by the Else Kröner-Fresenius-Stiftung (Else Kröner-Fresenius Exzellenzstipendium), the Gemeinnützige Hertie Foundation (medMS program) and received a research award from Novartis (Oppenheim award 2020). He received travel support and a research grant from Novartis.

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Vitreomacular interface abnormalities in multiple sclerosis; a novel signature of disability

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Introduction: Optical coherence tomography (OCT) allows high-resolution visualization of the retina, including vitreomacular interface abnormalities (VMIAs), such as epiretinal membranes. Correlations between blood-retinal barrier (BRB) dysfunction and VMIAs exist. Since BRB disruption may occur in multiple sclerosis (MS), elucidating VMIAs' clinical relevance in people with MS (PwMS) is of interest, and remains largely unexplored.
Objectives/Aims: To investigate the clinical (expanded disability status scale [EDSS] and visual function [VF]) measures, and retinal layer thickness differences between PwMS with (VMIA+) and without VMIAs (VMIA-).
Methods: In this cross-sectional study, 1463 PwMS (2926 eyes) underwent Cirrus HD-OCT imaging, with automated macular layer segmentation. VMIA presence was recorded. The VMIA+ and VMIA- groups were age and sex matched. EDSS, VF, and retinal layer thicknesses were analyzed using linear regression. Odds ratios (ORs) were estimated using logistic regression.
Results: VMIAs were found in 95 PwMS (prevalence = 6.5%). The mean age and sex distribution of the VMIA+ (60.2 years, 72% female) and VMIA- (57.5 years, 79% female) cohorts were comparable. VMIA presence was associated with higher EDSS (difference 0.7, CI: 0.1-1.4, p=0.03), with the odds of having an EDSS>4 2.2 times higher in VMIA+, as compared to VMIA- (CI=1.21-4.16, p=0.01) PwMS. Inner nuclear layer (INL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE) thicknesses were -0.98 μm (p=0.05), -2.84 μm(p=0.002) and -0.76 μm(p=0.001) respectively lower in the VMIA+ cohort. VF outcomes were similar between the groups.
Conclusions: Our findings suggest VMIAs may identify an MS phenotype associated with greater disability, that is unrelated to visual dysfunction. Retinal inflammation disrupting BRB may activate Müller glia, potentially explaining why VMIA presence in PwMS may correlate with greater disability. Müller glia, normally located in the INL, and RPE cells may potentially migrate, possibly explaining INL and RPE thickness reductions in PwMS with VMIAs. Furthermore, disrupting the highly susceptible photoreceptors by VMIAs might reduce ONL thickness.

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Using sector-to-channel correlation between mfVEP and OCT to study trans-synaptic degeneration in multiple sclerosis

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Introduction: Neurodegeneration is the main cause of disability accumulation in multiple sclerosis(MS), the neuronal/axonal loss can spread among the central nervous system(CNS) by trans-synaptic degeneration(TSD). Studies reported that lesions in the optic radiation(OR) can result in TSD and cause neuronal loss in the retina, which can be assessed with optical coherence tomography(OCT). The inflammation/demyelination status along the visual pathway can be evaluated with multi-focal visual evoked potential(mfVEP).
Objectives/Aims: To use voxel-based morphometry(VBM) to combine OCT and mfVEP measurements based on their topological relationship with OR, and perform sector-to-channel correlations to investigate TSD longitudinally.
Methods: Baseline and 1-year follow-up of OCT and mfVEP were acquired on thirty-five people with MS(14 with early MS and 21 with newly-confirmed progressive MS). The OCT macula scans were reconstructed by VBM into sectors that topologically correspond to the mfVEP channels. Bilateral channels that originated from the same OR were averaged. Paired t-test was performed between baseline and follow-up and the sector-to-channel correlations were performed on the delta between the time points of the OCT and mfVEP parameters.
Results: Significant differences were found in mfVEP parameters, both increased or decreased at follow-up, while only atrophy was found in OCT. In one channel that showed atrophy of ganglion cell /inner plexiform layer(GCIPL), the atrophy was correlated with increased amplitude at the follow-up. In an adjacent channel, though no significant GCIPL atrophy was found, its thickness was negatively correlated with prolonged latency at the location, Interestingly, retinal ganglion cell layer(RNFL) that possibly projected from this sector(in the adjacent sector follows the direction of fiber projection) was found atrophy.
Conclusion: The correlation between thinner GCIPL and prolonged mfVEP latency could be related to retrograde TSD that originated from OR. The results are further supported by RNFL atrophy in the adjacent sector. On the other hand, the correlation between GCIPL atrophy and increased amplitude could be compensation mechanisms from the CNS. A bigger sample size and longer follow-ups are needed to confirm the current preliminary observation. Sector-to-channel offers opportunities to longitudinally monitor the TSD in CNS, which could be useful for evaluating the efficiency of novel neuroprotective treatments.

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Optic nerve head morphometry in multiple sclerosis using deep learning and geometric modelling

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Background: The optic nerve is one of the most prominent disease activity sites in multiple sclerosis (MS) with and without optic neuritis (ON). Optical coherence tomography (OCT) derived retinal layer thickness measures have been widely used to identify neuroaxonal tissue damage of optic nerve and retina in MS. However, the optic nerve head (ONH) shape has been difficult to assess due to its complex anatomy.
Objectives: To improve the diagnostic utility of OCT in MS.
Aims: To develop and investigate biomarkers derived from deep learning-based ONH segmentation combined with geometric modelling.
Methods: We trained a convolutional neural network on quality-controlled scans with reference segmentation produced by a previously developed method using active contours. The inner limiting membrane, Bruch's membrane, and Bruch's membrane opening (BMO) points were used as boundaries to then define a geometric model of the ONH and extract several parameters to describe the ONH shape. 3D ONH OCT volumetric images of 188 eyes of 95 MS patients (107 eyes without a history of ON (MS-NON) and 81 eyes with a history of ON (MS-ON)) and 110 eyes of 58 healthy controls (HC) were included to investigate the method performance in MS.
Results: From 17 parameters describing the ONH morphometry, 6 were significantly different between HC and MS-NON (p-value (p) (estimate (B))=Total Volume:0.021(0.11), Annular Volume:<0.001(0.13), EBMO Disk Area:0.002(-0.21), BMO Disk Area:0.002(-0.21), ILM Annular Area:0.002(0.21), ILM Annular Thickness:0.033(0.012)), 5 were significantly different between HC and MS-ON (p(B)=BMO-MRW Distance:<0.001(0.043), Total Volume:<0.001(0.22), Annular Volume:<0.001(0.20), BMO-MRW Area:0.023(0.15), ILM Annular Thickness:<0.001(0.032)), and 14 were significantly different between MS-NON and MS-ON (p(B)=BMO-MRW Distance:<0.001(0.02), BMO Volume:<0.001(0.054), Total Volume:<0.001(0.12), Annular Volume:0.006(0.065), BMO-MRW Area:<0.001(0.13), EBMO Disk Area:0.027(0.084), BMO Disk Area:0.041(0.076), ILM Annular Area:0.030(-0.082), ILM Annular Thickness:<0.001(0.018), BMO ILM Area:0.022(0.084), Cup to Disk Ratio:0.034(-0.026), Major-Minor Cup to Disk Area:0.044(-0.024), Annular Volume BMO Volume Ratio:0.008(-0.33), Total Volume BMO Volume Ratio:0.009(-0.36)).
Conclusions: ONH morphometry shows differences between MS eyes with and without prior ON and compared to HC. These results suggest that ONH morphometry may be a promising biomarker warranting further investigation.

Disclosure
S. Motamedi is named as inventor on a patent application titled "System and Method for Optic Nerve Head Shape Analysis".
J. Kauer-Bonin is an employee of Nocturne GmbH.
S. Yadav is co-founder and shareholder and was an employee of Nocturne GmbH and is named as inventor on a patent application titled "System and Method for Optic Nerve Head Shape Analysis".
E.M. Kadas is co-founder, employee, and shareholder of Nocturne GmbH, and is named as inventor on a patent application titled "System and Method for Optic Nerve Head Shape Analysis".
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F. Pau; is a cofounder and holds shares in technology start-up Nocturne GmbH, which has commercial interest in OCT applications in neurology; served on the scientific advisory boards of Novartis and MedImmune; received travel funding and/or speaker honoraria from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; is an associate editor of Neurology: Neuroimmunology & Neuroinflammation; is an academic editor of PLoS ONE; consulted for Sanofi Genzyme, Biogen, MedImmune, Shire, and Alexion; received research support from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Geynzme, Alexion, and Merck Serono; and received research support from the German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy-Jackson Charitable Foundation, and NMSS.
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A.U. Brandt is named as inventor on a patent application titled "System and Method for Optic Nerve Head Shape Analysis" and several other patents and patent applications describing methods for retinal image analyses, motor function analysis, multiple sclerosis serum biomarkers and myelination therapies utilizing N-glycosylation modification, is cofounder and holds shares of medical technology companies Motognosis GmbH and Nocturne GmbH, and is cofounder, member of the board and currently elected Secretary/Treasurer of IMSVISUAL.

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Optical coherence tomography angiography for differential diagnosis of multiple sclerosis and Sjögren's syndrome

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Background: Optical coherence tomography angiography (OCT-A) is a novel technique allowing non-invasive evaluation of the retinal vasculature. Retinal vessel loss of the superficial vascular complex (SVC) but not the deep vascular complex (DVC) occurs in patients with relapsing remitting multiple sclerosis (RRMS) in eyes with and without a history of optic neuritis (ON).
Aim: To test the capacity of retinal OCT-A for differential diagnosis of RRMS and related autoimmune disease that may affect the central nervous system (CNS).
Objective: To assess alterations of the retinal vasculature in patients with RRMS, primary Sjögren's syndrome (pSS), that may present as RRMS-mimic, and healthy controls (HC) and to search for associations with the visual functions and soluble markers for tissue damage.
Methods: Cross-sectional study involving patients with pSS, RRMS and HC. All patients underwent clinical examination, assessment of the low (LCVA 2.5%) and high (HCVA 100%) contrast visual acuity, retinal OCT, OCT-A and serum levels of the neurofilament light chain (NfL). Eyes with a history of ON, subclinical ON, substantial eye disease or failed quality control were excluded from the analysis.
Results: We included 36 patients with pSS, 36 patients with RRMS and 30 HCs with comparable sex ratios and ages. We recognized a thinning of the combined ganglion cell and inner plexiform layer (GCIP) in eyes from patients with RRMS (p=0.03) but not pSS (p=0.74) as compared to HC (median volumes RRMS 1.9 mm^3 [25%-75% interquartile range 1.8-2.0], pSS 2.0 mm^3 [1.9-2.1], HC 2.0 mm^3 [1.9-2.1], analysis of variance ANOVA p=0.03). Retinal vessel densities of the SVC were reduced in RRMS (p=0.03) and by trend in pSS (p=0.06) as compared to HC (median vessel density RRMS 25.2 % [23.6-26.8], pSS 25.4 % [23.2-26.9], HC 27.0 % [24.7-27.6], ANOVA p=0.02). Retinal vessel loss of the DVC was evident in patients with pSS (p=0.03) but not RRMS (p=0.27) as compared to HC (RRMS 25.6 % [24.0-26.0], pSS 24.9 % [23.4-26.3], HC 25.8 % [24.7-26.9], ANOVA p=0.03). There were no differences in NfL levels. Applying multivariate regression analysis corrected for age and sex, DVC vessel loss in pSS was associated with worse visual acuity (HCVA p=0.05; LCVA p=0.002).
Conclusions: Disease-specific phenotypes of the retinal architecture and vasculature might be evident during RRMS and pSS. OCT and OCT-A might be helpful for differential diagnosis of suspected autoimmune disease of the CNS.

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Achim Berthele has received consulting and/or speaker fees from Alexion, Bayer Healthcare, Biogen, Celgene, Novartis, Roche and Sandoz/Hexal, his institution has received compensation for clinical trials from Alexion, Biogen, Merck, Novartis, Roche, and Sanofi Genzyme; all outside the submitted work.
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Longitudinal retinal vessel loss indicates progressive grey matter atrophy in patients with relapsing remitting multiple sclerosis

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Background: Optical coherence tomography angiography (OCT-A) is a novel technique that allows high-resolution assessment of the retinal vasculature. Retinal vessel loss of the superficial (SVC)

but not the deep vascular complex (DVC) occurs in patients with relapsing remitting multiple sclerosis (RRMS) in eyes with and without a history of optic neuritis (ON).

Aim: To integrate retinal vessel pathology into the pathophysiological concept of RRMS.

Objectives: To search for associations between longitudinal alterations of the retinal vasculature, disability and brain atrophy in patients with RRMS.

Methods: Prospective longitudinal cohort study including patients with RRMS. All patients underwent clinical examination including assessment of the expanded disability status scale (EDSS), retinal structure OCT, OCT-A (Heidelberg Engineering Spectralis) and cerebral MRI at baseline and during annual follow-up visits over up to 24 months. OCT-A segmentation was performed after thorough quality control and vessel densities of the SVC and DVC were calculated. Eyes with a history of former ON, suspected subclinical ON or retinal disease were excluded. We extracted MRI volumina of the grey and white matter, cortical thickness, lesion volume and count. Annual changes of OCT, OCT-A, MRI measures and EDSS values were calculated and multivariate linear regression models corrected for age, sex, disease duration and disease modifying therapies were applied.

Results: We included 79 patients with RRMS (53 females), aged 38 years (median, 25-75% interquartile range [IQR] 32-47), a disease duration of 12 months (IQR 2-49) and a median EDSS of 1 (IQR 0-2). As expected, longitudinal loss of the retinal ganglion cell and inner plexiform layer (GCIP) was associated with grey matter atrophy (β=0.02, 95% confidence interval [CI] 0.01-0.04, p=0.01). Moreover, longitudinal SVC vessel loss was linked to both grey matter loss (β=0.05, 95% CI 0.02-0.09, p=0.005) and white matter loss (β=0.10, 95% CI 0.01-0.19, p=0.04). Surprisingly, longitudinal DVC vessel loss was associated with progressive grey matter loss (β=0.05, 95% CI 0.02-0.09, p=0.006). The association of both longitudinal SVC and DVC vessel loss with grey matter atrophy remained robust when additionally correcting for GCIP loss.

Conclusions: ON-independent longitudinal vessel loss of the SVC and DVC might be linked to brain atrophy in patients with RRMS over time. OCT-A might be a novel tool to evaluate neurodegeneration in RRMS.

Disclosure

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CM serves as medical advisor at Heidelberg Engineering.

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CZ has served on scientific advisory boards for Philips and Bayer Schering; serves as co-editor on the Advisory Board of Clinical Neuroradiology; has received speaker honoraria from Bayer-Schering and Philips and has received research support and investigator fees for clinical studies from Biogen Idec, Quintiles, MSD Sharp & Dome, Boehringer Ingelheim, Inventive Health Clinical UK Ltd., Advance Cor, Brainsgate, Pfizer, Bayer-Schering, Novartis, Roche, Servier, Penumbra, WCT GmbH, Syngis, SSS Internartional Clinical Research, PPD Germany GmbH, Worldwide Clinical Trials Ltd., Phenox, Covidien, Actelion, Medivation, Medtronic, Harrison Clinical Research, Concentric, Penumbra, Pharmtrace, Reverse Medical Corp., Premier Research Germany Ltd., Surpass Medical Ltd. and GlaxoSmithKline.

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Optical coherence tomography is associated with cognitive and physical disability independently of other biomarkers

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Objective: We aimed at evaluating the relative role of Optical coherence tomography (OCT) next to serum neurofilament light chain (sNfL) and magnetic resonance imaging (MRI), for assessing cognitive and physical disability in multiple sclerosis (MS).

Methods: Cross-sectional study with 100 MS patients (63 female, age: 50.4±11.5 years(y); disease duration: 18.7± 9.8y; education: 14.1±3.3y, 80% with relapsing remitting MS) and 52 matched healthy controls (HC; 34 female, age: 51.4±13.7y; education: 16.0±3.3y). All subjects underwent an OCT to assess the mean peripapillary retinal nerve fiber layer (pRNFL) thickness, and the volume of the ganglion cell-inner plexiform- (GCIPL) and inner nuclear layers (INL). For patients with prior optic neuritis, we included only the non-affected eye and for the rest, we took the average OCT measures of both eyes. Brief International Cognitive Assessment for Multiple Sclerosis and the Expanded Disability Status Scale (EDSS) were used to quantifycognitive and physical disability. sNfl levels were measured and T2 lesion volume (T2LV) and brain parenchymal fraction (BPF) were assessed on MRI, using GruSEG and FreeSurfer respectively.

Results: Compared to HC, patients had lower mean pRNFL thickness ($p < 0.001$) and GCIPL volume ($p < 0.001$), but INL volume did not differ ($p = 0.093$).

After correction for age, vision and education, pRNFL thickness was associated with the symbol digit modalities test (SDMT) in patients ($\beta = 0.2$, $p = 0.030$). In a multivariate analysis including sNfL, BPF and T2LV, pRNFL ($\beta = 0.19$, $p = 0.044$) and T2LV ($\beta = -0.24$, $p = 0.023$) were the only predictors that remained associated with the SDMT.

Mean pRNFL thickness and GCIPL volume showed associations with EDSS ($\beta = -0.37$, $p < 0.001$ and $\beta = -0.46$, $p < 0.001$). In a multivariate analysis including sNfL, BPF, and T2LV, GCIPL volume was the strongest predictor of the EDSS ($\beta = -0.32$, $p < 0.001$), followed by sNfL ($\beta = 0.18$, $p = 0.024$).

Conclusions: OCT measures, as markers of neuroaxonal loss, are associated with cognitive and physical disability in MS patients independently of serum- (sNfL) and MRI- (BPF, T2LV) markers. Furthermore, GCIPL was the strongest predictor of physical disability. With the advantage of being a quick, patient-friendly examination, needing only minimal post-processing, OCT can play a major role in the stratification of MS patients at risk of higher cognitive and physical disability.

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NCF has nothing to disclose.

MS has nothing to disclose

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Correlation of optic coherence tomography and angiography with cognitive functions in multiple sclerosis

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Introduction: Optical coherence tomography (OCT) and OCT-angiography are non-invasive techniques used to assess retinal structures and blood flow. Retinal nerve fiber length(RNFL) and Ganglion Cell Inner Plexiform Layer(GNIPL) thickness are affected in multiple sclerosis (MS) patients even if there is no optic neuritis (ON) history. Because the optic nerve is an anatomical extension of the brain and overall brain volume correlates with disability accumulation, and cortical thickness correlates with cognition in MS, the pathological process could also affect retinal layers.
Aims: This study investigates retinal nerve fiber thickness and retinal capillary blood flow in relation to cognitive functions.
Methods: OCT and OCT-angiography were performed only on eyes without ON history. For patients with both eyes unaffected (ON-) mean value of both eyes was used as a single data; the other group comprised data from unaffected eyes of patients with ON history only in one eye (ON+). Thicknesses of GCIPL and RNFL were calculated in superior(S), inferior(I), temporal(T), and nasal(N) quadrants(q). Cognitive performance was assessed using Brief International Cognitive Assessment in Multiple Sclerosis tool (*SDMT*; Symbol Digit Modalities Test;*CVLT*-II; California Verbal Learning Test second edition;*BVMT-R*; Brief Visuospatial Memory Test-Revised).
Results: 238 eyes from 119 patients were evaluated. 38 (31,9%) patients had a history of optic neuritis. In the ON(+) group, there was a positive correlation with SDMT and ITq of RNFLand with all quadrants of GCIPL($p<0,05$). CVLT-II and BVMT-R also showed a positive correlation with Sq and Tq of GCIPL ($p<0,05$). In the ON(-) group, there was no correlation between SDMT and CVLT with RNFL and GCIPL thickness. BVMT-R results showed a negative correlation with RNFL in S and IT, IN quadrants, and GCIPL in all quadrants ($p<0,05$). There was no correlation between OCTA and cognitive parameters.
Conclusions: No clear associations between cognitive functions and OCT results and the history of ON were found. OCT results and cognitive functions should be interpreted in conjunction with brain and cortical atrophy.

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Hemi-macular atrophy in multiple sclerosis: a potential representation of trans-synaptic neurodegeneration extending beyond the inner retina

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Introduction: Trans-synaptic degeneration (TSD) is a putative mechanism of neuronal injury in multiple sclerosis (MS). Retrograde TSD following pathology of the posterior visual pathway has been implicated as a cause of homonymous hemi-macular atrophy (HMA) of the ganglion cell/inner plexiform layer (GCIPL). HMA is recognizable on optical coherence tomography (OCT) images, and its study in MS could give insight into disease-related TSD.
Objectives/Aims: To explore the prevalence of HMA in people with MS (PwMS), and whether it is associated with differences in retinal layer thicknesses and disability measures.
Methods: In this cross-sectional study, 241 healthy controls (HCs) and 1130 PwMS underwent Cirrus HD-OCT, with automated macular layer segmentation. To facilitate the identification of HMA in PwMS, we used a normalized asymmetry ratio (NAR) for each eye, defined as the temporo-nasal GCIPL difference divided by the thicker side's hemi-macular GCIPL thickness. Extreme NAR in PwMS was $<1^{st}$ or $>99^{th}$ percentile for NAR in HCs. PwMS with HMA (HMA-PwMS) were defined as having extreme NAR in both eyes, or in the eye without optic neuritis (ON) history (non-ON) in the case of known unilateral ON in the

fellow eye. HMA-PwMS were matched to non-HMA-PwMS 1:2 according to age, sex, and race using propensity score matching. Linear regression models were used in analyses.
Results: 79 PwMS (143 eyes) had HMA (prevalence 6.9%). The HMA-PwMS had a mean age of 50.1 years (SD 12.4 years), 72.2% were female, and 31.6% had progressive MS. Compared to matched non-HMA-PwMS, HMA-PwMS had lower GCIPL (diff: -5.7 μm [95%CI -7.6 to -3.8]; p<0.001), inner nuclear layer (INL) (diff: -0.9 μm [95%CI -1.6 to -0.1]; p=0.02), and outer nuclear layer (ONL) (-1.9 μm [95%CI -3.4 to -0.4]; p=0.02) thicknesses. HMA-PwMS also had higher expanded disability status scales (EDSS) scores compared to non-HMA-PwMS (diff: 0.5 [95%CI 0.1 to 0.9]; p=0.02).
Conclusions: We found that HMA-PwMS exhibit thinner inner and outer retinal layers and higher EDSS scores than non-HMA-PwMS. HMA may identify PwMS in whom TSD is an additional mechanism of neurodegeneration and warrants further exploration.

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Imaging and non-imaging biomarkers - Fluid Biomarkers

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Cerebrospinal fluid analysis in a paediatric cohort of patients with MOG antibody – associated disorders

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Introduction: Myelin oligodendrocyte glycoprotein antibody-associated disorders (MOGAD) are a broadening spectrum of acquired demyelinating diseases with a higher incidence in paediatric compared to adult patients. Present recommendations for the detection of MOG-antibodies indicate serum or plasma as the specimen of choice, while the relevance of cerebrospinal fluid (CSF) for MOG-Abs testing is not established.
Objectives and aims: The aim of this study is to analyse the clinical relevance of MOG-Abs in CSF in a cohort of paediatric patients with acute demyelinating diseases by comparison with control patients.
Methods: Thirty-seven paediatric patients with MOGAD have been enrolled from the French national reference centre for rare neuro-immune diseases. Thirteen paediatric patients with multiple sclerosis (MS) and 11 paediatric patients with other neurological disorders (OND) were included as controls. The 61 participants have been tested for MOG-Abs in serum and CSF with live cell-based assays (CBA) technique.
Results: MOG-Abs were detected in the serum of all MOGAD patients, while the test for MOG-Abs in serum and in CSF was negative for the totality of MS and OND patients. According to the presence of MOG-Abs in CSF, MOGAD patients were divided into a *single positive*-group (for which MOG-Abs were only detected in serum) and a *double positive*-group (for which MOG-Abs were detected in serum and CSF). No significant differences were found in age at disease onset, sex, MRI findings at onset, EDSS score at onset and at last follow-up between the two groups. Although not statistically significant, in the *double positive*-group we found a trend of higher presentation at onset as transverse myelitis as well as a higher tendence to a relapsing disease course compared to the *single positive*-group. A trend of higher delta median fluorescence intensity (MFI) ratio (delta MFI of MOG-Abs in LCR/delta MFI of MOG-Abs in serum) in the MOGAD relapsing compared to MOGAD non-relapsing patients has also been detected. The protein levels in CSF were significantly higher in the *double positive* compared to the*single positive*-group (p<0.05).
Conclusions: *Double-positive* patients present higher inflammatory CSF with a more often relapsing disease course. These findings need to be confirmed in a wider cohort.

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Liquid biopsy: miRNAs signatures in multiple sclerosis patients

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Background: One of the most recent and evolving approaches to characterize early-stage biomarkers is liquid biopsy. It implies collection and analysis of non-solid biological tissues, without the need to undergo the invasive procedure for disease prognosis. A liquid biopsy can be used for screening of cell free (CF)-DNA and exosomes derived from specific cell/tissue type. Liquid biopsy studies in multiple sclerosis (MS) are scarce.
Objectives: To identify liquid biopsy markers that can be used for better diagnosis and clinical classification in MS patients.
Methods: Thirty-one untreated MS patients and nine healthy controls (HC) were included in the study. The MS group comprised 11 patients with relapsing-remitting multiple sclerosis (RRMS) [eight females / three males; mean age (standard deviation): 43.5 (10.4) years], 11 secondary-progressive multiple sclerosis (SPMS) [eight females / three males; mean age (standard deviation): 46.6 (7.4) years], 9 primary-progressive multiple sclerosis (PPMS) [six females / three males; mean age (standard deviation): 44.1 (9.1) years]. Total exosomes were isolated from serum samples using the *Total Exosome Isolation Kit*, subsequently total miRNA was isolated from exosome by using Total Exosome RNA & Protein Isolation kit. Isolated miRNAs were used for performing miRNA 4.1 microarrays profiling.
Results: Five significantly differentially expressed miRNA between controls and RRMS were selected from the discovery cohort: *hsa-mir-3944*(p=0.0004), *hsa-mir-3194* (p=0.0006), *hsa-mir-4745* (p=0.001), *hsa-mir-5006* (p=0.001) and *hsa-mir-4655* (p=0.001). The expression of the following five miRNA was significantly increased in SPMS patients as compared to HCs: *hsa-mir-6893* (p=0.003), *hsa-mir-7844* (p=0.004), *hsa-mir-3613* (p=0.005), *hsa-mir-1183* (p=0.005) and *hsa-mir-4481* (p=0.005). Interestingly, only one miRNA, *hsa-mir-320d-1* (p=0.01), showed augmented expression in PPMS patients as compared to HC.
Conclusions: Preliminary findings support a role for differentially expressed miRNA to discriminate between different clinical forms of MS and HC. Validation of selected miRNAs and analysis of CF-DNA methylation patterns are currently underway. By comparing the CF-DNA (serum) methylation pattern with a reference methylome atlas available (for cell types and tissue) will allow us to inference of cell type specific origin.

Disclosure

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X Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS".
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Serum neurofilament light chain levels at disease onset and high efficacy treatments to predict disability progression among patients with a CIS

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Introduction: Serum neurofilament light chain (sNfL) is a promising biomarker to predict future disease activity and treatment response in multiple sclerosis (MS). Associations with disability outcomes are less conclusive. Unmet needs for sNfL for clinical practice are a reliable cut-off and to determine the optimal time of analysis. Besides, interaction of sNfL, high-efficacy disease-modifying treatments (HE-DMTs) and future disability has been poorly investigated.
Objectives: To assess the prognostic value of sNfL to predict the risk of 6-month confirmed disability progression (CDP) and reaching an Expanded Disability Status Scale (EDSS) of 3, and the subsequent annualized relapse rate (ARR). We also explored the effect of HE-DMTs to change the course of the disease.
Methods: Observational study performed at Hospital Universitario Ramón y Cajal referral MS centre. All patients with a clinically isolated syndrome (CIS) with available blood samples within 12 months from disease onset were included. sNfL were analyzed with SIngle MOlecule Array (SIMOA®). Univariable and multivariable Cox regression models were used to estimate outcomes.
Results: Three hundred and twenty-nine patients were included, 229 (69%) women with a median (IQR) age at baseline of 34.2 (27.3–42.7) years and a median (IQR) time of follow-up of 5.44 (3.00–8.95) years. sNfL >10 pg/ml were associated with a higher risk of 6-month CDP (adjusted-HR of 3.53, 95% CI 1.91–6.54, $p<0.001$) and reaching an EDSS of 3 (aHR of 6.10, 95% CI 3.00–12.4, $p<0.001$). Analyses restricted to subjects with sNfL obtained more than 60 days since a relapse showed even higher risks of

6-month CDP (aHR of 4.57, 95% CI 1.93–10.8, p = 0.001) and EDSS of 3 (aHR of 7.10, 95% CI 2.66–18.9, p<0.001). sNfL standardized score >1.5 (calculated from a healthy normative dataset) provided also increased risks, though to a lower level. Whenever a HE-DMT was started, detrimental outcomes were counteracted, with similar risks of 6-month CDP and EDSS of 3 among patients with both high and low levels. ARR did not differ between patients with high and low levels until end of follow-up. When censoring until start of HE-DMTs, ARR was significantly higher among patients with high than low levels of sNfL (p=0.03), and markedly decreased afterwards in both cohorts (p<0.001).

Conclusions: sNfL obtained within first year of disease can accurately predict disability progression and future clinical activity. Patients with high levels are optimal candidates to receive HE-DMTs early during the disease.

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Multivariate proteomic analysis and the relationship with axonal pathology in multiple sclerosis: a longitudinal 5-year diffusion tensor imaging study

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Background: In addition to conventional and non-conventional MRI outcomes, there is an increase interest in use of serum-derived biomarkers. These biomarkers can be easily and cheaply obtained through frequent blood draw. Therefore, development of a comprehensive proteomic assay with good prognostic and treatment-responsive properties may significantly improve the extent to which persons with multiple sclerosis (pwMS) are routinely monitored.

Objective: To determine the predictivity of a multivariate proteomic assay for concurrent and future microstructural axonal brain pathology in a heterogeneous group of pwMS.

Methods: A proteomic analysis was performed on serum samples from 202 pwMS (148 relapsing-remitting MS and 54 progressive MS) at the baseline and 5-year follow-up. Concentration of 21 proteins that are related to several pathways of MS pathophysiology were derived. The extent of microstructural axonal brain pathology was quantified by a 3T MRI-based diffusion tensor imaging (DTI). Fractional anisotropy (FA) and mean diffusivity (MD) of normal-appearing brain tissue (NABT), normal-appearing white matter (NAWM), gray matter (GM), and T2 and T1 lesions were calculated. Age, sex and body-mass index (BMI)-adjusted step-wise regression models were used.

Results: Higher glial fibrillary acidic protein (GFAP) was associated with development of future disability progression (p=0.004). GFAP was the most common and highest ranked proteomic biomarker associated with greater concurrent microstructural CNS damage (p<0.001). Moreover, higher baseline GFAP levels were significant predictors of future wide-spread microstructural damage as measured by NABT FA or MD (p<0.001), NAWM FA (p<0.0012), GM MD (p<0.011) and T2 lesions MD (p<0.001) at the 5-year follow-up. Serum levels of MOG, NfL, contactin-2 and ostepontin proteins were additionally and independently associated with worse concomitant and future axonal pathology.

Conclusions: Multiple proteomic biomarkers are independently associated with greater axonal brain pathology and superior predictive ability when compared to single serum-based measure. Serum GFAP levels are predictive of future disability progression and axonal pathology.

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Machine learning identifies a combination of immunological and clinical parameters as the best predictor of MS disease progression

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Background: Multiple Sclerosis (MS) is thought to be initiated by pathogenic T effector cells (Teff, $CD4^+$ and $CD8^+$) migrating into the central nervous system (CNS). Regulatory T cells (Treg) are a key component of immune tolerance and protect against autoimmune disease. Teff and Treg use cellular adhesion molecules (CAMs) and chemokine receptors (CCR) to migrate towards and into the CNS. Currently, there are no good predictors of MS disease progression. This study sought to investigate whether the CAM and CCR signature on Teff and Treg, combined with clinical information, can predict MS progression.

Objectives & Aims: Unravel the mechanisms by which Teff and Treg cross the BBB into CNS and investigate whether this migratory signature in combination with clinical data can predict disease progression.

Methods: The expression of cellular adhesion molecules LFA-1, VLA-4, ALCAM, CD6, MCAM, P-selectin, L-selectin and αvβ3 has been studied on Teff and Treg present in the peripheral blood of MS patients (N=141; RRMS, CIS, SPMS, PPMS) and healthy controls (N=43; HC) using FACS. Furthermore, the expression of chemokine receptors CCR2, CCR3, CCR5, CCR6, CXCR4 and CX3CR1 and Treg functional markers ST2L, PSGL-1, CD147 have also been investigated. Subsequently these data have been correlated with patient data (retrospective and prospective clinical parameters reflective of MS disease course e.g. EDSS, MRI lesion load, annual relapse rate, 3-5 year follow up). Using classical, supervised machine learning (ML)(Random Forrest), we investigated which immune, clinical, and MRI parameters contribute to disease progression.

Results: VLA-4, MCAM, CD6, ST2L, PSGL-1, CCR3, CCR6, and CXCR4 are differentially regulated in MS patients compared to healthy control individuals. Treg expression of CCR5 and CCR6 seems to be linked to progressive MS disease types. We identified two clinical (sex and presence of pyramidal lesions) and two immune parameters ($CD8^+CD6^+$ and $TregST2L^+$ cell populations) as strong predictors of disease progression. The robustness of the prediction algorithm was improved when clinical and immune models were combined.

Conclusions: The migratory signature of Treg and Teff is different in MS patients compared to healthy individuals, and within MS subtypes, which may have an effect on disease progression. The preliminary ML findings support our hypotheses that a combination of clinical and immunological data builds the best prediction model for disease progression.

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Blood serum proteome correlates of multiple sclerosis disease progression as evaluated by clinical and brain atrophy outcomes: a 5-year longitudinal study

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Background: Multiple sclerosis (MS) patients progress through a complex, heterogeneous disease course spanning decades, currently evaluated in a mostly qualitative way. Quantitative measurement of disease progression (DP) in the serum proteome would greatly enhance the care for MS patients.
Objectives: To quantify proteome correlates of DP in two ways: evolution of disability progression, and development of brain atrophy.
Methods: We examined blood serum samples from 143 MS patients at baseline and five-year follow. An additional 59 patients had baseline samples only, for a total of 202 patients. Multiple clinical and imaging data were collected for each patient, including Expanded Disability Status Score (EDSS), clinical assessments, and MRI brain volumetry. Serum samples were analyzed on a custom assay panel, measuring concentrations of 20 proteins associated with MS disease activity (DA) and DP in previous studies. A DP status for each patient was obtained from EDSS changes using a standardized definition for MS clinical trials. We also used MRI volumetric measurements to assess brain atrophy. The association between each protein and endpoint was investigated in 3 ways: protein concentrations at baseline (predictive), protein concentrations at follow-up (descriptive), and the change in protein concentrations (shifts) to infer progression endpoints.
Results: 3 proteins showed significant univariate association (independent t-test) with EDSS DP: GFAP (t=2.1, p=1.9e-2, predictive; t=1.7, p=5.0e-2, descriptive), BAFF (t=1.7, p=4.3e-2, descriptive; t=2.0, p=2.3e-2, shift), and IL-12B (t=1.9, p=2.7e-2, shift). Significant univariate associations between GFAP and CXCL13 and changes in brain structure volumes (after Bonferroni correction for both multiple proteins and endpoints) were found, including: whole brain, gray matter and lateral ventricles. Multivariate methods also were used to model DP in both endpoints. Impacts of DP were seen in the serum proteome from both strategies.
Conclusions: Measurable effects of MS DP clinical and brain atrophy outcomes can be detected in the serum proteome. Extensions to this study will include: additional progression endpoints at 5 years (e.g. optical coherence tomography, neuropsychological assessments), and assessment of previously validated DA and pathway scores relative to inflammatory lesion counts. These results will broaden our understanding of DP correlates through the peripheral proteome.

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Clinical phenotypes from blood serum protein concentration

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Background: Novel techniques for measurement of disease activity (DA) and progression (DP) through serum proteomics can improve the management of multiple sclerosis (MS). A multivariate proteomic MS DA test using 18 biomarkers has been analytically and clinically validated. Due to the complexity of treatment and heterogeneity in the biological pathways contributing to MS pathophysiology, identifying distinct clusters of biomarker profiles can enable proteomic-based MS subtyping and support clinical interpretability of MSDA test results.
Objectives: To identify distinct clinical phenotypes in MS patients as defined by unsupervised clustering of serum protein concentration samples. We aim to measure differences in clinical variables of interest, such as DMT, MSDA score level, and disease duration, across cluster groups.
Methods: A total of 222 patient samples from a matched serum-MRI study from Rocky Mountain Multiple Sclerosis Clinic were assayed in the MSDA test to generate DA and biological pathway scores reflecting DA status. We used unsupervised clustering techniques to identify groups of protein profiles to identify clinical phenotypes associated with over or under-expression of 18 different proteins. We examined MS DA/pathway score distributions relative to key clinical variables across clusters.
Results: We found six clusters with significant deviations from population median levels across them in DA score. Additionally, we see differences in: DMT, age, and disease duration between

clusters. Associations between these phenotypes and individual age/sex corrected protein concentrations up or down-regulated in each cluster were established with ANOVA (continuous variables) or χ^2 test (categorical variables). Statistically significant differences across clusters were demonstrated in: DA score (p=2.2e-3), DA score category (p=1.6e-3), BMI (p=7.8e-6), disease duration (p=3.7e-2), sex (p=1.7e-2).

Conclusions: We find evidence for six pheno-clusters in protein concentration data which map into differences in DA/pathway scores, as well as several clinical variables. These pheno-clusters will be further evaluated in a cohort of >500 patients analyzed in a real-world setting. These clusters will serve as the kernel of patient profiles for further exploration of variables of interest including: DA/Pathway score distributions in clinically stable vs. active patients, the impact of duration of DMT, and for comparisons of DMTs with diverse mechanisms of action.

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Plasma sphingolipid as an adjunct biomarker in patients with neuromyelitis optica spectrum disorder

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Introduction: Sphingolipids are major components of neuronal membrane and myelin sheath, also function as cell signaling molecules.

Objectives: In this study, we aimed to investigate plasma sphingolipids as biomarkers for neuromyelitis optica spectrum disorder (NMOSD) and compare its clinical value with that of neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP), which are currently known biomarkers for NMOSD.

Methods: We recruited consecutive anti-aquaporin-4-antibody (AQP4-Ab) seropositive NMOSD patients who visited Asan Medical Center between June 2018 and April 2020. Patients were simultaneously enrolled and sampled when they visited the hospital. We measured plasma ceramides (Cer), sphingosine (SO), sphingomyelins (SM), hexosylceramides (HexCer), lactosylceramides (LacCer), and gangliosides (GD3 and GM3) with liquid chromatography-tandem mass spectrometry. We also measured serum NfL, and GFAP with ultrasensitive single-molecule array assays. Partial least square discriminant analysis was performed to identify biomarkers for differentiating NMOSD from controls and for subgroups based on disease disability (expanded disability status scale [EDSS]), and activity (attack within 2 months).

Results: The mean age of the patients with NMOSD (n = 81) was 52 years, 73 (90.1%) patients were female, and mean EDSS score was 3.7. We identified C24_Cer for differentiating NMOSD from controls and C14_Cer, C16_Cer, and C24:1_Cer for classifying patients with EDSS ⩾ 3.5. Moreover, levels of C16_LacCer, C18_LacCer, C34:1_GM3, and C38:1_GM3 increased when attack occurred. In differentiating attack from remission, C18_LacCer levels showed the AUROC of 0.695 (95% CI: 0.558–0.831), while GFAP levels showed the AUROC of 0.842 (95% CI: 0.748–0.936). Of note, C18_LacCer x GFAP levels showed the AUROC of 0.870 (95% CI: 0.787–0.953). These disease activity markers had no correlation with age and disability, in contrast to serum NfL and GFAP, which increased with age and disability. In two patients with attack, the levels of C18_LacCer and C18_LacCer x GFAP differentiated attack which could not be differentiated by the level of GFAP.

Conclusion: We identified two types of plasma sphingolipids biomarkers associated with disease disability or activity. Plasma sphingolipids might be useful as an adjunct biomarker in patients with NMOSD with AQP4-Ab.

Disclosure

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Cerebrospinal fluid soluble CD27 is a highly sensitive marker of CSF inflammation and is associated with B cell activity in relapsing remitting multiple sclerosis

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Introduction: Cerebrospinal fluid (CSF) soluble CD27 (sCD27) is highly sensitive for intrathecal inflammation in multiple sclerosis (MS) and other neuroinflammatory conditions, has a strong discriminatory ability in differentiating between relapsing-remitting MS (RRMS) and symptomatic controls, and has both

prognostic value and is responsive to treatment effects. Although CSF sCD27 is recognized as a T cell activation marker, it has also been shown to correlate with markers of B cell activity such as IgG index and soluble B cell maturing antigen (sBCMA) in MS.
Objectives: To examine the relation between CSF sCD27 and CSF T and B cells.
Aims: To test our hypothesis that CSF sCD27 is associated with B cell activity in MS.
Methods: CSF cells and CSF from 35 RRMS patients and 8 symptomatic controls (SC) were analysed using flow cytometry for T and B cell phenotyping and Mesoscale electrochemiluminescence multiplex assay for analysis of CSF sCD27 and sBCMA levels.
Results: CSF sCD27 levels were significantly ($p < 0.0001$) increased in RRMS (median 10881 ng/l) versus SC (median 1294 ng/l). In a receiver operating curve analysis, CSF sCD27 levels were able to discriminate between RRMS and SCs with an area under the curve (AUC) of 0.98. CSF sBCMA, CSF $CD20^+$B cell and CSF $CD3^+$T cell frequency were also significantly increased in RRMS versus SC and had AUCs of 0.97, 0.94 and 0.92 respectively. In RRMS patients CSF sCD27 correlated with IgG index ($rho = 0.81$; $p < 0.0001$), sBCMA ($rho = 0.95$; $p < 0.0001$), CSF cell count ($rho = 0.62$; $p < 0.001$) and CD20+ B cell frequency ($rho = 0.38$; $p = 0.026$), but not with CSF T cell frequency.
Conclusions: We provide new data indicating that CSF sCD27 is associated with CSF B cell activity in RRMS and confirm the high sensitivity of CSF sCD27 of intrathecal inflammation in RRMS and its strong ability to discriminate between RRMS and SCs.

Disclosure
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Renal function influences serum neurofilament light chain levels in patients with multiple sclerosis

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Introduction: Serum neurofilament light chain (sNFL) is a biomarker of neuroaxonal damage in neurological diseases, useful in the follow-up of patients in clinical practice. Recent studies have reported an association between sNFL levels and renal function in older adults with diabetes and healthy controls, in which the renal function was assessed with serum creatinine levels and calculation of glomerular filtration rate (GFR).
Objectives: To analyze the influence of the renal function in sNFL levels in a wide cohort of patients with multiple sclerosis (pwMS) in order to determine if sNFL concentration should be adjusted to the renal function for a correct interpretation.
Methods: 301 pwMS according to the 2017 McDonald criteria were studied. Serum NFL levels were determined using the NF-light Advantage SR-X kit for the Quanterix single molecule array (SIMOA). Serum creatinine was measured using the kinetic Jaffe method, with the Alinity c Creatinine Reagent kit according to the manufacturer's instructions. GFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation with serum creatinine, age, sex and ethnic origin as variables.
Results: In pwMS over 40 years old (n=130) a trend to sNFL-creatinine (r=0,172; p=0,052) and a clear correlation sNFL-GFR (r=-0,423; p=0,000) was observed. In pwMS below 40 years no correlation with GFR was found.
Conclusions: In this preliminary study we have found that renal function influences sNFL levels in pwMS over 40 years old. Although more studies are needed to confirm these findings, adjustments for renal function should be considered when interpreting sNFL levels.

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Expression of the cell senescence marker p16ink4a is elevated in MS patients and reduced in those on B-cell depleting therapies

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Introduction: Telomere attrition is associated with disability accumulation in MS. Downstream of telomere attrition and a key component to immunosenescence is the expression of cellular senescence markers including p16ink4a.
Objectives: We sought to determine differences in p16ink4a expression in PBMCs in participants with MS and healthy controls as well as association of p16ink4a expression level with MS disability score and disease modifying therapy treatment exposure.
Methods: Patients meeting diagnostic criteria for multiple sclerosis, relapsing or progressive phenotype, and healthy controls were recruited for a cross-sectional pilot study. Participants were block recruited into 3 age groups (<30, 30-50 and >50) to ensure sampling across the lifespan. RNA was extracted from participant

peripheral blood mononuclear cells (PBMCs) and qRT PCR was employed to determine differential expression of p16INK4a using primers (Thermo Fisher) specific for the p16 product of CDKN2A. Expression levels were normalized with a housekeeping gene GAPDH. Univariate analyses were completed with nonparametric tests Wilcoxon rank sum test and Spearman correlation. Multivariable modeling was completed with linear and logistic regression after appropriate variable transformation.

Results: Included were 42 participants with MS (71% female, ages 25-70) and 34 healthy controls (68% female, ages 23-65). The median normalized expression level of p16INK4a was higher (p=0.06) in MS participants (0.27, IQR 0.20-0.44) compared with controls (0.21, IQR 0.12-0.28). Female gender was associated with greater p16ink4a expression in controls (p=0.033) but not in participants with MS (p=0.88).p16INK4a expression level was not correlated with the measured MS disability outcomes including EDSS.A third of MS participants were on B cell depleting treatments. Those on B cell depleting agents had lower p16INK4a expression levels (0.23, IQR 0.18-0.33) near that of the healthy controls.

Conclusions: Patients with MS may have higher burden of cells expressing the senescence marker p16ink4a. This aging marker may be altered by use of lymphocyte depleting treatments. There were no large associations of this senescence marker with disability scores in this modest pilot sample with high rates of use of B cell depleting agents.

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Neurofilament light-chain and CSF parameters do not change after SARS-COV-2 vaccination in patients with MS

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Introduction: Coronavirus disease 2019 (COVID-19) ranges from paucisymptomatic course to severe pneumonia and life-threatening conditions. Although the efficacy and safety of that vaccines in counteract COVID-19 have been established yet, patients with Multiple Sclerosis (MS) are still concerned about vaccination believing that vaccines may worsen their underlying disease.

Objectives: To assess the effect of the new COVID-19 vaccines in a cohort of patients with MS, Dementia, Parkinson disease and atypical parkinsonismson neurofilament light chain (NfL) and other cerebrospinal fluid (CSF) parameters.

Aims: to determine possibile variation of CSF parameters indicating blood brain barrier disruption and to calculate NfL levels comparing different time points since vaccination against SARS-CoV-2.

Methods:We enrolled patients admitted to the Neurologic Unit of University Hospital "Paolo Giaccone" who underwent lumbar puncture (LP) between February 2021 and December 2021. CSF parameters and NfL were compared between unvaccinated and vaccinated patients at three different intervals from vaccination (<4 weeks, 4-8 weeks, 8 weeks). Also, these parameters were evaluated between patients with MS and patients with Dementias, Parkinson disease and atypical parkinsonisms.

Results: A total of 116 patients underwent LP (median age 59 years, [37-51]; 50% females); n=14 (<4 weeks), n=10 (4-8 weeks), n=25 (>8 weeks) and n=25 (unvaccinated) respectively were included in the final analysis. No significative differences emerged between vaccinated and unvaccinated patients for TPc (p=0.2), CSF glucose (p=0.5), CSF/S_{Glu}ratio (p=0.3), number of cells per mm^3(p=0.7) and CSF-NfL (p=0.6). When comparing vaccinated and unvaccinated patients according to underlying neurological diagnosis, no further differences emerged evaluating CSF parameters between groups (overall p>0.5). CSF-TPc and NfL positively correlated with participants' age (p=0.03) while number of cells per $mm^3$was inversely correlated (p<0.0001).

Conclusion: NfL and CSF parameters did not differ between vaccinated and unvaccinated patients. COVID-19 vaccines are not associated with neuroinflammation and neuro-axonal degeneration in people with MS and other neurological diseases

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P660

Mitochondrial measures in neuronally-enriched extracellular vesicles predict brain and retinal atrophy in multiple sclerosis

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Introduction: Mitochondrial dysfunction plays an important role in multiple sclerosis (MS) disease progression. Plasma extracellular vesicles enriched for neuronal origin (NEVs) are a potential source of novel biomarkers in MS and some of these are derived from mitochondria and contain functional mitochondrial components.
Objective: To evaluate the relationship between levels of mitochondrial complex IV and V activity in NEVs and brain and retinal atrophy as assessed using serial magnetic resonance imaging (MRI) and optical coherence tomography (OCT).
Methods: Our cohort consisted of 48 people with MS. NEVs were immunocaptured by targeting neuronal marker L1 cell adhesion molecule from plasma and mitochondrial complex IV and V activity levels were measured using commercial assays. Subjects underwent OCT every 6 months and brain MRI annually. The associations between baseline mitochondrial complex IV and V activities and brain substructure and retinal thickness changes were estimated utilizing linear mixed-effects models.
Results: Participants were predominantly female (79%), had a mean age of 44.7 years, median disease duration of 12.5 years and median EDSS of 1.75. The median follow-up duration was 3.4 years for MRI and 4.9 years for OCT. We found that higher baseline mitochondrial complex IV activity levels (per one SD increase) were associated with faster whole brain volume (WBV) (β=-0.15%/year; 95% CI: -0.24 to -0.07; p=0.001), cortical gray matter (GM) (β=-0.18%/year; 95% CI: -0.33 to -0.03; p=0.018), subcortical GM (β=-0.30%/year; 95% CI: -0.50 to -0.10; p=0.003), as well as peripapillary retinal nerve fiber layer (pRNFL) (β=-0.17μm/year; 95% CI: -0.32 to -0.01; p=0.034) and ganglion and inner plexiform layer (GCIPL) (β=-0.10μm/year; 95% CI: -0.16 to -0.04; p=0.001) atrophies, while higher baseline mitochondrial complex V activity levels (per one SD increase) were associated with slower WBV (β=0.15%/year; 95% CI: 0.05 to 0.25; p=0.004), cortical GM (β=0.16%/year; 95% CI: 0.003 to 0.31; p=0.046), subcortical GM (β=0.32%/year; 95% CI: 0.13 to 0.52; p=0.001), and GCIPL (β=0.07μm/year; 95% CI: 0.01 to 0.13; p=0.025) atrophies.
Conclusions: Our results suggest that NEVs in the periphery may provide a means to assess neuronal mitochondrial health and serve as a potential biomarker of disease progression. Additional larger longitudinal studies will be required to validate these findings.

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Evaluation of two automatic image-processing approaches for oligoclonal band detection: an expert system and a deep learning model

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Introduction: Cerebrospinal fluid (CSF) restricted oligoclonal bands (OCB) are the established immunological biomarker for multiple sclerosis diagnosis. Isoelectric focusing (IEF) and immunoblotting is the gold standard technique to detect OCB. Quantifying OCB remains a complex task: IEF lanes are often contaminated by band-like artefacts. Moreover, samples with low immunoglobulin G concentrations produce low-contrast lanes with faint bands hard to distinguish visually. Hence, the current analysis is subject to misinterpretations and inter-and intra-expert variabilities. We developed two automatic image-processing models to refine OCB detection in IEF. The first knowledge-driven model (OCB-ES) was designed to reproduce human decision-making processes by combining expert guidelines into relevant rules. The second data-driven model (OCB-DL) autonomously extracted relevant OCB features using a convolutional deep neural network without embedding human knowledge.
Objectives: To evaluate the ability of (i) the two developed models and (ii) three experts blinded to each other's interpretation to reproduce a visual on-membrane expert consensus analysis considered to be the ground truth.
Methods: We retrospectively evaluated 982 CSF lanes from two French cohorts: POLAR and Expert-IEF. Lanes were randomly distributed into 833 for training models and optimizing algorithms' parameter values and 149 for testing to assess performance on unseen data. At least three OCBs were required to designate a lane as oligoclonal. The performance of lane classification was evaluated in terms of sensitivity (SE) and specificity (SP).

Furthermore, the two models were compared in function of the number of detected OCB using the area under the ROC curve (AUC).
Results: 97 (65%) test lanes were deemed oligoclonal by the expert consensus. The three experts had the following evaluation scores: SE (0.85, 0.86, 0.84) and SP (0.79, 0.89, 0.81), respectively. OCB-ES and OCB-DL reached similar scores with SE (0.82, 0.85) and SP (0.82, 0.84) respectively. OCB-DL slightly outperformed OCB-ES however the AUC difference between OCB-DL (0.93) and OCB-SE (0.90) was not significant ($p = 0.14$).
Conclusions: Our developed models successfully reproduced expert visual analysis and are promising easy-to-use decision support systems for OCB detection.

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The Expert-IEF retrospective study protocol was approved by the Institutional Review Board (IRB 00013355) of the Lille Catholic Hospitals (GHICL) (approval 14 December 2021, reference RNIPH-2021-37).
FH, SB, LP, NV, JP, PH, VC and GF declare no current conflict of interest, but their institutions are negotiating a technology transfer with a company. Any future royalties will be used as a research funding by the authors' institutions and no royalties will be granted to the authors personally. The PhD funder and the company had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

P662
Serum neurofilament light chain identifies multiple sclerosis patients with severe focal axonal damage in a 6-year longitudinal cohort

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Introduction: Immunomodulatory therapies are effective in reducing the relapse rate, while only marginally being able to control disability progression in patients with multiple sclerosis (MS). While serum neurofilament light chain (sNfL) levels have been shown to best correlate with acute signs of inflammation (e.g., relapses, gadolinium-enhancing lesions), its role for forecasting progressive biology and irreversible axonal damage in MS is less clear (see e.g., *Bittner et al., Brain 2021; Uphaus et al. EBiomedicine 2021*).
Objective: To determine the ability of sNfL, an emerging blood marker of axonal damage, to dissect distinct measures of disease severity and predict future "no evidence of disease activity" (NEDA) status at six-year follow-up (y6) in a cohort of relapsing-remitting MS patients.
Methods: 153 patients were included with a median follow-up time of six years (IQR 4-7). Serum was collected at baseline (y0) and y6; sNfL levels were measured by single molecule array.
Results: Patients experiencing Expanded Disability Status Scale (EDSS) progression or new persistent T1-lesions at y6 showed increased sNfL levels already at y0 compared to stable patients or patients suffering only from inflammatory activity (defined as relapses, new T2 hyperintense or gadolinium-enhancing lesions). Due to the strong association of y0 sNfL with development of persistent T1 lesions at y6 – confirmed by linear regression analysis – we incorporated absence of persistent T1 lesions to the NEDA-3 concept (NEDA-3^{T1}). sNfL significantly improved the prediction of NEDA-3^{T1} status (0.697 95%CI 0.616-0.770 vs. 0.819 95%CI 0.747-0.878, $p < 0.001$) compared to a cumulative risk score summarizing factors differentiating patients with and without NEDA-3^{T1} status. Patients with sNfL values $\leqslant$ 8.6 pg/ml showed a 76% risk reduction for evidence of disease activity or development of persistent T1 lesions (EDA^{T1}) at y6 (Hazard ratio 0.244, 95%CI 0.142-0.419, $p<0.001$) compared to patients with sNfL values $>$8.6 pg/ml.
Conclusions: sNfL levels are associated with severe focal axonal damage as reflected by development of persistent T1 lesions. Y0 sNfL values predicted NEDA-3^{T1}-status at six-year follow-up.

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P663
Serum neurofilament light levels in relation to the Brain-Age Paradigm in normal ageing

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Introduction: Serum neurofilament light (sNfL) is a promising biomarker that increases upon neuro-axonal injury and neurodegeneration in many neurological conditions including multiple sclerosis (MS). In MS, higher sNfL levels have been associated with disease activity, progression and response to disease modifying treatments. The Brain-Age paradigm is a machine learning approach that predicts brain-age from neuroimaging data, whereas the difference between chronological age and the age predicted by this paradigm, the brain predicted age difference (Brain-PAD), has been suggested as a neuroimaging marker for disease monitoring and brain health in MS besides reflecting age-associated neurodegeneration. Studies have shown that sNfL levels also rise in normal ageing, which was further correlated to brain volume changes.
Aims: To investigate whether sNfL levels correlate with brain-PAD in a community-dwelling cohort.
Methods: We included 328 neurologically normal individuals participating in a community-dwelling cohort study free of a history of previous stroke or dementia. There were 193 females. Age ranged from 38 to 85 years, with a median of 68.11 (IQR: 55.90 – 73.18) years. Brain-PAD was measured using neuroimaging data attained from T1-weighted MRI, and sNfL was quantified by a single molecule array (Simoa) assay.
Results: sNfL correlated with chronological age ($r=0.73$, $p<0.001$) and brain-predicted age ($r=0.65$, $p<0.001$). However, sNfL was unrelated to brain-PAD ($r=0.038$, $p=0.50$). Further analyses revealed no differences in brain-PAD comparing individuals within the lowest and the highest sNfL quartile ($p=0.57$), with a mean brain-PAD of 0.79 ± 6.03 and 1.42 ± 7.97 years respectively.
Conclusions: Although sNfL correlated with chronological and brain predicted age, no correlation was found regarding brain-PAD. This could be due to a lower brain-PAD variation in our community-dwelling cohort. Further studies are needed investigating the relation of sNfL with brain-PAD in MS across different disease courses.

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P664
Use of individual measure and z-scores to monitor disease course in relapsing multiple sclerosis: a 1-year prospective study in a single center

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Introduction: Existing data suggest that serum neurofilament (sNFL) is an adequate tool to monitor disease activity in multiple sclerosis (MS). Population-based standards of sNFL levels have been recently proposed as cut-off measures to detect activity in persons with relapsing forms of MS (pwRMS). However, sNFL levels are variable between pwRMS, and the exact algorithm to diagnose disease activity is not defined yet.
Objectives: To assess the performance of individual sNFL values vs. Z-score to monitor inflammation in pwRMS.
Methods: A prospective cohort of 101 pwRMS were followed for 1 year. Clinical examination and sNFL assessment were performed and registered every three months. MRIs were performed annually or when disease activity was suspected. Baseline sNFL was defined as the sNFL measure at study inclusion in the absence of disease activity. Reference sNFL level was defined as the lowest individual sNFL measure obtained during the year in the absence of disease activity. BMI-adjusted Z-score, provided by Benkert and cols. 2022, was registered for baseline, reference, and activity points. Active disease was considered if the patient experienced clinical relapse or had radiological activity in the MRI (new T2-lesions or gadolinium-enhanced lesions). Non-parametric tests were used as data did not follow a normal distribution.
Results: Median baseline sNFL levels were 6.56 (4.98 – 8.38)- Z score 0.55 (-0.39 – 1.31). Median reference sNFL levels were 4.71 (4 – 5.87)- Z score -0.47 (-1.17 – 0.25). Twenty patients (25%) had disease activity during follow-up. Median sNFL in these patients was 8.57 pg/ml (7.02 – 11.45) with an increase of 11% in the baseline level: 0.74 (-1.26 – 2.86; $P = 0.138$) and of 77% in the reference level: 3.63 (2.2 – 5.34; $P = 0.0005$). Z-score during disease activity was 1.13 (0.5 – 2.14), overlapping with control levels in the population-based normogram. In our cohort, none of the individual sNFL measures or baseline Z-score predicted disease activity in the first year of follow-up, but patients with relapse at inclusion were more prone to have disease activity.
Conclusions: Z-score is a helpful tool to identifying pwRMS vs. control patients and assess response to treatment at the population level. However, establishment of an individual sNFL reference value in the first year of follow-up might help to better diagnose ongoing inflammation. Baseline sNFL was not as sensitive as reference sNFLfor this outcome.

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P665
Identifying multiple sclerosis biomarkers in blood using high-sensitivity technologies

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Introduction: Multiple sclerosis (MS) is an inflammatory disease characterized by demyelination and neuro-axonal degeneration in the central nervous system (CNS). Except for neurofilament light protein, identification of biomarkers has been difficult to assess in the blood, presumably due partly to sensitivity.
Objectives and aims: To detect traces of disease activities in the periphery and identify low-abundance protein biomarkers, this study conducts an exploratory examination of the plasma proteome of MS using proximity extension technology, a high-sensitivity multiplex PCR-based immunoassay.
Methods: A case-control cohort consisting of 52 MS cases (relapsing-remitting=30, progressive=22) and 17 healthy controls were enrolled at the Karolinska University Hospital (Stockholm, Sweden). EDTA plasma was analyzed for 1157 unique protein targets across thirteen proximity extension assay panels. Protein associations to disease outcomes and related clinical measures were assessed using a multivariable linear regression model corrected for sex and age at sampling.
Results: Adenosylhomocysteinase (AHCY) and corticotropin-releasing hormone (CRH) protein levels were higher among MS cases than controls, while fatty acid-binding protein 2 (FABP2) was lower among those with relapsing-remitting disease than controls ($P_{discovery}<0.05$, $P_{replication}<0.05$), although not significant after multiple test corrections. Furthermore, pleiotrophin (PTN) and cysteine-rich angiogenic inducer 61 (CYR61) levels were higher in progressive MS than in relapsing-remitting disease ($P<0.0002$, $P_{FDR}<0.05$), and cornulin (CRNN) and chemokine 13 (CXCL13) were associated with more severe disability at sampling ($P<0.0001$, $P_{FDR}<0.05$), independent of disease course. Cathepsin F (CTSF) was positively correlated with disease duration (P=4.1x10-5, $P_{FDR}=0.044$), while ribonucleotide diphosphate reductase subunit M2B (RRM2B) level correlated with intrathecal immunoglobulin production (IgG Index) in relapsing-remitting MS (P=1.7x10-5, $P_{FDR}=0.018$).
Conclusions: We provide several candidates for characterizing MS, particularly progressive disease, which may help monitor disease progression and treatment response in a clinical setting.

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P666
The quantification of NLRP3 in cerebrospinal fluid and the analysis for the relationship to the disease severity in the central nervous system demyelinating disorders: a pilot study

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Introduction: The NLRP3 is one of the key players constituting the inflammasome which is activated by various external signals and promotes caspase-1 activation to induce programmed cell death. Although the results that NLRP3 could be a potential biomarker for progressive multiple sclerosis (MS) were recently published, few studies have analyzed the level of NLRP3 in cerebrospinal fluid (CSF) in the various types of the central nervous system (CNS) demyelinating disorders.
Aim: We aimed to determine whether the CSF of patients with relapsing-remitting MS (RRMS), neuromyelitis optica spectrum disorder (NMOSD), and anti-MOG antibody-associated disorder (MOGAD) has significantly different NLRP3 levels by disorders and whether there is a correlation between NLRP3 level and the disease severity.
Methods: We identified the patients diagnosed with RRMS, NMOSD, and MOGAD from 2012 to 2021 at a single center. Then the patients with CSF samples, collected at the acute phase of attack and stored at the −80 degrees deep freezer, were included in the final set. The CSF NLRP3 level was quantitatively analyzed using a commercial ELISA kit.
Results: A total of 36 patients were included in the final set, 18 with RRMS (mean age 31.7, range 19-51), 9 with NMOSD (mean age 53.4, range 27-72), and 9 with MOGAD (mean age 40.7, range 20-64). The CSF NLRP3 level was highest in NMOSD (8.29 ± 3.87ng/mL, mean±SD), followed by MOGAD (5.92 ± 2.59ng/mL) and RRMS (3.34 ± 1.89ng/mL), which was statistically significant ($p<0.01$). When an EDSS ⩾ 6 at the time of CSF sampling was defined as a 'severe' attack and an EDSS < 6 as a 'non-severe' attack, the number of patients with a severe attack in RRMS, NMOSD, and MOGAD was 2, 4, and 3, respectively. In the comparison, the 'severe' group in RRMS had a higher median NLRP3 level than the 'non-severe' group (6.194 vs. 2.584), which was statistically significant (p=0.03). Similarly, in the NMOSD (10.84 vs. 6.547) and MOGAD (7.606 vs. 4.659), the median NLRP3 levels were higher in the 'severe' group than in the 'non-severe' group, but with no statistical significance.
Conclusion: In this study, the CSF NLRP3 level showed the significantly highest value in NMOSD, which can reflect the aggressiveness of the inflammatory response by disease. Further studies

using a larger scale of patients and the pair analysis of CSF and blood samples will be needed to establish the role of NLRP3 as a diagnostic and prognostic biomarker in CNS demyelinating diseases.

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P667

Serum neurofilament light chain and subcortical atrophy in a large population of people with multiple sclerosis

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Introduction: Serum neurofilament light chain (sNfL) is a promising biomarker for measuring disease outcomes in people with multiple sclerosis (MS). Longitudinal studies evaluating the association between sNfL and subcortical brain volume changes are sparse.
Objective/Aims: To examine association of sNfL with change in subcortical volume in a large population of people with MS.
Methods: The MS Partners Advancing Technology and Health Solutions (MS PATHS) network is an international consortium of 10 MS Centers in the United States and Europe. Standardized collection of clinical information and biosamples are acquired during clinic visits. sNfL was measured in 6,993 MS and 201 healthy control (HC) participants, using a high-throughput immunoassay (Siemens Healthineers). Age-specific cut-points of sNfL levels were derived using HC data; patients with sNfL levels $\geq$ or $<$ the age-specific 97.5th percentile in HCs were classified as having elevated sNfL (sNfL-E) or normal sNfL (sNfL-N), respectively. Additional analyses were performed including the age-normalized sNfL Z-score as a continuous variable (modeled flexibly with splines). Eligible participants were those with standardized brain MRI acquisitions $\leq$1 year of sNfL measurement and MRI follow-up of $\geq$1 year. We performed whole brain segmentation using Multi-Atlas CRUISE and harmonized across scanners and sites via longitudinal ComBat to estimate subcortical gray matter (GM) volume fractions. Analyses applied multivariable-adjusted mixed effects models.
Results: Of the 2141 people with MS with measured sNfL and prospective MRI follow-up (72% female; mean age 45.5y [SD: 11.1y]; 25% progressive), 317 (15%) participants were classified as sNfL-E and were followed for a median of 2.1 years (IQR 1.6-2.9y). In general, individuals with sNfL-E had faster subcortical atrophy when compared with those with sNfL-N (-0.53%/year vs -0.38%/year; $p<0.001$). Multivariable-adjusted annualized rates of change in the thalamus (-0.58% vs -0.37%; $p<0.001$), putamen (-0.65% vs -0.48%; $p=0.001$), and globus pallidus (-0.56% vs. -0.35%; $p<0.001$) were faster for sNfL-E compared to sNfL-N. Analyses including sNfL Z-scores were consistent. Likewise, analyses restricting to those with MRIs within 3 or 6 months of sNfL measurement were similar.
Conclusions: Elevated sNfL is associated with faster subcortical brain atrophy, which is notable as gray matter volume loss is strongly predictive of longer-term clinical disability in people with MS.

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P668

Increased serum glial fibrillary acidic protein (GFAP) levels predict disease progression in B cell depleted patients with progressive MS

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Introduction: In MS, acute inflammatory activity leads to strongly increased serum neurofilament light chain (sNfL) levels, while its capacity to detect disability progression is less clear. Serum (s) GFAP, an astrocytic intermediate filament, has been proposed as a promising biomarker to capture progression in MS.
Objectives: To compare the value of sGFAP and sNfL as prognostic markers of confirmed disability progression (CDP) in patients with progressive MS (pwPMS) under B-cell depleting therapy (BCDT: ocrelizumab (OCR) or rituximab (RTX)).
Methods: sGFAP and sNfL were measured using the Simoa Neurology 2-plex B assay in 83 pwPMS under BCDT (39 PPMS and 44 SPMS; 38 OCR and 45 RTX) followed in the SMSC. The first sample available after ⩾9 months of treatment was used (median [IQR] time since start: 12.1 [10.7,16.6] months; follow-up: 2.6 [1.8-3.4] years). For sGFAP, age-, sex- and BMI-adjusted Z scores based on healthy controls (HC, n=259; 485 samples) were derived (according to Benkert et al. 2022). In multivariable analyses, we investigated factors associated with sGFAP and sNfL Z scores (dependent variables in separate models), including the development of future CDP. Time to CDP was analysed using Cox regression models with sGFAP and sNfL Z score as predictors (using individual, combined and adjusted models).
Results: 36.1% of pwPMS experienced CDP. Overall, sGFAP Z scores were increased more than sNfL Z scores (median [IQR]: 1.3 [0.4,2.3], $p<0.1x10^{-4}$ vs 0.7 [-0.3,1.5], $p=0.3x10^{-4}$; mean in HC: Z=0). Increased sGFAP Z scores were associated with younger age, lower BMI, higher EDSS, shorter time since therapy start (all $p<0.05$) and was nearly 1 unit higher in patients with future CDP (0.84 [0.26,1.42], p=0.005), while no significant predictors of sNfL Z scores were found beside BMI (p=0.03). sGFAP or sNfL levels did not differ in OCR vs RTX treatment. Both biomarkers were prognostic of CDP in univariable analyses, but in the combined model only sGFAP remained significant (Hazard ratio per Z score unit increase 1.6 [1.1,2.3], p=0.02, sNfL 1.2 [0.8,1.9], p=0.46). The prognostic capacity of sGFAP for CDP

risk improved after stratification by Z scores: (above vs below) Z=1: n=47/36, HR 3.3 [1.4,8.1], p=0.009; Z=1.5: n=39/44, HR 3.7 [1.6,8.6], p=0.003; Z=2: n=30/53 HR 6.2 [2.8,14.1], p<0.001.
Conclusions: sGFAP may be a more sensitive biomarker of CDP risk than sNfL. The increase of both markers observed in this study indicates continuing progression under BCDT.

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P669
Do we have reliable predictors of future disease activity in patients after the first demyelinating event suggestive of MS?

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Introduction: Early and reliable predictors of individual disease activity are lacking. Therefore, initiation of high-efficacy treatments in patients with ongoing disease activity is often delayed.
Objectives: To identify predictors of disease activity in patients with a first demyelinating event suggestive of multiple sclerosis (MS) treated initially with intramuscular interferon b-1a.
Methods: We included 100 patients from the SET study with available data. We investigated the predictive role of baseline

demographics, clinical, and paraclinical measures recorded at disease onset. Cox proportional hazards models adjusted for age and gender were used to analyze predictors of relapsing activity and confirmed (6 months) disability worsening.
Results: In total, 76 (76%) of the patients experienced new relapses and 23 (23%) had confirmed worsening disability during the follow-up (mean 10.4, range 5.0-12.4 years). The markers associated with a higher risk of new relapse included: the presence (hazard ratio [HR] 4.3; 95% confidence interval [CI]: 2.5-7.4; $p<0.001$) and greater number of contrast-enhancing lesions at baseline (HR 14.9; 95% CI: 5.6-39.4; $p<0.001$), higher concentration of neurofilament light chain (NfL) level in cerebro-spinal fluid (CSF) (HR 2.1; 95% CI: 1.1-4.3; p=0.032) and in serum (HR 2.2; 95% CI: 1.1a-4.3; p=0.024) at screening. All patients with contrast-enhancing lesion, 88% of patients with serum (s) NfL levels over 90th percentile (based on healthy controls), but only 53% of patients with sNfL levels under the 30th percentile experienced future relapse. Other baseline predictors such as lesion burden, global and regional brain atrophy, CSF measures, disability status, vitamin D levels or demographic measures were not associated with future disease activity. Except for low brain parenchymal fraction (HR 1.4; 95% CI 1.0-1.9; p=0.041), we did not find any baseline predictors of the confirmed disability worsening.
Conclusions: At the onset of the disease, only the presence of contrast-enhancing lesions and increased levels of NfL were associated with an increased risk of future relapsing activity. These results may contribute to the identification of patients who benefit from early initiation of high-efficiency immunomodulatory treatments. This study supports the previous findings suggesting that prediction of clinical disease activity in MS at an individual patient level is very challenging.

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Imaging and non-imaging biomarkers - Other Biomarkers

P670
Relationship between brain hypoxia and functional connectivity (FC), measured with near-infrared spectroscopy (NIRS), in multiple sclerosis (MS)

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Introduction: Using near-infrared spectroscopy (NIRS), we found that 40% of individuals with MS have reduced cerebral tissue oxygen saturation (S_tO_2) in the microvasculature of the cortex, and thus have hypoxia. We reported previously that there was reduced brain functional connectivity (FC), measured using NIRS, in individuals with MS. However, the impact of hypoxia on MS is unknown. Hypoxia may relate to inflammation or impaired neurovascular coupling. As a result, hypoxia may cause, or be correlated with, reduced brain FC.
Objectives: Using frequency-domain NIRS (fd-NIRS) and functional NIRS (fNIRS), we aimed to determine if hypoxia was correlated with reduced brain FC in individuals with MS.
Aims: To determine if hypoxia is associated with reduced brain coherence, a measure of brain FC, in MS.
Methods: Healthy control (HC), normoxic MS, and hypoxic MS participants (n=10/group) were grouped based on S_tO_2 values. S_tO_2 values that were 2xSD below the HC group mean were defined as hypoxic ($S_tO_2<55.7\%$). fNIRS was applied in the premotor and prefrontal cortices during rest, finger-tapping, and a battery of neurocognitive tests. When computing coherence, we split data into two frequency windows (low-frequency window (LFW)=0.015-0.079Hz and high-frequency window (HFW)=0.08-0.20Hz). The former is associated with vasomotor reactivity, while the HFW is related to cerebral autoregulation. A Pearson correlation coefficient was computed to assess the linear relationship between S_tO_2 and resting-state coherence.
Results: There was a significant difference between groups for resting-state intra-hemispheric coherence in the prefrontal cortex (p=0.012 for LFW and p=0.013 for HFW). Coherence was lower in the hypoxic MS group when compared to the HC group (p=0.008 for LFW and p=0.009 for HFW). Group differences were also present during finger-tapping and neurocognitive tasks. Using Pearson correlation, we found a significant relationship

between S_tO_2 and resting-state coherence in the prefrontal cortex for both LFW (R=0.54, p=0.002) and HFW (R=0.48,p=0.007).
Conclusions: Hypoxia in individuals with MS may relate to impaired brain function based on reduced FC. fNIRS measures of hemodynamic coherence in MS could provide novel information on brain function, be a biomarker of disease progression, and benefit therapeutic approaches in MS.

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P671
Can we detect radiological disease activity in multiple sclerosis using digital biomarkers?

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Introduction: In the past years digital biomarkers for monitoring multiple sclerosis (MS) have emerged, enabling frequent data collection from the patient's own environment. However, their validity should be strengthened and their value in clinical practice must still be proven.
Objective: Here we cross-sectionally compared smartphone-based Symbol Digit Modalities Test (sSDMT) and Two Minute Walk Test (s2MWT) outcome values for persons with multiple sclerosis (PwMS) with and without radiological disease activity.
Methods: Data of the APPS-MS study, a one-year cohort study of 60 persons with RRMS where weekly sSDMT and s2MWT were administered with MS sherpa®, were used. Additionally, patients were monitored with conventional clinical measures at baseline and subsequently every three months. We evaluated the presence of radiological disease activity on contrast-enhanced MRI scans. Digital biomarker mean level values, computed with a state space model (measurements close to the clinical visit outweigh those further from the clinical visit), were compared between PwMS with and without gadolinium enhancing (GD+) lesions, using independent samples t-tests. All scans with corresponding mean level values were included in the analyses separately.
Results: GD+ lesions were present on 26 out of 194 MRI scans, corresponding to 15 out of 54 PwMS. The mean level value of the sSDMT scores in the group with GD+ lesions was 4.3 points lower than that of the group without GD+ lesions ($P<0.01$). The mean level value of the s2MWT scores in the group with GD+ lesions was 19 meters lower than that of the group without GD+ lesions ($P<0.05$).
Conclusion: Mean level scores of MS sherpa® sSDMT and s2MWT were respectively 4 points en 19 meters lower during presence of GD+ enhancing lesions in patients with RRMS. This difference suggests a potential role for digital biomarkers in detecting radiological disease activity in MS, using frequent smart-phone-based self-monitoring.

Disclosure
P.C.G. Molenaar, I.G. Bucur, K.H. Lam, B. Moraal, T.M. Heskes, V. de Groot and E.M.M. Strijbis declare no conflict of interest. P. van Oirschot is an employee of MS Sherpa B.V. (industry partner). B.M.J. Uitdehaag reports research support and/or consultancy fees from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva, and Immunic Therapeutics. J. Killestein reports speaker fees and grants from Biogen, Celgene, Genzyme, Immunic, Merck, Novartis, Roche, Sanofi and Teva.
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P672
Psychomotor assessment using fitts tapping test in multiple sclerosis: reproducibility and validation study

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Introduction: Studies suggest that persons with multiple sclerosis (pwMS) experience continuous and subclinical physical worsening which accumulates from the start or before the disease diagnosis. Therefore, validating highly sensitive and reproducible tests of physical and cognitive functioning that can capture subclinical disease activity is highly warranted.
Objectives and aims: To determine the reproducibility and validity of Fitts tapping test in pwMS.
Methods: Thirty newly-diagnosed pwMS (within 2-years of diagnosis and Expanded Disability Status Scale; EDSS ⩽2.0), 30 persons with migraine (pwM) and 30 healthy controls (HCs) underwent psychomotor assessment using the Fitts tapping test, O'Connor hand dexterity test, and visual reaction time test. Hand motor function was further measured using hand dynamometer. The subjects also provided patient-reported outcomes (PROs) using the 36-Item Short Form Survey (SF-36). Intrarater and interrater reproducibility was acquired on 2 HCs by two

independent operators. Test-retest reproducibility was determined in 5 pwMS over 1-week follow-up. Eight pwMS returned for the same test procedures 2 years after the baseline visit. Bland-Altman plots were used to determine minimally detectable worsening and logistic regression models determined the ability of the psychomotor tests to differentiate between newly-diagnosed pwMS from HCs.

Results: Fitts tapping test exhibited high intrarater and interrater reproducibility (interclass correlation coefficient of 0.961, $p<0.001$). The test-retest demonstrated minimally detectable change of 15%. PwMS had significantly slower Fitts completion time and O'Connor dexterity time when compared to pwM and HCs ($p<0.001$ for both). Higher Fitts difficulty levels (4^{th} and 6^{th} difficulty) and average performance on O'Connor test were able to differentiate newly-diagnosed pwMS from HCs with 80% accuracy ($p<0.01$). Slower Fitts tapping performance was correlated with worse patient-reported limitations due to physical health and overall physical health ($p<0.001$). Over the 2-year follow-up, and despite being clinically stable (no change in EDSS), 6 out of 8 (75%) pwMS had more than 15% worsening in their average Fitts tapping time.

Conclusion: Fitts tapping test is a highly reproducible test for measuring psychomotor performance and hand dexterity in pwMS. Fitts tapping test can capture insidious worsening in psychomotor performance (cognitive and motor slowing) in early stages of MS.

Disclosure

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P673

Investigating fluctuations of spontaneous EEG topographies in fatigued patients with multiple sclerosis

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Background: Fatigue is a common symptom in patients with Multiple Sclerosis (PwMS) that is highly disabling, affecting the quality of life. Several functional studies have found that PwMS experiencing fatigue showed altered connectivity. However, how fatigue symptoms might effect the functioning of resting-state networks still remains poorly understood.

Objectives: To compare EEG microstates (McSt), across broadband and spectral decomposition, in order to investigate the group differences between fatigued (patF) and non-fatigued (noF), respectively, in PwMS and healthy controls (HCs). We hypothesized that patF-PwMS might show altered spontaneous fluctuation McSt compared to noF-PwMS.

Methods: 44 PwM and 24 HCs, matched for age and sex, were enrolled. Patients had to be cognitively preserved and with EDSS<3. All participants underwent to administration of Modified Fatigue Impact Scale (MFIS) and to 15-min of high-density EEG recording (256ch); closed-eyes. EEG data were filtered 1-30Hz, ICA-corrected for artifacts and downsampled to 256Hz. Each recording was also filtered into the 5 traditional EEG frequency bands (delta, theta, alpha1, alpha2, beta). McSt analysis identified a set of voltage maps representing the EEG activity for all participants, across broadband and frequency bands. Differences between groups were assed using parametric (T-test) or non-parametric (Mann-Whitney) statistical test according to the normality test; alpha=0.05.

Results: 26% of PwMS had patF and no difference was found with respect to HCs (17% patF; p=0.373). The MFIS-total scores distribution has shown a strong trend towards higher values in PwMS compared to HCs; in the subscale of physical fatigue, the PwMS had significantly higher values than HCs (p=0.039). We found seven McSt across participants and McSt-7 (salience network) had a significant decreased activity in patF- than noF-PwMS for broadband, theta and alpha1. In HCs, McSt-1 (auditory network) was found significantly increased in patF- than noF-HCs for broadband and low frequencies.

Conclusions: Microstate analysis reveled altered fluctuations of EEG topographies when PwMS and HCs experienced pathological level of fatigue. However, a different impact was observed: McSt-7 activity, correlated to salience network, decreased in patients with MS and McSt-1 activity, associated to auditory processing, increased in controls. Knowledge of the neural mechanisms of underlying MS fatigue could inform more effective treatment strategies.

Disclosure

Disclosures within last 3 years

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Blood-derived-extracellular vesicles as biomarker of response to treatment in multiple sclerosis

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Background: Several disease modifying treatments (DMT) have been developed for modulation of the immune system in Multiple Sclerosis (MS). However, given that the natural disease course of MS is unpredictable, the benefit of each treatment for individual patient is unknown. Thus, a biomarker that predict the response or failure to treatment could help with treatment decisions to bring precision medicine to MS patients. In this regard, extracellular vesicles (EVs) released from B and T lymphocyte could act as biomarker of immune system state in Multiple Sclerosis.
Aims: We propose to analyze the role of circulating EVs as biomarker for treatment response.
Methods: EVs from blood of 86 patients with recurrent remittent MS (42 treated patients with different DMTs and 44 naïve controls) were isolated using Exoquick ultra kit. From total blood-EVs, we isolate EVs specifically derived from B and T lymphocytes by immunoprecipitation using the surface markers CD20 and CD3, respectively and their levels and diameter were studied using Nanosight. We analyzed treatment effects on circulating EVs.
Results: Patients treated with different disease modifying treatments showed higher levels of T lymphocyte-derived EVs than naive patients (p=0,001). B and T lymphocyte-derived EVs were larger in treated patients (p=0,05, p=0.001, and p=0,026, respectively). EV released from B lymphocytes correlated with the different mechanism of action of DMTs (p=0.001).
Conclusions: Treatments for MS modify levels and size of immune system-derived EVs, suggesting that these EVs may play an important role as a marker of treatment response.

Disclosure
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The authors declare that they have no competing interests.

P675
Fecal metagenomics may discriminate between patients with first demyelinating episode in the context of clinically isolated syndrome and/or relapsing-remitting multiple sclerosis and patients with later stages of the disease

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Background: Recent studies have linked alterations in the overall profile of the gut microbiome with Multiple Sclerosis (MS), as well as with the activity of the disease.
Aim - objectives: We hereby aim to evaluate the potential of fecal metagenomics to discriminate across the early stages of health-to disease continuum in MS.
Methods: We compared the gut microbiomes of 42 patients (53% females, mean age= 40yrs, mean BMI= 26Kg/m^2) either with a first demyelinating episode in the context of Clinically Isolated Syndrome (CIS) and/or Relapsing-Remitting MS (early RRMS) or with RRMS beyond the first episode, with 30 age and BMI matched healthy controls (HC) Greek individuals (74% females, mean age= 38yrs, mean BMI= 26Kg/m^2). Microbiomes were profiled through 16s rRNA amplicon sequencing from fecal samples.
Results: Microbial richness was significantly decreased in patients with a first demyelinating episode compared to healthy controls (mean OTU richness in HC= 257, mean OTU richness in patients=219, P=0.013). β-diversity differed between patients and healthy controls (P=9.9e-04), but did not differ when we compared microbiome profiles of CIS and early RRMS with RRMS patients' profiles (P>0.63). When compared to healthy controls, patients with a first demyelinating episode were found to have a decreased abundance of short-chain fatty acid bacteria, including *Roseburia* (mean abundance in HC=5.11%, patients=3.09%; P=0.0082). Moreover, patients with RRMS exhibited decreased abundance of *Faecalibacterium* (mean abundance, RRMS=5.59%, CIS+early RRMS=9.21%; P=0.0089) and a trend for increased abundance of*Blautia* (mean abundance, RRMS=4.45%, CIS+early RRMS=3.10%; P=0.074), compared to patients with a first demyelinating episode.
Conclusion: We hereby provide evidence that fecal microbiome alterations differentially characterize the early stages of CIS – fist demyelinating episode in the context of RRMS – RRMS continuum, thus highlighting the potential of fecal metagenomics as a marker of health-to-disease transition for MS.

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Using transcranial magnetic stimulation to investigate the acute effects of translingual neurostimulation in individuals with multiple sclerosis

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Introduction: Non-invasive neuromodulation techniques have emerged as a promising treatment to facilitate rehabilitation for individuals with Multiple Sclerosis (MS). One neuromodulation method, translingual neurostimulation (TLNS), involves electrical stimulation of the tongue. Paired with physiotherapy, TLNS improves motor function in individuals with MS. Despite preliminary findings supporting the benefits of TLNS and physiotherapy, the actual mechanisms underlying TLNS is not known. Functional brain imaging devices such as transcranial magnetic stimulation (TMS) can help elucidate how TLNS may work to influence plasticity and recovery.
Objectives/Aims: The goal of this study is to use TMS to probe the effects of TLNS on corticospinal excitability in individuals with multiple sclerosis.
Methods: Participants (n=24) were recruited from a clinical trial in which individuals with MS (EDSS 3-6) were randomized to receive either a real or modified TLNS device combined with physiotherapy for gait and balance. TMS variables, including resting motor threshold (RMT) and active motor threshold (AMT) were measured pre and post 20 minutes of TLNS treatment.
Results: A repeated measures ANOVA using mixed models was conducted to investigate differences in corticospinal excitability pre and post TLNS treatment between the real and sham treatment groups. Comparing pre and post RMT values, there were no significant differences in maximum stimulator output (%MSO), motor evoked potential (MEP) amplitude or MEP latency between the real and sham groups ($p>0.1$). Similarly, comparing pre and post AMT values, there was no significant difference in %MSO, MEP amplitude, MEP latency or cortical silent period (CSP) between the real and sham groups ($p>0.1$).
Conclusion: Our preliminary examination of TMS variables, RMT and AMT, indicate that 20 minutes of TLNS did not increase corticospinal excitability in individuals with MS. Future research will interrogate additional TMS variables and overall brain activation through changes in cerebral blood flow.
KeyWords: Multiple Sclerosis, Neuromodulation, Translingual Neurostimulation, Functional Brain Imaging, Transcranial Magnetic Stimulation

Disclosure

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Subclinical vascular disease markers and coagulation disorders in multiple sclerosis

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Background and objectives: In the pathophysiology of Multiple Sclerosis (MS), there is a poorly defined vascular component that conditions a decrease in cerebral blood flow. In addition, patients with MS have a higher incidence and prevalence of cardiovascular disease compared to the general population. However, possible markers of subclinical vascular disease and if MS carries a greater risk of thrombophiliahave not been studied. We designed a case-control study with the aim of using ultrasound techniques to determine possible markers of vascular disease and coagulation disorders in patients with MS.
Methods: Patients with MS and controls were matched for age, sex, and prevalence of vascular risk factors. To analyze possible subclinical vascular disorders we used transcranial doppler, carotid, transthoracic echocardiogram and flow mediated vasodilatation study in brachial artery. Basic coagulation and a complete thrombophilia study using coagulative and chromogenic tests were also performed.
Results: 120 individuals were included, 60 patients with multiple sclerosis and 60 healthy controls. Patients with MS presented higher values of carotid pulsatility index (1.05 ± 0.27 vs 0.86 ± 0.16; $p < 0.001$) and resistance index (0.58 ± 0.11 vs 0.54 ± 0.07; $p = 0.021$); decreased mean intracranial velocity (46.3 ± 9.7 vs 52.1 ± 19.2; $p = 0.030$); depressed left ventricular systolic function (11.67% vs 0%; $p = 0.006$) and reduced free protein S activity compared to the control group (13.3% vs 0%; $p = 0.003$). We have not found differences in the parameters that analyze the presence of carotid atherosclerosis and systemic endothelial dysfunction.
Conclusions: Ultrasound studies such as carotid and transcranial Doppler and echocardiography are useful in MS patients to detect subclinical carotid and cerebral vascular disease suggestive of small vessel disease and left ventricular dysfunction. The coagulation study detected a slight deficiency of protein S, which, in combination with other risk factors for hypercoagulability, could lead to a higher risk of thrombosis.

Disclosure

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Pathophysiological mechanisms of motor fatigue in people with multiple sclerosis: new insights from advanced neurophysiological techniques

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Introduction: Motor fatigue is one of the most invalidating and poorly treated symptoms in people with Multiple Sclerosis (pwMS).
Objectives and Aims: We investigated whether pwMS show more motor fatigue than healthy controls (HC) and tested the hypothesis that increased motor fatigue in pwMS is generated at the central nervous system level due to changes in brain network connectivity, and sensorimotor network activation.
Methods: Twenty relapsing-remitting pwMS, and 15 HC performed repeated blocks of first dorsal interosseous muscle (FDI) maximal voluntary contraction (MVC) until exhaustion. We measured the motor endurance index as the number of completed blocks*force exerted, normalized across participants. Peripheral, central, and supraspinal motor fatigue were assessed by measuring changes across blocks in the superimposed twitches evoked by peripheral nerve and transcranial magnetic stimulation (TMS). Brain network connectivity and sensorimotor network activation before and after the fatiguing task were assessed respectively by resting-state EEG small-world index (SWI), and by source reconstructed TMS-evoked potentials (TEPs) elicited by primary motor cortex stimulation.
Results: Motor endurance was significantly less in pwMS compared to HC ($p=0.036$). We found higher central ($p = 0.03$) and supraspinal motor fatigue ($p < 0.001$), and no differences in peripheral motor fatigue ($p = 0.69$) in pwMS compared to HC. Fatigue was associated with opposite effects on SWI in the theta frequency band ($p = 0.006$) and on TEPs in the sensorimotor network (FDR corrected permutation-based analysis $p < 0.05$) in HC compared to pwMS. Theta SWI and TEPs were reduced post-fatigue in HC, whereas both were increased post-fatigue in pwMS. Post fatigue modulation of TEPs correlated directly with supraspinal fatigue ($p=0.029$).
Conclusions: Cortical mechanisms play a major role in motor fatigue in pwMS. Motor fatigue in pwMS is associated with abnormal fatigue-related modulation of brain networks resting-state connectivity and sensorimotor network activation. Our results could be used to develop new treatments targeting motor fatigue in pwMS.

Disclosure

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Unraveling the power spectrum in multiple sclerosis phenotypes: an explorative magnetoencephalography study

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Introduction: Multiple sclerosis (MS) occurs in distinct clinical phenotypes. Previous EEG and MEG studies have found specific changes in oscillatory brain activity related to clinical status MS patients. However, these changes remain understudied in the clinical MS phenotypes.
Objectives and aims: To investigate changes in the power spectrum in MS phenotypes and their relation to cognitive impairment.
Methods: MEG resting-state and structural MRI, and cognitive (brief repeatable battery of neuropsychological tests, expanded with the Concept shifting-, Stroop-, and Memory comparison tests) data was collected in 171 people with MS (pwMS) and 64 healthy controls. Relative power (RP) was compared between MS phenotypes (132 relapsing-remitting (RRMS), 25 secondary progressive (SPMS) and 14 primary progressive (PPMS) patients and HC using a beamforming approach.
Results: Globally, RRMS and SPMS showed statistically significant higher alpha1 RP vs HC. Regionally, higher occipital theta RP, higher occipital/frontal/parietal/basal ganglia/limbic/thalamic alpha1, and lower hippocampal alpha2 RP were found in RRMS. In SPMS higher hippocampal/thalamic theta, higher frontal/parietal/insular/limbic/basal ganglia/thalamic alpha1 and higher frontal/parietal alpha2, and lower insular/hippocampal/basal ganglia/thalamic beta was found. In PPMS lower parietal/insular/limbic gamma RP, and lower parietal/limbic/insular beta were found compared to HC.
Conclusions: Overall, slowing of oscillatory activity is seen in MS patients, which is in line with previous research. This slowing differs between MS phenotypes, and is most pronounced in the RRMS and SPMS subtype. Conversely, we found a shift toward higher frequencies in PPMS patients. This study proposes new insights into the power spectrum of MS and revealed clinically relevant power changes.

Disclosure
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Magnetoencephalography as a potential predictor of clinical progression in patients with multiple sclerosis: a longitudinal study

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Introduction: Disability progression in people with multiple sclerosis (pwMS) is difficult to predict using structural MRI measures. Neurophysiological markers based on techniques such as magnetoencephalography are known to be predictive in other neurological conditions, but remain understudied in MS.
Objectives and aims: To evaluate how disability progression correlates with oscillatory brain activity in MS.
Methods: 109 people with MS (pwMS) and 37 healthy controls (HC) underwent MEG, 3T MRI, and clinical evaluation (expanded disability status scale, EDSS) at two time points (mean interval 4.6y, range 2.2-7.6y). Clinical progression was defined as an increase in EDSS score of 1 point for baseline EDSS ⩽5.5, or a .5 point increase for baseline EDSS ⩾ 6. MEG relative power (RP) was analyzed in 6
frequency bands (delta, theta, alpha1, alpha2, beta, gamma) at a whole brain and regional level using a beamforming approach and the Brainnettome atlas. RP at baseline and follow-up was compared between HC/pwMS, and pwMS who progressed clinically vs. non-progressors. Binary logistic regression including all MEG measures was used to identify the best predictors of clinical decline.
Results: Baseline MEG measures showed a statistically significant decrease in beta RP in MS (HC .307 SD=.05; pwMS .289 SD=0.5; p<.05), particularly in fronto-parietal areas and the thalamus, while occipital alpha 1 RP was increased (HC .136, SD=.07, pwMS .164, SD=.08, P<.04). This increase in alpha1 persisted at follow-up, together with a reduction of hippocampal alpha 2 RP (HC .125, SD=.02, pwMS .114, SD=.03, P<.02). A decrease between baseline and follow-up delta band RP (global, fronto-temporal and thalamic, P<.001) was the best predictor for EDSS progression, together with age and baseline EDSS. While not included in the regression model, temporal/occipital gamma and temporal/hippocampal/thalamic alpha1 only increased significantly (p<0.05) in patients with EDSS progression between FU/BL. Additionally, frontal/parietal alpha2 decreased significantly only in non-progressors.
Conclusions: Disability progression in MS is related to changes in relative power. Specifically, a decrease in delta band RP between baseline and follow-up was the best predictor of clinical progression.

Disclosure
LR, NB, IN, ES, AH declare no disclosures of interest. M.M. Schoonheim serves on the editorial board of Neurology and Frontiers in Neurology, receives research support from the Dutch MS Research Foundation, Eurostars-EUREKA, ARSEP, Amsterdam Neuroscience, MAGNIMS and ZonMW and has served as a consultant for or received research support from Atara Biotherapeutics, Biogen, Celgene/Bristol Meyers Squibb, Genzyme, MedDay and Merck. Bernard M.J Uitdehaag: reports research support and/or consultancy fee from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva, and Immunic Therapeutics. Cornelis. J. Stam: member of editorial board of Network Neuroscience.

P681
What if it's not MS? Long-term outcomes in other paediatric monophasic and multiphasic demyelinating syndromes

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Introduction: PaediatricAcute Demyelinating Syndromes (pADS) can manifest with relapses following a single episode. Criteria have been established to help diagnose multiple sclerosis (MS) from first presentation; but predicting risk of relapse and long-term outcome is more difficult in other pADS.
Objectives: To examine a historical cohort of pADS for possible predictive features of relapse such as initial diagnosis, age of onset, myelin oligodendrocyte antibodies (MOG Abs) and cerebrospinal fluid (CSF) oligoclonal bands (OCB); and test whether long-term outcome was worse in non-relapsing and relapsing syndromes distinct from MS
Aims: To investigate risk of relapse and outcome in non-MS pADS
Methods: 269 children presenting with demyelination (median age 8.95y, IQR=9.57y; 143M, 126F) were recruited from 14 UK

paediatric neurology centres (2010-2014, Absoud et al., 2011); with median follow-up 7.2y, IQR 3.4y. For children without an MS course, a Chi² test was used to determine monophasic syndromes prone to become multiphasic. 59 of them were selected for a binary logistic regression using the variables age of onset, presence of CSF OCB or MOG Abs at onset, controlling for gender, to predict a relapsing course. A subgroup of non-MS pADS received long-term assessments of fatigue, quality of life, neuropsychiatric symptoms and disease severity. Long-term school, motor, bowel, bladder, and vision-related difficulties were compared to children with MS.

Results: Children with non-MS multiphasic syndromes relapsed at median 0.5y, IQR 0.9 after onset. Observation of multiphasic course at last follow-up differed across initial demyelinating phenotypes (χ^2=15.3, p=.004), with Transverse Myelitis being significantly less likely to relapse (p=.01), NeuroMyelitis Optica Spectrum Disorder significantly more (p=<.01). The regression (R^2=0.23; p=.037) showed MOG Abs to be a predictor of relapse (OR=4.96;p=.017). Monophasic and multiphasic children did not significantly differ in long-term outcomes. The non-MS group did not differ in difficulties compared to MS (school: 17% vs 15% MS; motor: 20% vs 30% MS; vision: 12% vs 22% MS; bladder: 15% vs 9% MS).

Discussion: The risk of developing a relapsing course in pADS depends on initial diagnosis. MOG Abs are associated with relapse. Similar long-term difficulties are seen in both groups. Even monophasic diseases can lead to neurodisability. All children with ADS should be followed-up and early rehabilitative interventions offered.

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Therapy - Immunomodulation/ Immunosuppression

P682
Vagus nerve stimulation attenuates disease severity in a rat EAE model of multiple sclerosis

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Introduction: Despite multiple approved therapies available for treating multiple sclerosis (MS), there remains a need for new therapeutic options. Vagus nerve stimulation (VNS) can activate neuro-immune reflexes that attenuate inflammation, increase T_{reg} populations, and is neuroprotective in the central nervous system (Immunol Rev 2012; 248(1):188). We hypothesized that VNS would be ameliorative in an experimental autoimmune encephalomyelitis (EAE) model of MS.

Aims: To explore the effect of VNS on disease manifestation and burden in a standard rodent model of MS.

Methods: VNS devices (SetPoint Medical, CA) were fully implanted in 6-week-old female Lewis rats. Following recovery, EAE was induced with myelin basic protein (0.1 mg/rat) and complete Freund's adjuvant (Hooke Laboratories, CT). Conscious rats were treated with VNS or Sham VNS from 7 days post-induction (DPI), the day prior to the typical onset of clinical symptoms, through 21 DPI. As positive control, additional rats were orally gavaged QD with teriflunomide (3 mg/kg, 1 mg/kg, vehicle) on the same schedule. Clinical scores were recorded daily in a treatment-blinded manner (0-5 scale). Spinal cord (SC) sections were H&E stained for infiltrating immune cells.

Results: VNS decreased disease manifestation and burden compared to the sham treatment. Total AUC of clinical score vs. DPI was significantly reduced (30 %, p <0.01). Reductions in SC-infiltrating immunocytes during the onset, peak and remitting stages of EAE were observed. In addition, there was no statistical difference between the VNS group and the high dose teriflunomide group, nor between the sham VNS group and the vehicle group.

Conclusions: These data indicate that daily VNS reduced disease manifestation and total burden in a semi-established model of rat EAE, similar in degree to high dose teriflunomide. Immunocyte infiltration into the SC was reduced in the VNS treated rats. To further investigate the underlying mechanisms of these neuroprotective effects, glial and immunocyte targets are being investigated.

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Monotherapy for multiple autoimmune diseases: the novel use of ofatumumab for concurrent multiple sclerosis and autoimmune hepatitis

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Introduction: Autoimmune hepatitis (AIH) has been reported in patients with multiple sclerosis (MS), either concurrently or after treatment with immunomodulatory drugs including interferon-beta and steroids. Typically, those patients are treated with steroids and azathioprine as the first line of treatment according to AIH guidelines. However, azathioprine, methotrexate, and mycophenolate mofetil have been shown to be minimally effective or potentially worsen the disease course of MS. Several studies have suggested a role for B cell-driven autoimmune liver injury in AIH and a few cases of refractory AIH successfully

treated with rituximab, an anti-CD20 monoclonal antibody, have been reported in the literature. Based on these results and the well-known role of B-cells in the underlying pathophysiology of MS, we postulated that anti-CD20 therapy may be effective in treating patients with concurrent MS and AIH.
Objectives/Aims: Investigate efficacy of anti-CD20 therapy for concomitant MS and AIH
Methods: Case report
Results: We report the case of a 49-year-old previously healthy female who presented with characteristic MRI findings and symptoms consistent with relapsing-remitting MS (RRMS). On routine labs at initial presentation, she was incidentally found to have ALT/AST in the low 1000s. Extensive work up was done including a liver biopsy that showed AIH without cirrhosis. The patient was started on oral prednisone followed by ofatumumab, another anti-CD20 monoclonal antibody approved for treatment of RRMS, as steroids were weaned. The patient's liver enzymes returned to normal ranges within 12 weeks and have remained so now for 4 months. Additionally, she has had no new clinical or imaging findings suggestive of MS disease activity.
Conclusions: We present this as the first-reported case of the use of an anti-CD20 monoclonal antibody to successfully treat both MS and AIH concurrently.

Disclosure
Drs. Awad and Elsbernd have no conflicts of interests or financial disclosures to declare regarding this submission. This case report was prepared primarily by physicians while in the employment of the US Federal government. The views expressed herein are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force and Department of Defense or the U.S. Government.

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NEDA-4 with ublituximab versus teriflunomide in the ULTIMATE I and II studies in participants with relapsing multiple sclerosis

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Introduction: Ublituximab is a novel monoclonal antibody targeting a unique epitope of CD20. Ublituximab is glycoengineered for enhanced antibody-dependent cellular cytotoxicity and is administered in 1-hour maintenance infusions after the first infusion. In ULTIMATE I and II, ublituximab significantly improved annualised relapse rate as well as number of gadolinium-enhancing (Gd+) T1 lesions and new/enlarging T2 lesions, and a higher proportion of participants achieved 3-parameter no evidence of disease activity (NEDA) versus teriflunomide in participants with relapsing multiple sclerosis (RMS).
Objectives/aims: To evaluate 4-parameter NEDA (NEDA-4) with ublituximab versus teriflunomide in pooled post hoc analyses of ULTIMATE I and II using different annual brain volume loss (BVL) thresholds.
Methods: The Phase 3 ULTIMATE I (N=549) and II (N=545) studies evaluated ublituximab 450 mg intravenous infusion every 24 weeks or teriflunomide 14 mg oral once daily for 96 weeks in participants with RMS. Pooled post hoc analyses evaluated the proportion of participants achieving NEDA-4 at Week 96, re-baselined at Week 24. NEDA-4 was defined as no confirmed relapses, no T1 Gd+ lesions, no new/enlarging T2 lesions, no 12-week confirmed disability progression, and BVL less than the defined threshold. BVL was evaluated using 0.4%, 0.8%, and 1.2% annual thresholds.
Results: A significantly higher proportion of ublituximab- versus teriflunomide-treated participants achieved NEDA-4 (Weeks 24-96, re-baselined) at the 0.4%, 0.8%, and 1.2% annual BVL thresholds: 44.2% versus 13.5% (odds ratio [OR], 5.479 [95% confidence interval (CI), 4.026-7.457]), 68.0% versus 19.0% (OR, 10.099 [95% CI, 7.497-13.603]), and 71.9% versus 19.6% (OR, 11.689 [95% CI, 8.640-15.812]), respectively ($P<0.0001$ for all). Lower rates of BVL with ublituximab versus teriflunomide were observed for each annual BVL threshold (Weeks 24-96, re-baselined): 0.4%, 49.5% versus 54.0%; 0.8%, 21.2% versus 25.8%; and 1.2%, 16.1% versus 18.8%, respectively.
Conclusions: Because BVL is predictive of long-term disability progression and cognitive decline, inclusion of BVL in NEDA analyses may provide a more comprehensive evaluation of disease activity and progression and might be predictive of long-term disability. In pooled post hoc analyses across a range of annual BVL thresholds, significantly more participants achieved NEDA-4 with ublituximab versus teriflunomide in ULTIMATE I and II.

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Immunity following SARS-CoV-2 vaccination in autoimmune neurological disorders treated with rituximab or ocrelizumab

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Introduction: B cell-depleting therapy targeting CD20 molecule with rituximab (RTX) or ocrelizumab (OCR) affects humoral immune response after vaccination. It remains unclear whether these therapies influence T-cell-mediated immune response against SARS-CoV-2 after immunization.
Aims: We aimed to evaluate the humoral and cellular immune response to the COVID-19 vaccine in a cohort of patients with multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), and myasthenia gravis (MG).
Methods: Patients with MS (83), NMOSD (19), MG (7) under RTX (n=47) or OCR treatment (n=62) were vaccinated twice with mRNA BNT162b2 vaccine. Antibodies were quantified using the SARS-CoV-2- IgG chemiluminescence immunoassay targeting the spike protein. SARS-CoV-2-specific T-cell responses were quantified by interferon γ release assays (IGRA). Immunocompetent vaccinated individuals (n=41) were included as controls.
Results: Almost all immunocompetent controls developed antibodies against the SARS-CoV-2 trimeric spike protein, but only 42.05% of the patients under anti-CD20 (RTX or OCR) treatment seroconverted. There was no correlation between circulating B cells and the levels of antibodies. Even patients with a low proportion of circulating $CD19^+$ B cells (<1%, 71 patients) had detectable SARS-CoV-2 specific antibody responses. This response was even higher in patients with longer than 3 weeks intervals of vaccination. SARS-CoV-2 specific T cell response measured by released interferon γ was detected in 94.39% of the patients, independently of a humoral immune response.
Conclusions: The majority of MS and NMOSD patients developed SARS-CoV-2-specific T cell response. The data suggest that vaccination can induce SARS-CoV-2-specific antibodies in a part of anti-CD20 treated patients. The response represented by levels of antibodies was better in individuals, who completed vaccination within more than 3 weeks.

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An interim analysis of efficacy and safety data in Black and Hispanic patients with multiple sclerosis receiving ocrelizumab treatment in the CHIMES trial

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Introduction: The disease activity of multiple sclerosis (MS) varies by racial and ethnic groups. Black and Hispanic patients are underrepresented in MS trials, and these patients may have higher MS incidence, faster disease progression and/or an increased risk of progression to disability vs White patients. The CHIMES trial (NCT04377555) was designed to evaluate disease activity and response to ocrelizumab (OCR) in Black and Hispanic patients.
Aims: To analyze the interim efficacy and safety data for OCR treatment in Black and Hispanic patients with relapsing MS (RMS).
Methods: This prospective, open-label, single-arm, Phase IV study included patients with RMS who self-identified as Black or Hispanic, were aged 18-65 y and had Expanded Disability Status Scale (EDSS) scores of 0-5.5 points at screening. Patients received two 300-mg OCR infusions 14 days apart, and 600 mg every 24 weeks for 1 year, with an optional 3-year extension. The interim data cutoff was 30 March 2022, and included patients who completed 1 year of OCR treatment. The primary outcome was no evidence of disease activity (NEDA), defined as proportion of patients free from a protocol-defined event at Week 48, which included relapse, confirmed disability progression at Week 24, T1 gadolinium (Gd)-enhancing lesion or new and/or enlarging T2 lesions. Additional outcomes were clinical evaluations and adverse events (AEs).
Results: Overall,182 patients are enrolled in the CHIMES trial. This interim analysis included 49 patients, 36 (73.5%) Black and 13 (26.5%) Hispanic. Mean (SD) age was 33.3 (8.1) years, weight was 90.6 (23.9) kg and 85.7% of patients were female. Patients had a mean (SD) time since first MS symptoms of 3.8 (5.1) years and time since RMS diagnosis was 1.6 (3.4) years. Baseline mean (SD) EDSS score was 2.5 (1.5), Gd-enhancing T1 lesions was 2.5 (3.9) and total T2 lesion volume was 21.7 (21.8) cm^3. The proportion of patients with NEDA was 40.8% (95% CI 27.0%–55.8%). A total of 38 patients experienced ⩾1 AE, 3 had a serious AE and 22 had an infusion-related reaction. No deaths occurred.
Conclusions: The CHIMES interim analysis provides essential preliminary data for OCR treatment response among Black and Hispanic patients. More information for the full population in CHIMES is needed to better understand disease activity and to further explore treatment response.

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Attenuation of immune activation in patients with multiple sclerosis on a wheat free diet: a pilot crossover trial

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Introduction: Western lifestyle has been associated with an increase in relapsing-remitting multiple sclerosis (RRMS). In mice, dietary wheat amylase-trypsin inhibitors (ATIs) activate intestinal myeloid cells and augment T cell-mediated systemic inflammation. Moreover, ATIs promote a pro-inflammatory intestinal dysbiosis by a direct interaction with the microbiota.
Aim: To investigate whether wheat- and thus ATI-reduced diet might exert beneficial effects in RRMS patients with modest disease activity.
Methods: In this 6-month, cross-over, open-label, bi-centric proof-of-concept trial, twenty RRMS patients with stable disease course were randomized to either three months of a standard wheat-containing diet with consecutive switch to a >90% wheat-reduced diet, or vice versa. Main outcome measures were changes of peripheral blood immune cell phenotypes, health-related quality of life assessed (SF-36), disease stability (Expanded Disability Status Scale, EDSS), relapse-rate, and serum neurofilament light chain levels.
Results: We observed decreased frequencies of pro-inflammatory $CD14^{+}CD16{+}{+}$ monocytes and a concomitant increase of non-inflammatory $CD14{+}{+}CD16^{-}$ monocytes during the wheat-reduced diet interval in the per protocol analysis. This was accompanied by an improvement in pain-related quality of life in SF-36.
Conclusions: A wheat- and thus ATI-reduced diet was associated with changes in monocyte subsets towards a non-inflammatory phenotype and improved pain-related quality of life in RRMS patients. This highlights the potential of a wheat (ATI) reduced diet as a complementary approach accompanying immunotherapy.

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Disease outcomes with ublituximab in treatment-naive participants: subpopulation analyses of the phase 3 ULTIMATE I and II studies in participants with relapsing multiple sclerosis

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Introduction: Ublituximab is a novel monoclonal antibody targeting a unique epitope of CD20. Ublituximab is glycoengineered for enhanced antibody-dependent cellular cytotoxicity and is administered in 1-hour maintenance infusions after the first infusion. In ULTIMATE I and II, ublituximab significantly improved annualised relapse rate (ARR) versus teriflunomide in participants with relapsing multiple sclerosis.
Objectives/Aims: To evaluate efficacy with ublituximab in treatment-naive participants enrolled in ULTIMATE I and II.
Methods: The Phase 3 ULTIMATE I (N=549) and II (N=545) studies evaluated ublituximab 450 mg intravenous infusion every 24 weeks or teriflunomide 14 mg oral once daily for 96 weeks. Pooled post hoc subpopulation analyses (unadjusted) evaluated efficacy measures at Week 96 in participants who had not received prior disease-modifying therapy (DMT) at the time of enrolment in ULTIMATE I and II. The pooled treatment-naive population included 345 ublituximab and 377 teriflunomide participants evaluable for ARR, 12-week confirmed disease progression (CDP), 12-week confirmed disability improvement (CDI), and Multiple Sclerosis Functional Composite (MSFC), and 340 ublituximab and 372 teriflunomide participants evaluable for magnetic resonance imaging measures.
Results: In the treatment-naive population, the unadjusted ARR was 0.095 and 0.223 for ublituximab versus teriflunomide, respectively ($P<0.0001$). By Kaplan-Meier estimate, significantly more ublituximab than teriflunomide participants achieved 12-week CDI at Week 96: 11.2% versus 5.5%, hazard ratio (95% confidence interval), 2.031 (1.174-3.513; P=0.0095). The total number (least squares means) of gadolinium-enhancing T1 lesions and new/enlarging T2 lesions per scan was 0.031 versus 0.791 and 0.390 versus 4.144 for ublituximab versus teriflunomide ($P<0.0001$ for both). The change from baseline in MSFC score was 0.53 versus 0.28 for ublituximab versus teriflunomide (P=0.0047). No evidence of disease activity rates (Weeks 24-96, re-baselined) with ublituximab (n=324) versus teriflunomide (n=350) were 82.7% versus 23.1% ($P<0.0001$). Occurrence of 12-week CDP was low in both treatment groups.
Conclusions: In pooled post hoc analyses of ULTIMATE I and II, ublituximab was associated with significant treatment benefit across multiple efficacy measures at Week 96 versus teriflunomide in participants who had not received prior DMT, and similar or improved versus the overall ublituximab population.

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P689
Temporal evolution of humoral and T-cell specific immune response to COVID-19 mRNA vaccine in multiple sclerosis

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Background: Although a full course of vaccine against Sars-Cov-2 is effective in most patients with MS (PwMS), the duration of the protection and the efficacy of a booster dose remain poorly explored, especially across different disease modifying treatments (DMTs).
Aims: To characterize humoral and T-cell immune response along time and following third dose of COVID-19 vaccination in PwMS.
Methods: From an established cohort evaluated at baseline (T0), PwMS were recruited after 24 weeks (T1) from the first cycle of mRNA vaccine and 4 weeks after third dose (T2). At each time-point we evaluated the serological response by measuring the anti-Region-Binding-Domain (RBD). Cell-mediated response was analyzed by computing interferon (IFN)-γ in response to spike peptides.
Results: The baseline cohort consisted of 134 PwMS [mean age 46.6±10.8 years; F:92; mean disease duration 15.1±9.4 years; 26.9% ocrelizumab (OCR) 30.6% fingolimod (FTY), 16.4% cladribine (CLA), 26.1%IFN-ß-1a (IFNB)]. Of them, 109 were reassessed at T1, 78 at T2 and 64 completed all evaluations. In the whole cohort there was a significant reduction ($p<0.0001$) in anti-RBD rate from T0 [76% positive, median 52.8 BAU/ml Interquartile Range (IQR) 1150.9] to T1 (57.8% positive, median 13.2 BAU/ml IQR 95.98] and a significant 20- and 5-fold increase in median titer at T2 (75% positive, median 272.3 BAU/ml IQR 4212.3) from T1 and T0 respectively ($p<0.0001$). Median IFN-γ level at T2 was significantly higher than those evaluated at T1 ($p<0.0001$) and T0 ($p=0.009$). These latter results were consistent across all DMTs. At T1 the highest detectable anti-RBD response was found in CLA (100%, median 87.7 BAU/ml IQR 22) and IFNB (93.5%; median 126.3 BAU/ml IQR 149.2) cohort, while PwMS treated with FTY and OCR showed 60% (median 8.25 BAU/ml IQR 34.3) and 21% (median 0.8 BAU/ml IQR 6) rate of anti-RBD response respectively. At T2 100% PwMS showed positive anti-RBD response except those treated with OCR (23.8% positive, median 0.6 BAU/ml IQR 4.1). IFN-γ-S-specific T-cell response was reduced in FTY cohort at both T1 and T2 (3.3 % positive, median 0.8 pg/ml IQR 3.1 and 0.6 pg/ml IQR 2.4 respectively).
Conclusions: A third dose of COVID-19 vaccine reinforces both humoral and cell-mediated immune response in PwMS on DMTs. Despite vaccination, PwMS treated with OCR and FTY show lower humoral and T-cell specific immune response respectively, suggesting the need of specific treatment to halt COVID-19 in case of infection.

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P690

GB7208 is a novel, highly potent and selective CNS-penetrant BTK inhibitor for neuroinflammatory and neurodegenerative diseases

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Introduction: Bruton's tyrosine kinase (BTK) mediates signaling downstream of B cell and Fragment crystallisable receptors suggesting an important role in autoimmune disease. BTK inhibitors (BTKi) are being explored in neuroinflammatory/neurodegenerative diseases including Multiple Sclerosis (MS) but have modest selectivity and/or limited central nervous system (CNS) penetration. GB7208 has been designed as an orally available, irreversible small molecule BTKi optimized for best-in-class potency, selectivity, and brain exposure.

Objective: Evaluate the pharmacologic properties of GB7208 in preclinical models.
Methods: Selectivity of GB7208 was assessed in kinome scans against 349 kinases. Irreversibility of GB7208 was evaluated by measuring time-dependent inhibition and residence time. The pharmacokinetic profile of GB7208 was assessed in multiple species for both intravenous (IV) and oral routes. Both biochemical and cell-based assays were employed for evaluation of GB7208 potency and inactivation kinetics. To assess BTK target occupancy within the CNS, naïve mice with intact blood brain barrier (BBB) were dosed with GB7208 followed by perfusion, brain dissection and processing into lysates that were analyzed for unoccupied BTK in a probe-based ELISA assay.
Results: GB7208 was highly selective in a kinome scan against 349 kinases and importantly lacked activity against EGFR, a known liability of several BTKi. GB7208 potently inhibited BTK*in vitro* and demonstrated properties of irreversibility, such as time-dependent inhibition and residence time >300 minutes. Importantly, GB7208 demonstrated rapid BTK inactivation kinetics (Kinact/Ki) in both peripheral and CNS tissue, a critical parameter for irreversible inhibitors. In mice with an intact BBB, GB7208 demonstrated a high brain to plasma ratio vs. other BTKi. In non-human primates, GB7208 demonstrated a brain to plasma ratio approximating 0.8. Finally, when compared with other BTKi, GB7208 showed excellent target occupancy in the brain of naïve mice with intact BBB.
Conclusions: GB7208 has been designed as an orally available, selective, irreversible small molecule BTKi optimized for best-in-class potency, selectivity, and brain exposure. The pharmacologic features of GB7208 support further investigation in neuroinflammatory/neurodegenerative diseases such as MS, where BTK is a critical signaling node contributing to activation and function of pathogenic B cells and microglia within the CNS.

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P691
Cytokine profile of cell-mediated immune responses to SARS-CoV-2 mRNA and protein-based vaccines in patients with multiple sclerosis

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Background: Disease-modifying therapies (DMTs) in patients with multiple sclerosis (pwMS) are known to impact the cellular immune response to SARS-CoV-2 vaccines. In this study, we aim to elucidate a broader cytokine profile of involved T cells for various DMTs.
Methods: 131 pwMS on different DMTs vaccinated with SARS-CoV-2 mRNA vaccines were recruited for this prospective cohort. Blood was drawn post 2nd and 3rd dose. Using a cartridge based multiplex assay (ELLA™), interleukin (IL)-5, IL-10, IL-2, IL-4, IL-17A, IL-13, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) were measured in blood stimulated with SARS-CoV-2 antigens (Ag) to evaluate T cell response. In comparison, SARS-CoV-2 spike antibodies were measured. mRNA vaccine non-responders were administered NVX-CoV2373 protein-based vaccine, and the corresponding immune responses were measured.
Results: After two mRNA vaccines, IFN-γ, and IL-2 responses were significant and comparable between patients treated with glatiramer acetate (GA) and those untreated (UT). There was also a lower but significant IL-4 and IL-5 response for GA and UT respectively. 100% of GA and UT patients had a positive antibody response (mean 4230 U/ml and 1774U/ml respectively). In ocrelizumab (OCR) patients, IFN-γ and IL-2 responses were higher compared to GA and UT patients. Lower but significant IL-5, IL-4, and IL-13 responses were found. B cell immunity was much lower as only 32% showed a positive antibody response (mean 337 U/ml). For patients on sphingosine-1-phosphate receptor (S1PR) modulators, only 6.4% had a positive T cell response even after 3 doses. However, 87% had a positive B cell response (mean 725 U/ml).
No relevant change in IL-17, IL-10, or TNF-α concentration was observed among the previously mentioned DMT groups despite TNF-α levels being elevated in all groups upon SARS-CoV2 Ag challenge. Similar patterns were also seen after the third mRNA dose.
Conclusion: This study corroborates known data that the T helper cell type 1 response is the main T-cell response to SARS-CoV-2 mRNA vaccines with the highest response seen in OCR patients. A lower T helper cell type 2 response is observed and is variable depending on treatment modalities. This however is not the case for patients on S1PR modulators whose cellular responses were severely diminished.

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P692
Pilot study: vagus nerve stimulation reduces microglia around a demyelinating lesion in a lysolecithin-induced demyelination model

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Introduction: Multiple Sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system (CNS), with

immune-mediated demyelination as its hallmark. This demyelinating process results from the attack of autoimmune T cells and is further increased by pro-inflammatory cytokines, produced by resident cells like activated microglia and other immune cells. Current therapies primarily target peripheral immune mechanisms but have little effect on the CNS innate immune system. Vagus nerve stimulation (VNS) shows potential to tackle this therapeutic gap by exerting an anti-inflammatory effect via activation of the locus coeruleus-noradrenergic pathway.
Objectives: This study investigates the effect of VNS on demyelination and neuroinflammation in rats.
Methods: A focal demyelinating lesion was induced by bilaterally injecting 1 µl of 0,5% lysolecithin solution in the corpus callosum of female Lewis rats. One minute of VNS (1.0 mA, 10 Hz, 250 µs) (N = 4) or one minute of sham (N = 5) was given daily from 2 days before until 2 days after the injection. Euthanasia was performed 3 days post-injection, corresponding with the peak of inflammation and demyelination. Demyelination volume of the lesion was assessed by a Luxol Fast Blue staining; the presence and number of microglia and astrocytes were assessed by a Iba1 and GFAP immunofluorescence staining respectively. Differences between groups were assessed with a Mann Whitney U test.
Results: A significant decrease in Iba1+ cells was found in the border around the lesion of VNS rats compared to sham (p=0.027). No significant effects were found when analysing the Iba1 intensity of the lesion (p=0.221), the Iba1+ cells within the lesion (p=0.221), the GFAP intensity of the lesion (p=0.221), the GFAP+ cells within the lesion (p=0.624), and the GFAP+ cells in the border around the lesion (p=0.327). Demyelination volume did not significantly differ (p=0.806) between VNS (0.42±0.12 mm³) and sham (0.33±0.15 mm³).
Conclusions: VNS induced a significant decrease in microglia around the lesion. Microglia play a key role in the inflammatory lesion formation and are also found in the rim around smouldering lesions, which are associated with greater disease severity. Our findings show a first indication that VNS might be therapeutic in neuroinflammation. Due to the complex role of microglia, further investigation with microglia subtype characterization and a larger sample size is needed.

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P693
Evobrutinib, a Bruton's tyrosine kinase inhibitor, acts on microglia: implications in treatment of progressive multiple sclerosis mechanisms

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Introduction: In multiple sclerosis (MS), persisting disability can derive from acute relapses or alternatively, from slow and steady progression independent of relapse activity, termed chronic progression. Therapeutically controlling progression independent of relapses (PIRA) in MS, remains a major challenge. One promising strategy may be to reduce chronic neuroinflammation by the inhibition of the enzyme Bruton's tyrosine kinase (BTK), which is centrally involved in the activation of both B cells as well as myeloid cells, such as macrophages and microglia.
Objectives: In the present study, we analysed the potential of the BTK inhibitor evobrutinib as a therapeutic strategy in halting progression in MS.
Methods: Primary microglia were generated from newborn C57BL/6 mice and activated by combinations of IFN-gamma and/or GM-CSF and/or LPS. For adoptive transfer experiments, C57BL/6 mice were immunised with MOG peptide 35-55 and isolated draining lymph node cells were cultivated in the presence of anti-IFN-gamma antibody, IL-12 and MOG peptide 35-55. Subsequently, the fully differentiated purified T cells were injected intraperitoneally into recipient mice. Prior to transfer, recipients had received evobrutinib (10m/kg) or vehicle control starting 3-7 days daily and treatment continued; thereafter, microglial activation/modulation was assessed by ELISA and flow cytometry.
Results: *In vitro*, we demonstrated a reduction of pro-inflammatory properties of microglia by BTK inhibition with evobrutinib, while enhancing phagocytosis in primary murine microglial-like cells. In the passive EAE model of MS, which excludes the involvement of peripheral immune cells, *in vivo* evobrutinib treatment reduced the expression of markers involved in activation and antigen presentation on microglia.
Conclusion: BTKi by evobrutinib downregulates inflammatory properties of microglia. These data highlight the therapeutic potential of BTKi with evobrutinib in ameliorating underlying processes associated with chronic progression in MS.

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The MultipleMS prospective cohort study: Clinical characteristics and treatment of patients with multiple sclerosis in 7 European countries

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Introduction: The main objective of the MultipleMS consortium is to develop novel personalized medicine approaches for multiple sclerosis (MS) patients. We have initiated a prospective European cohort involving centres from Belgium (BE), Denmark (DK), Germany (GER), Italy (IT), Norway (NO), Spain (ES) and Sweden (SW). Newly diagnosed MS patients were phenotyped by clinical assessment and imaging. Biosamples were analyzed by immune phenotyping, biomarker analyses and multi-omics approaches to identify molecular markers associated with disease progression.

Objective: To analyze baseline characteristics of patients enrolled in the MultipleMS study.

Aim: To evaluate differences in clinical phenotypes and treatment approaches across the participating centres.

Methods: The demographic, clinical and treatment data of 510 MS patients were analyzed and compared between the centres using Chi-squared and Kruskal-Wallis tests.

Results: The median age at onset was 33 years (interquartile range (IQR) 27-40) and did not differ between centres, with a median time from first symptom to diagnosis of 180 days (IQR 53-719) and median Expanded Disability Status Scale (EDSS) at inclusion of 1.5 (IQR 1-2). Clinically isolated syndrome was diagnosed in 7.1%, relapsing-remitting MS in 88.2%, primary-progressive MS in 4.5% and secondary-progressive MS in 0.2%. 9.8% did not receive immunotherapy within the first year. Dimethyl fumarate was the most prescribed drug in BE (61.3%), GER (30.5%) and IT (29.1%) and the second most prescribed drug in ES (23.8%) after glatiramer acetate. In SW 89.9% of the patients received Rituximab (vs. 0-21.4% in other centres) and in DK, the most commonly used drug was Ocrelizumab (26% vs. 0-7.3% in other centres). Baseline EDSS scores in the SW cohort were significantly higher compared to BE and GER, while Danish patients displayed higher relapse rates and higher EDSS scores as compared to ES, GER and BE. In NO, 31% of patients were treated with Cladribin (vs. 0-6% in other centres) without a significant difference in EDSS scores or relapses compared to other countries.

Conclusions: We recorded modest differences in clinical phenotypes (relapse rates and baseline EDSS scores) of enrolled MS patients across participating centers, which contrasted with striking differences in choice of first line therapies. This suggests that country-specific treatment practices and guidelines exert a greater impact on channeling to therapy than clinical characteristics.

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Natalizumab continuation versus switching to ocrelizumab in RRMS patients: an observational analysis

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Introduction: In contrast to natalizumab (NTZ), only anecdotal cases of progressive multifocal leukoencephalopathy have been reported with ocrelizumab (OCR), thus representing a valid alternative to NTZ when JC virus serologies turn positive after two years.
Objectives: To compare two cohorts of patients who continued on NTZ or were changed to OCR after at least two years of NTZ treatment.
Methods: In this retrospective analysis of prospectively recorded data, we included patients with relapsing-remitting multiple sclerosis (RRMS) who were on treatment with NTZ for at least 2 years after January 2018 and were either continued on NTZ or changed to OCR after JC virus positivity. Primary endpoint was time to first relapse from the treatment decision moment, assessed by Kaplan-Meier. Secondary endpoints were proportion of no evidence of disease activity (NEDA), annualized relapse rate, progression of EDSS score and presence of gadolinium-enhancing or new T2-hyperintense lesions after one year, assessed by chi-square and Mann–Whitney U testsas appropriate.
Results: Out of 67 included patients, 40 continued on NTZ and 27 changed to OCR. Baseline characteristics between groups were not different. Mean follow-up time was 2.58 ± 0.75 years. 25% of the patients who continued on NTZ presented a relapse after 1.53 ± 0.51 years, compared to 0.75 ± 0.42 for OCR ($p=0.451$). Annualized relapse rate after one year was significantly lower for the NTZ group versus the OCR group (0.18 ± 0.45 and 0.33 ± 0.55 respectively, $p=0.03$). No differences in proportion of NEDA, progression of EDSS score or radiological activity outcomes after one year were detected.

Conclusions: Switching to OCR after two years of NTZ treatment might entail a higher risk of relapses during the first year compared to NTZ continuation, without differences in mid-term activity outcomes.

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Oral n-acetylglucosamine in multiple sclerosis patients raises n-glycan branching and modifies serum cytokine levels

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Objectives: N-acetylglucosamine (GlcNAc) is a rate limiting substrate for cell surface N-glycan branching and has been demonstrated to suppress autoimmune T and B cell responses, promote re-myelination and limit neuro-axonal damage in mouse models of MS. In humans reduced levels of a marker of endogenous serum GlcNAc associate with MS severity. We sought to assess safety and bioactivity of oral GlcNAc supplementation in MS patients.
Methods: Forty-seven Multiple Sclerosis (MS) patients stable on glatiramer acetate therapy were sequentially recruited from UC Irvine MS program for a dose-escalation study. After 4 weeks observation, GlcNAc was given orally daily in three doses (3, 6, and 12 grams (g) divided three times per day) over four weeks. Blood was drawn weekly for 4 weeks prior to initiation and during GlcNAc treatment. Two weeks after stopping GlcNAc, blood was drawn weekly x 3 in the 6g and 12g groups.Primary endpoint was safety and N-glycan branching on $CD4^+$T cells, established by the binding of*Phaseolus vulgaris* leucoagglutinin (L-PHA). Secondary/exploratory endpoints were changes in levels of serum GlcNAc, serum cytokine levels, and 4-week-confirmed improvement in the Expanded Disability Status Scale (EDSS).
Results: Fifty-one subjects with MS were screened with 38 female and 9 male MS patients enrolled (mean age 54±9 years). [AUB1]There were 13, 18, and 16[AUB2] subjects in the 3, 6, and 12-gram treatment groups respectively. GlcNAc was safe and well tolerated with all subjects completing the 4-week treatment without dose reduction. Adverse events included increased flatulence/loose stool in 8 subjects on the 12-gram dose[AUB3] and one relapse during the treatment phase of the 6g dose. At the 6g and 12g but not the 3g doses, L-PHA binding was elevated on activated but not resting $CD4^+$ [AUB4]T cells in a dose dependent fashion. Serum GlcNAc levels were increased in all dose groups, while levels of IFNg were decreased at all doses and serum IL-6 was decreased at 12g dose. 4-week confirmed improvement in EDSS was observed in 22% of subjects at 6g and 31% of subjects at 12g.
Conclusion: GlcNAc was well-tolerated and was biologically active in MS patients. Mild but tolerable gastrointestinal side effects were observed in the 12-gram dose. Randomized double blind studies are warranted to further explore the potential of oral GlcNAc on myelin repair and neurodegeneration in MS.

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Cladribine effects on T and B cell subsets and T cell reactivity in multiple sclerosis

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Introduction: Cladribine therapy is an efficacious treatment for multiple sclerosis (MS), however, its mechanism of action remains incompletely understood.
Objectives: The aim of this study was to investigate the treatment effects of cladribine on the circulating T and B cell subsets and T cell reactivity towards central nervous system (CNS) antigens.
Aims: The effect of cladribine treatment was studied one year after the initiation of treatment.

Methods: In this study, frequencies and absolute counts of peripheral T and B cell subsets and B cell cytokine production from untreated patients with relapsing-remitting MS (RRMS) and patients treated with cladribine for one year were measured using flow cytometry. T cell reactivity was assessed using a fluorospot assay.
Results: We found that one year after initiation of cladribine treatment, a depletion of $CD4^+$ T cells was persisting whereas $CD19^+$ B cell counts were reconstituted in patients with RRMS. Follicular helper T (Tfh) cells and their effecter subsets producing cytokines exerting distinct B cell helper activity were reduced, and the peripheral B cell pool was skewed towards a naïve and anti-inflammatory phenotype one year after initiation of cladribin treatment. Finally, cladribine treatment significantly reduced reactivity to the recently identified CNS-enriched autoantigen RAS guanyl-releasing protein 2 (RASGRP2) but not reactivity to myelin basic protein and myelin oligodendrocyte glycoprotein.
Conclusions: Together these studies of T and B cell subsets suggest that cladribine treatment modulates B-T cell crosstalk and dampens their effector functions. Our studies also suggest that treatment results in a specific reduction of T cell reactivity to RASGRP2 which is an autoantigen expressed in B cells and brain cells.

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Factors related to favorable response to plasma exchange in acute relapses of inflammatory demyelinating diseases: a multicenter experience

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Background: Plasma exchange (PE) can improve the recovery of patients with severe relapses of CNS demyelinating diseases (CNS-DD) unresponsive to corticosteroids.
Objectives: We aimed to (1) assess the response rate and (2) identify predictors of good response to PE.
Methods: This was a retrospective, non-interventional study, that collected the information of all patients treated with PE at 3 Spanish hospitals between 2012-2021 and met the following criteria: 1) severe relapse of CNS-DD unresponsive to at least one course of methylprednisolone (MTP, 1gr x 3-5 days); 2) maximum of 3 months between attack onset and PE treatment; and 3) to have received between 5 to 10 exchanges. Improvement at 6 months after PE was defined as a return to pre-relapse Expanded Disability Status Scale (EDSS) score; or decrease $\geqslant$1 or 1.5 points for patients with EDSS nadir $\leqslant$ 7.5 or $\geqslant$8, respectively; or improvement in $\geqslant$2 lines on the visual acuity chart for patients with optic neuritis (ON). Uni and multivariate logistic regression models were used to determine factors associated with improvement.
Results: Ninety patients were included (65.6% female, median (IQR) age of 42 (32-51.75) years, and pre-relapse EDSS score of 1.5 (0-3.0)). The most frequent diagnoses were multiple sclerosis (44, 49%), idiopathic CNS-DD (25, 28%), and AQ4-positive neuromyelitis optica spectrum disorder (14, 16%). Relapses phenotype were myelitis (36%), ON (23%), multifocal/disseminated forms (22%), brainstem/cerebellum lesions (10%) and pseudotumoral lesions (8.9%). Median EDSS score at PE initiation was 5.0 (4.0-7.0). In one center, 32 patients received 200 mg of rituximab pre- and post-PE.
Median time between MTP and PE was 18 (7-34) days. Patients received a median of 7 (6-7) exchanges, and 30% of them required further therapy (mostly new courses of MTP, 70%). Improvement was achieved by 77% of patients (40% experienced a full recovery), and the final EDSS score was 3.0 (2.0-4.0). Younger age (p=0.04) and lower pre-relapse EDSS score (p=0.01) were independently associated with improvement. Other variables such as type of CNS-DD, relapse phenotype, number of exchanges, or the addition of rituximab did not influence the response.
Conclusion: PE produced a clinical important improvement in a large proportion of patients with severe CNS-DD. Younger age and lower baseline disability are predictors of a favorable response.

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A multicentre, open label, single-arm, phase 3b study (CONSONANCE) to assess the effectiveness and safety of ocrelizumab in patients with primary and secondary progressive multiple sclerosis: year 2 interim analysis

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Introduction: The approval of ocrelizumab (OCR) for the treatment of primary progressive MS (PPMS) showed that the course of progressive MS (PMS) can be altered with effective treatment; however, direct evidence across the spectrum of PMS, including secondary progressive MS (SPMS), is still lacking.
Objective: CONSONANCE (NCT03523858) is a single-arm, phase 3b, 4-year study designed to evaluate for the first time the effectiveness and safety of OCR in patients with SPMS or PPMS. Year 2 results are reported.
Methods: Patients with active or non-active PMS but showing disability progression in the past 2 years were enrolled. Primary outcomes are (1) proportion of patients with no evidence of progression (NEP) defined as no progression confirmed for ⩾24 weeks on Expanded Disability Status Scale (EDSS), no ⩾20% increase in timed 25-foot walk test (T25FWT), no ⩾20% increase in nine-hole peg test (9HPT) time, and no MS-related death or treatment discontinuation due to efficacy failure; (2) proportion of patients with no evidence of progression and no active disease (NEPAD) defined as NEP plus no protocol-defined relapse, no new/enlarging T2 lesions (N/E-T2, re-baselined at week 24), and no T1 gadolinium-enhanced lesions.
Results: Patients (n=629; SPMS n=324, PPMS n=305) had mean (SD) age of 48.5 (9.2) years and 52.3% were female. At baseline (BL), median (IQR)/mean (SD) EDSS scores were 6.0 (4.5–6.0)/5.3 (1.3) for patients with SPMS and 5.0 (4.0–6.0)/4.8 (1.3) for PPMS. Overall median times for 9HPT and T25FWT were 27.9 and 9.4 seconds, respectively. Over 2 years, 311/586 (53.1%) patients had NEP (SPMS 55.8%; PPMS 50.2%; progression was mostly driven by increases in T25FWT) and 283/588 (48.1%) had NEPAD (SPMS 49.5%; PPMS 46.7%; acute activity predominantly driven by N/E-T2 lesions). Overall EDSS remained stable from BL to year 2 (mean [SD] change of +0.07 (0.79) points). In patients with EDSS ⩾2.0 at BL (n=526), 24-week confirmed disability improvement in any of the components (EDSS, T25FWT, 9HPT) was observed in 29.8% of cases. Rates of serious AEs and serious infections were 7.6/100PY and 3.2/100PY, respectively. Eight deaths were reported (COVID=6, pulmonary embolism=1, non-small cell lung cancer=1).
Conclusions: Over a 2-year period, treatment with OCR was associated with comparable rates of NEP and NEPAD in patients with SPMS and PPMS, and with functional improvement in about one-third of patients. Safety outcomes were consistent with known safety profile.

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B-cell depletion and return in participant subgroups of the phase 3 ULTIMATE I and II studies of ublituximab versus teriflunomide in participants with relapsing multiple sclerosis

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Introduction: Ublituximab is a novel monoclonal antibody targeting a unique epitope of CD20. Ublituximab is glycoengineered for enhanced antibody-dependent cellular cytotoxicity and is administered in 1-hour maintenance infusions after the first infusion. In ULTIMATE I and II, ublituximab significantly improved annualised relapse rate in participants with relapsing multiple sclerosis (RMS).

Objectives/Aims: To evaluate B-cell depletion and return with ublituximab in participant subgroups in ULTIMATE I and II.

Methods: The Phase 3 ULTIMATE I (N=549) and II (N=545) studies evaluated ublituximab 450 mg intravenous infusion every 24 weeks or teriflunomide 14 mg oral once daily for 96 weeks in participants with RMS. Pooled post hoc analyses evaluated the kinetics of B-cell depletion and return in ublituximab-treated participants. Evaluated subgroups included age (<38 years versus ⩾38 years), gender (men versus women), and body mass index (BMI) (<30 kg/m^2 versus ⩾30 kg/m^2). The proportion of participants experiencing B-cell return, defined as >10 cells/μL, was also evaluated at each timepoint.

Results: In the overall ublituximab-treated pooled population, participants had a 96.2% reduction from baseline in the mean number of CD19+ B cells starting at Week 1 Day 2, which remained consistent through Week 96 (97.6% reduction). Prior to the first open-label extension (OLE) infusion, mean B-cell numbers had increased to 23.8% of baseline. The kinetics and extent of B-cell depletion were similar for all subgroups evaluated. At Weeks 96, 100, 104, and OLE Day 1 (24, 28, 32, and mean 55 weeks after the last dose), 3.7%, 7.7%, 15.1%, and 62.4% of all participants had B-cell return, respectively. Mean B-cell levels (cells/μL) at the first OLE visit (mean 50-55 weeks after last dose) were slightly higher for the subgroups aged <38 years (63.5 versus 37.7 for ⩾38 years), BMI <30 kg/m^2 (54.4 versus 31.4 for ⩾30 kg/m^2), and men (57.3 versus 51.0 for women). Participant and disease characteristics were similar among those with and without B-cell return observed at least once between Week 12 and Week 96 (inclusive); no formal statistical testing was performed.

Conclusions: In ULTIMATE I and II, peripheral B-cell numbers declined rapidly after the first ublituximab infusion and remained low during treatment, as expected with ublituximab's mechanism of action. B-cell depletion with ublituximab was consistent across evaluated participant subgroups.

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P701

Multiple sclerosis patient types, treatment patterns, and therapy selection considerations: patient-level retrospective chart audit data comparison by managing physician specialty

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Introduction: Patients diagnosed with multiple sclerosis (MS) may be managed by either a general neurologist (GN) or an MS specialist (MSS).
Objective: To compare patient types, treatment patterns, and the disease-modifying therapy (DMT) selection process among MS patients recently initiated on a DMT by specialty.
Aim: To identify differences in patient types, treatment patterns, and the DMT selection process between specialties.
Methods: 208 US neurologists completed a survey and contributed chart reviews for a retrospective, cross-sectional audit between Nov 30, 2021 and Jan 24, 2022, on MS patients who started their first DMT within the prior 3 months. Analyses were restricted to data collected from GN (n=100 physicians; n=567 charts) and MSS (n=103 physicians; n=505 charts).
Results: Compared with GN, MSS contributed more charts for patients diagnosed with PPMS (9% and 4%) and fewer charts for patients diagnosed with RRMS (72% vs. 81%). More patients managed by MSS vs. GN were reported as having unfavorable long-term prognosis (25% vs. 20%).
DMT treatment differed by specialty: more patients managed by GN vs MSS were treated with glatiramer acetate (GA) agents (20% vs. 13%) and oral DMTs (47% vs. 40%) and fewer were treated with monoclonal antibody DMTs (22% vs. 34%). GA (15% vs. 7%), teriflunomide (8% vs. 5%), and dimethyl fumarate (10% vs. 6%) use was more common among patients managed by GN and ocrelizumab (9% vs. 17%) and ponesimod (1% vs. 2%) use was less common.
The selection of the current DMT was highly influenced by the belief that the DMT was the best option for the patient for both GN and MSS (47% and 44%). However, MSS were more influenced by the specific mechanism of action (MOA; 38% vs. 25%) and the DMT being appropriate in JCV seropositive patients (4% vs. 2%). GN were more influenced by payer preference (16% vs. 10%), payer mandates (9% vs. 6%), pregnancy planning/breastfeeding considerations (6% vs. 3%), and the perception that the patient was highly adherent with medical instructions (19% vs. 12%).
Conclusions: For treatment-naïve MS patients recently initiated on their first DMT, patient types, DMT treatment, and DMT selection drivers varied between specialties. GN were more likely to treat patients with platform DMT options and be influenced by market access considerations and perceptions of patients' adherence to treatment. MSS were more likely to treat patients with more severe disease and be influenced by the DMT's MOA.

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P702

Selection of disease-modifying therapies in elderly MS patients: Data from a nationwide registry

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Introduction: In the last two decades, life expectancy in individuals with multiple sclerosis (MS) has risen, in line with that of the general population. However, clinical trials of existing disease-modifying therapies (DMTs) have systematically excluded older patients, limiting our knowledge on the safety and efficacy of these treatments in later adulthood.
Objective: To evaluate the types of DMTs prescribed in older patients with MS, compared to those recommended in younger patients.
Methods: Patients were recruited from the Argentine registry for MS and NMOSD (RelevarEM, NCT 03375177). Two different groups were selected: patients with relapsing remitting MS under 35 years of age and patients older than 50. Demographic, clinical, and radiological characteristics were assessed. Patients were classified as having a highly active disease (HAD) (one relapse in the last 6 months, and/or 2 relapses in the last year, and/or 2 or more new T2/Gd lesions on MRI) or no HAD. The type of DMT prescribed was classified as low efficacy (interferons, glatiramer acetate, teriflunomide, and dimethyl fumarate) or high efficacy (fingolimod, cladribine and monoclonal antibodies). Chi-square or Fisher's exact test was used to compare categorical variables, and Student t-test to compare continuous variables. STATA 13 statistical software was used for data analysis.
Results: A total of 1460 patients (65% females) were included. In the HAD group (241 patients), 198 were young (82.2%) and 43 elderly (17.8%). Median EDSS was 2.6 vs 3.9, respectively ($p<0.01$). Elderly MS patients were mostly prescribed low efficacy DMTs (61%). Conversely, younger MS patients received high efficacy treatments in 71% of cases ($p=0.01$). No HAD group included 1219 patients, 893 young (73%), and 326 elderly (27%). EDSS was 1.8 vs 3.4, respectively ($p<0.01$). Most elderly patients received low efficacy DMTs compared to younger individuals with MS (66% versus 44%; $p<0.01$).
Conclusion: Types of DMT prescribed in patients with MS seem to be influenced by age, regardless of levels of disease activity. It is essential to improve therapeutic risk/benefit ratios in the older population with MS, to better prevent disease progression in this age group.

Disclosure
Authors declare no potential conflicts of interest.

P703
Differences in prescribing patterns for the treatment of multiple sclerosis between neuroimmunology subspecialists and other providers at duke university hospital

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It is unclear what the best treatment strategy for patients with multiple sclerosis (MS) is and whether it consists of escalation therapy or early intensive treatment. Prior observational studies have shown that early use of high-efficacy disease modifying therapies for MS may reduce the likelihood of worsening disability and advancing to a progressive stage of disease. There are ongoing prospective studies looking at various outcomes for escalation versus early intensive treatment. In this study we investigate whether there are differences in practice patterns between neuroimmunology providers and providers without subspecialty training in the care of patients with MS. With a rapidly growing armamentarium of treatment options, identifying the best ways to approach the care of patients living with MS is of the utmost importance. As more research shows greater benefit with early intensive treatment it will be important to educate general neurologists to increase the use of high efficacy therapies. In this study we aimed to determine whether there are differences in practice patterns between subspecialized neuroimmunology providers and providers without subspecialty training in the care of patients with Multiple Sclerosis (MS) at Duke University Hospital (DUH). Adult patients with a diagnosis of MS within the past 3 years were identified using SlicerDicer and divided into those receiving care from a neuroimmunology subspecialist and those receiving care from a provider without subspecialty training. These two groups were then analyzed to see the percentage of patients prescribed specific MS medications. These percentages were compared with a Z score to evaluate for a significant difference in the percentage of patients in each group. There was a significant difference in prescribing patterns with intermediate and high efficacy MS medications prescribed in 42.2% of patients seen by MS specialists (1008/2386) and 16.1% of patients seen by other providers (683/4240), $Z = 23.426$, $p = 0.0002$. There are significant difference in prescribing patterns at DUH with providers without subspecialty training prescribing high efficacy medications less often emphasizing the need to understand why this difference exists and increase education about the optimal treatment of MS.

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P704
A study of activated and naïve T regs and B cell subsets for 30 months after the use of cladribine

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Introduction: A short term course of cladribine has a prolonged effect on the clinical course of MS.The exact mechanism of this phenomenon is unknown.
Objectives: To examine the effect of cladribine on T regulatory cells (Treg) using markers of activation and chemokine receptors and comparing this to the effect on B cell subsets.
Methods: Peripheral blood was collected from healthy donors and MS patients prior to cladribine therapy and then at 1, 6, 12, 24 and 30 months post therapy. Peripheral blood mononuclear cells (PBMC) were isolated from whole blood using Ficoll-Hypaque density gradient centrifugation. Fresh PBMC ($1x10^6$) were stained with panels of antibodies for activated and naïve Treg (CD4, CD127, CD25, Foxp3, CD45RA, CXCR3, CCR6, CCR4) and B cell subset (CD45, CD19, CD27, CD21, IgD, IgM, CD38, CD24) identification. For Treg staining, cells were first stained with chemokine receptors for 15 minutes at room temperature in the dark before staining for other surface markers CD4, CD25, CD127 and CD45RA, before staining for Foxp3. For B cells, cells were stained with the full panel of antibodies for 30min.Phenotypic analysis was performed on stained PBMC using a FACSCanto II flow cytometer (BD Biosciences) and FACS DIVA 8.0 software. The data was analysed using Flojo software to examine changes in naïve and activated Treg and B cell subsets. Ratios and absolute numbers including the ratio of Treg to B cell subsets were calculated. Data was analysed using GraphPad Prism and significance was set as $p<0.05$.
Results: The most dramatic effects were the early increases in the ratios of Treg to all B cells in patients treated with cladribine compared with HD. However this effect dissipated after 3 months. The more persistent effects were seen in an increased ratio of Treg to memory B cells, marginal zone B cells, transitionalB cells, and switched and unswitched memory B cells. There was a significantly higher ratio of Treg to memory B cells at 3mth (2.62 vs 0.36, $p<0.05$), 12mth (1.993 vs 0.31, $p<0.001$) which stayed higher until 30-mth post cladribine. As absolute numbers ($x\ 10^9/L$) also, 3mth (18.73 vs 1.038, $p<0.001$).
Conclusion: The data suggests that an increased ratio of activated Treg to activated B cells may contribute to the prolonged effect of cladribine therapy.

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P705
Comparative effectiveness of autologous haematopoietic stem cell transplantation with immune reconstitution therapies in relapsing-remitting MS

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Intro: Chemotherapy with autologous hematopoietic stem cell transplantation (AHSCT) has been increasingly used in highly active multiple sclerosis (MS). Information about its comparative effectiveness relative to immune reconstitution therapies is lacking.

Aim: This study emulated pairwise trials of comparative effectiveness of AHSCT vs. alemtuzumab, cladribine tablets and mitoxantrone (an older, broadly immunosuppressive therapy).

Methods: Patients with relapsing-remitting MS from 6 AHSCT MS centres in Ottawa, Uppsala, Sheffield, Bergen, Sydney and Melbourne were combined with patients from MSBase. Included patients were treated with AHSCT or one of the study therapies and had sufficient information recorded before and after the start of the treatments (baseline). Groups were matched on a propensity score derived from sex, age, disability score (EDSS), number of relapses 12 and 24 months before baseline, time from MS onset, the most effective prior therapy and country. The pairwise-censored groups were compared on annualised relapse rates (ARR), hazards of relapses and 6-month confirmed EDSS worsening and improvement.

Results: The matched patients had high mean disease activity (>0.9 relapses in the prior year), mean EDSS 3-4.5, and matched follow-up of 2-3 years.Alemtuzumab (n=284) and AHSCT (n=122) were associated with similar ARR (mean±SD 0.13±0.31 vs. 0.11±0.35), risk of relapses (hazard ratio 0.79, 95%CI 0.46-1.37), similar risk of EDSS worsening (hazard ratio 0.82, 95%CI 0.33-2.03) and EDSS improvement (hazard ratio 1.07, 95%CI 0.74-1.57). Cladribine (173) and AHSCT (65) were associated with similar ARR (0.16±0.48 vs. 0.10±0.38), risk of relapses (0.63, 0.22-1.77), EDSS worsening (0.51, 0.08-3.14) and EDSS improvement (1.24, 0.44-3.78). Compared to Mitoxantrone (91), AHSCT (30) was associated with lower ARR (0.35±0.74 vs. 0.17±0.57) and a corresponding trend for the risk of relapses (0.48, 0.18-1.28). We did not find evidence for differences in EDSS worsening (0.49, 0.16-1.54) and EDSS improvement (1.19, 0.24-5.88).

Conclusion: In this limited cohort with highly active MS and moderate disability, the clinical effectiveness of AHSCT was comparable to two immune reconstitution therapies – alemtuzumab and cladribine. There was evidence for superior prevention of relapses by AHSCT than by mitoxantrone, but no evidence for difference in disability outcomes. Further comparison of AHSCT to these therapies in cohorts and trials over extended time is warranted.

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P706

Is disease-modifying therapy use in the multiple sclerosis a risk factor during the COVID-19 pandemic? A large cohort study

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Introduction: The role of ongoing disease-modifying therapy (DMT) in coronavirus disease 2019 (Covid-19) morbidity and mortality in people with multiple sclerosis (MS, pwMS) is uncertain. The MS International Federation recommends that pwMS continue their medication.
Objectives: To investigate the relationship between DMT used in MS patients and the risk of Covid-19 infection.
Aims: The MS cohort of 3402 people followed for Covid-19 infection was included in this longitudinal cohort study. The whole MS cohort was interviewed at least once for information about Covid-19, by text message, or by phone, during which 487 pwMS were determined with Covid-19 infection. A semi-structured interview,

which included questions related to COVID-19 symptoms, recovery status, and duration of symptoms, was developed and performed by a team consisting medical doctor, nurse, and physiotherapist. Clinical information was obtained from the patient's medical records.

Results: Of the 487 pwMS infected with Covid-19, 35 reported reinfections. The clinical and demographic profiles of participants were following: the mean age was 40.3±11.4, the mean disease duration was 10.7±8.2, the mean EDSS score was 1.7±2, 342 (70.2%) were female, 425 (87.3%) had relapsing-remitting MS, and 324 (6.5%) were working. The major differences regarding DMT between pwMS with and without Covid-19 infection were observed for fingolimod, ocrelizumab, and azathioprine. Forty-three (8.9%) people experienced the Covid-19 infection severely or critically; of those, 15 (34.9%) had MS treatment with ocrelizumab. Thirty-two (6.6%) patients reported that they were hospitalized; 12 (37.5%) of these had been treated for MS with ocrelizumab. Fifty percent of pwMS who were treated in intensive care (7/14 patients) and died (3/6 patients) were being treated with ocrelizumab. As a result of the regression analysis, any additional risk factor on Covid-19 related to MS treatments was not detected, while working/being active in social life has a risk factor on the Covid-19 infection and it is course.

Conclusions: The current data show that pwMS using ocrelizumab have a more severe course of Covid-19 infection than those using other DMTs. These data will guide the treatment of pwMS in cases of new Covid-19 variants or similar pandemic situations that may develop in the future.

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P707

Relationship between infections and absolute lymphocyte count during phase 3 and open-label extension trials of ozanimod in patients with relapsing multiple sclerosis

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Introduction: Ozanimod is a sphingosine 1-phosphate (S1P) receptor 1 and 5 modulator that is approved in multiple countries for treatment of adults with relapsing forms of multiple sclerosis (RMS). S1P receptor modulators decrease the peripheral blood absolute lymphocyte count (ALC) by reducing lymphocyte egress from secondary lymphoid organs.

Objectives: To describe the level of ALC at the time of first infection in patients with RMS who were treated with ozanimod 0.92 mg/d in phase 3 "parent" trials (SUNBEAM–NCT02294058; RADIANCE–NCT02047734) and an open-label extension (OLE) trial (DAYBREAK–NCT02576717).

Methods: Patients in the parent and OLE trials with ALC measured within 92 days before or after their first infection were included and were divided into 5 ALC groups: ⩾lower limit of normal (LLN) (group 1), 0.8×10^9/L–<LLN (group 2), 0.5–$<0.8\times10^9$/L (group 3), 0.2–$<0.5\times10^9$/L (group 4), and $<0.2\times10^9$/L (group 5). The incidence of total infections, serious infections, and opportunistic infections was assessed by ALC group in the parent (ozanimod 0.92 mg group) trials and the OLE (where all subjects received ozanimod 0.92 mg).

Results: During the parent trials, 762 patients treated with ozanimod 0.92 mg had a postbaseline ALC assessment. At the time of first infection, 3.9%, 3.5%, 15.4%, 13.0%, and 0.3% of these patients had ALC in groups 1-5, respectively. At the time of first serious infection, 0.1%, 0.1%, 0.4%, 0.3%, and 0% had ALC in groups 1-5, and at first opportunistic infection, 0.4%, 0.1%, 0.7%, 0.5%, and 0% had ALC in groups 1-5, respectively.

During extended observation in the OLE trial, 2251 patients had a postbaseline ALC assessment. At the time of first infection, 7.4%, 5.9%, 21.5%, 20.7%, and 1.0% of these patients had ALC in groups 1-5, respectively. At first serious infection, 0.1%, 0.3%, 1.1%, 1.2%, and 0.04% had ALC in groups 1-5, and at first opportunistic infection, 0.7%, 0.3%, 1.4%, 2.6%, and 0.1% had ALC in groups 1-5, respectively.

Conclusion: The majority of patients with any infection had ALC between 0.2×10^9/L and 0.8×10^9/L at time of first infection; few had ALC $<0.2\times10^9$/L at first infection. There was no association between serious infections or opportunistic infections and degree of lymphopenia in patients treated with ozanimod 0.92 mg in the parent or OLE trials.

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P708
Matching-adjusted indirect comparisons of diroximel fumarate, ponesimod, and teriflunomide for relapsing multiple sclerosis

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Introduction: Diroximel fumarate (DRF), ponesimod (PON), and teriflunomide (TERI) are oral disease-modifying therapies (DMTs) approved for treatment of relapsing multiple sclerosis. No randomized trials have directly compared DRF vs. PON or TERI.
Objectives: Using matching-adjusted indirect comparisons, we compared efficacy of DRF vs. PON and DRF vs. TERI for annualized relapse rate (ARR), 12-week confirmed disability progression (CDP), 24-week CDP, absence of gadolinium-enhancing (Gd+) T1 lesions, and absence of new/enlarging T2 lesions.
Methods: We used individual patient data from EVOLVE-MS-1, a 2-year, open-label, single-arm, phase 3 trial of DRF (n=1,057), and aggregated data from OPTIMUM, a 2-year, double-blind, phase 3 trial comparing the efficacy of PON (n=567) and TERI (n=566). To account for cross-trial differences, data from EVOLVE-MS-1 were weighted to match average baseline characteristics in OPTIMUM. Results are reported with PON or TERI as the reference (negative rate/risk differences for ARR and CDP indicate favourable outcomes for DRF; positive risk differences for absence of Gd+ T1 lesions and absence of new/enlarging T2 lesions favour DRF).
Results: After weighting, all groups were balanced on baseline variables. DRF and PON had similar efficacy for ARR (rate difference for DRF vs. PON: -0.02; 95% confidence interval [CI]: -0.08, 0.04), 12-week CDP (risk difference: -2.4%; 95% CI: -6.3%, 1.3%), and 24-week CDP (risk difference: -1.7%; 95% CI: -5.1%, 1.7%). DRF had higher proportions of patients without Gd+ T1 lesions (risk difference: 11%; 95% CI: 5.9%, 16%) and new/enlarging T2 lesions (risk difference: 35%; 95% CI: 28%, 41%) compared with PON. In the comparison of DRF and TERI, the rate difference for ARR (DRF vs. TERI) was -0.08 (95% CI: -0.15, -0.01), risk difference for 12-week CDP was -4.0% (95% CI: -8.0%, -0.11%), risk difference for 24-week CDP was -3.2% (95% CI: -6.7%, 0.13%), risk difference for the absence of Gd+ T1 lesions was 25% (95% CI: 19%, 30%), and risk difference for the absence of new/enlarging T2 lesions was 45% (95% CI: 39%, 52%).
Conclusions: DRF and PON had similar efficacy for ARR and 12- and 24-week CDP. However, DRF was associated with a higher proportion of subjects who did not have Gd+ T1 lesions and new/enlarging T2 lesions at the end of follow-up. DRF had greater efficacy than TERI for all clinical and radiological outcomes, except for 24-week CDP, in which there was similar efficacy.

Study Support: Biogen.

Disclosure
TJ, CS, KS, JBL, and IB are all employees of and hold stock/stock options in Biogen.

P709
Effect of SARS-CoV-2 vaccination on natural killer cell responses in multiple sclerosis

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Introduction: Anti-SARS-CoV2 vaccination induces specific T- and B-cell responses in healthy subjects (HS). In MS patients treated with anti-CD20 drugs, the antibody response is reduced or absent, whereas specific T-cell responses are maintained. It is not known whether and how vaccination affects innate responses mediated by natural killer (NK) cells in HS and in MS patients treated with anti-CD20 drugs.
Objective: To evaluate whether and how NK cells contribute to the immune response following anti-SARS-CoV2 vaccination in HS and in ocrelizumab-treated MS patients
Aims: The aims of this work were: 1) to evaluate the effects of anti-SARS CoV2 vaccination on the phenotype of NK cells from HS and from ocrelizumab-treated MS patients and 2) to evaluate how peptides from the SARS-CoV2 spike protein affect NK cell responses before and after anti-SARS-CoV2 vaccination.
Methods: We enrolled 21 MS patients treated with ocrelizumab and 20 HS. Peripheral blood mononuclear cells (PBMCs) were isolated from peripheral blood and stored under liquid nitrogen. Thawed PBMCs were cultured overnight in presence/absence of SARS-CoV2 peptides or peptides from the cytomegalovirus (CMV), with/without activating cytokines. Phenotype of NK cells through a 13-marker flow cytometry panel and intracellular production of IFN-γ were evaluated after culture.
Results: Findings: 1) Vaccination increased the proportion of $CD56^{dim}$ NK cells in HS and MS patients. $CD56^{pos}CD16^{neg}$ NK cells, more abundant in MS patients before vaccination, decreased thereafter. Lower pre-vaccination activation capability of NK cells from MS patients compared to HS in response to stimulus with cytokines was reverted by vaccination. 2) Before vaccination, peptides from the SARS-CoV2 protein downregulated the production of IFN- γ from NK cells of HS, but not ocrelizumab-treated MS patients, who had significantly lower baseline IFN-γ NK cells 3) After vaccination, peptides from the SARS-CoV2 protein did not affect the production of IFN- γ from NK cells of HS.
Conclusions: The results of this work demonstrate anti-SARS-CoV2 vaccination increases the proportion of effector $CD56^{dim}$

NK cells in HS and ocrelizumab-treated patients. Spike peptides inhibit the function of NK cells from HS before, but not after vaccination. Such phenomenon may contribute to the pathogenicity of SARS-CoV2 in unvaccinated subjects.

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P710
Mesenchymal stem cells for multiple sclerosis: effect of treatment on peripheral immune cells

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Introduction: Autologous, bone marrow-derived mesenchymal stem/stromal cells (MSC) have shown promising results in the treatment of the animal model of multiple sclerosis (MS) due to their immunomodulatory and neuroprotective features. Based on these data, an international, multicenter, randomized, double blind, cross-over, phase I/II, clinical trial, Mesenchymal Stem Cells for Multiple Sclerosis (MESEMS), was conducted.
Objectives: To evaluate the effect of treatment with autologous MSC on peripheral immune cells in MS.
Aims: To assess the changes in phenotype of peripheral immune cells in patients treated with MSC compared to placebo and to correlate such changes to MRI and clinical activity.
Methods: 38 patients with MS from three centers participating to the MESEMS clinical trial were enrolled. From blood samples drawn throughout the study, peripheral mononuclear blood cells were isolated at each center and frozen; cells were shipped to the coordinating center for flow cytometric staining and analysis. T-, B- and NK immune cell subsets were evaluated with a standardized flow cytometry panel. Anova for repeated measures was employed to evaluate differences in the immune cell trend in the first 24 weeks of treatment and paired t-test was employed to evaluate the change in immune cell subsets in the first 4 weeks after treatment with MSC towards placebo.
Results: 27/38 patients had immunological evaluations at all time points and were included in the present analysis. Treatment with MSC led to significant changes in the phenotype of circulating immune cells at 4 weeks: in detail, treatment with MSC led to increased frequency of transitional B cells (i.e. B regulatory cells), and CD4+ T regulatory cells; moreover, patients treated with MSC had higher CD4+T regulatory effector/naïve ratio. We did not find significant changes in the trend of T-B- and NK cell subsets throughout the first 24 weeks. Increase in CD4+ Tregs in the first 4-treatments weeks was observed in patients with no relapses in the following 20 weeks, compared to decrease of CD4+ Tregs in patients with relapses. Decrease of naïve CD4+ Tregs in the first 4 weeks of treatment was associated with higher MRI activity in the following weeks.
Conclusions: Treatment with MSC led to increased proportion of regulatory subsets among T and B lymphocytes. Clinical/MRI response to MSC treatment was associated to short-term increase in CD4+T regulatory cells.

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P711

Tracking the immune response to SARS-CoV-2 mRNA vaccines in ofatumumab treated RMS patients in a multicenter study (KYRIOS trial)

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Introduction: Recently developed SARS-CoV-2 mRNA vaccines have been shown to efficiently protect healthy individuals against COVID-19 and contribute greatly towards fighting the COVID-19 pandemic.
Aims: As only limited data is available for Multiple Sclerosis (MS) patients with immunosuppressive treatment, this study aims to understand the impact of ofatumumab treatment on the development of cellular and humoral immune responses to initial and booster SARS-CoV-2 mRNA vaccines.
Methods: KYRIOS is a prospective, open-label, two-cohort study including 34 MS patients at 8 sites in Germany. Patients receive initial or booster SARS-CoV-2 mRNA vaccination either before (cohort 1) or at least 4 weeks after starting ofatumumab treatment (cohort 2). As primary endpoint, the impact of ofatumumab treatment on development of SARS-CoV-2 reactive T-cells will be evaluated. Additionally, neutralizing antibodies will be assessed, and the immune responses will be monitored and phenotypically described for up to 18 months.
Results: Interim analysis will show the complete primary endpoint results of the KYRIOS study. All patients vaccinated during continuous ofatumumab treatment (5/5) developed an immune response as soon as one week after initial vaccination cycle. While the extent of T-cell response was not affected in ofatumumab treated patients, neutralizing antibodies titers were lower compared to the control group. After the first booster vaccine, the majority of ofatumumab patients (n=15) showed an increase in neutralizing antibodies to a comparable extend as the control group (n=8). Data show that seroconversion during continuous ofatumumab treatment is possible. In general, this analysis confirms first positive interim analysis data presented at AAN 2022.
Conclusions: KYRIOS data demonstrate that ofatumumab treated patients can mount specific immune responses towards SARS-CoV-2 mRNA vaccines. The presented data further emphasize the importance of considering both, humoral and cellular immune response, for interpretation of vaccine efficacy and the importance of booster vaccines in immunocompromised patients.

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P712

Diroximel fumarate in patients with relapsing-remitting multiple sclerosis: final safety and efficacy results from the phase 3 EVOLVE-MS-1 study

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Introduction: Diroximel fumarate (DRF), an oral fumarate for relapsing-remitting multiple sclerosis (RRMS), has the same active metabolite as dimethyl fumarate (DMF). DRF has similar efficacy/safety to DMF but with improved gastrointestinal (GI) tolerability.
Aims: Report final safety and efficacy of DRF in EVOLVE-MS-1.
Methods: EVOLVE-MS-1 (NCT02634307), a 96-week, open-label, Phase 3 study, assessed safety, tolerability, and exploratory clinical and MRI efficacy of DRF in adults with RRMS between 10Dec2015-11Nov2021. Patients either newly initiated DRF or rolled over from completing EVOLVE-MS-2 (NCT03093324), a randomised, blinded, Phase 3 study of DRF or DMF over 5 weeks.
Results: Overall, 1057 patients enrolled in EVOLVE-MS-1; 464 had completed EVOLVE-MS-2. Median (range) DRF exposure was 1.8 (0.0-2.0) years. Mean (standard deviation [SD]) age was 42.5 (10.8) years; 72.1% of patients were female. Mean (SD) time since diagnosis was 7.6 (7.3) years. Overall, 241 (22.8%) patients discontinued DRF; 85 (8.0%) discontinued due to adverse events (AEs).
AEs occurred in 938 (88.7%) patients; most (89.3%) were mild/moderate. GI AEs occurred in 337 (31.9%) patients; median (10^{th}-90^{th} percentile) duration was 10 (1-135) days. DRF was discontinued due to GI AEs in 7 (0.7%) patients. Flushing occurred in 288 (27.2%) patients; median (10^{th}-90^{th} percentile) duration was 12.5 (1-536) days. DRF was discontinued due to flushing in 5 (0.5%) patients. Serious AEs occurred in 123 (11.6%) patients. There were 4 (0.4%) deaths; 0 were considered related to study treatment.
At Week 96: adjusted annualised relapse rate (ARR) was 0.13; estimated proportion of patients who were relapse-free was

82.4%; and estimated proportion with no evidence of disease activity (NEDA-3) was 41.1%. Mean (SD) number of gadolinium-enhancing (Gd+) lesions decreased 72.7% from Baseline (1.1 [3.5]) to Week 96 (0.3 [3.0]). At Week 96, 91.1% of patients were Gd+ lesion-free vs 70.4% at Baseline. Mean (SD) number of new/newly enlarging T2 lesions was 2.1 (6.5) from Baseline to Week 48 and 1.3 (5.5) from Week 48 to Week 96.

Conclusions: Based on final EVOLVE-MS-1 outcomes, DRF showed favourable tolerability over 96 weeks. While 22.8% of patients discontinued DRF, discontinuations due to GI AEs (0.7%) and flushing (0.5%) were low. ARR on DRF was low; MRI showed decreases in disease activity. These data support DRF as a tolerable and effective treatment option for patients with RRMS.

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Disclosure

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MS: Employee of and holds stock/stock options in Biogen.

WC-B: Employee of and holds stock/stock options in Biogen.

HA: Employee of Biogen.

HC: Employee of and holds stock/stock options in Biogen.

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Preserved T cell but attenuated antibody response in MS patients on Fingolimod and Ocrelizumab following 2nd and 3rd SARS-CoV-2 mRNA vaccine

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Introduction: Immunosuppressed patients may not mount an adequate immune response to 2 doses of SARS-CoV-2 mRNA vaccine and are eligible to receive a 3rd dose. There is limited knowledge about T cell responses specifically in patients with multiple sclerosis (MS) who receive 3 doses of vaccine.

Objectives & Aims: To assess the SARS-CoV-2 spike antibody responses and T cell responses in MS patients on high efficacy immunotherapies and healthy controls (HC) who received 2 and 3 doses of SARS-CoV-2 mRNA vaccines.

Methods: This is a study of patients with MS, aged 18-65, on fingolimod (FIN) and ocrelizumab (OCR) for at least 3 months prior to 1st mRNA SARS-CoV-2 vaccine dose (BNT162b2 or mRNA-1273) and a cohort of HC. Blood samples were collected after 2nd (2-vax) and 3rd (3-vax) dose of mRNA vaccine. The proportion of patients and HC who exhibited seroconversion, demonstrating serum SARS-CoV-2 spike antibody levels >0.4 U/ml,was determined. T cell responses were examined in a subgroup of patients with MS and HC after 2-vax and 3-vax by flow cytometry.

Results: The proportion of patients who seroconverted after 2-vax was 8/33 (24.2%) in the OCR group, 5/7 (71.4%) in the FIN group, and 29/29 (100%) in the HC group (Fisher's exact test, $P=5.7*10^{-11}$). After 3-vax, 9/21 (40.9%) patients in the OCR group seroconverted as compared to 19/21 (90.5%) in the FIN group, and 7/7 (100%) in the HC group (Fisher's exact test for difference, $P=0.0003$). There was SARS-CoV-2 peptide reactive CD4+ and CD8+ T cell activation across all 3 groups (OCR 2-vax n=10, FIN 2-vax n=6, HC 2-vax n=8, OCR 3-vax n=9, FIN 3-vax n=10, HC 3-vax n=5) as compared to unstimulated condition after 2-vax and 3-vax (Mixed effects analysis, $P<0.0001$). There was an increase in the percentage of SARS-CoV-2 peptide reactive CD4+ T cells in HC and OCR group but not in FINgroupafter 2-vax and 3-vax. There was anincrease in the percentage ofIFNγandTNFαproducing CD4+ and CD8+ T cells in FIN group as compared to HC and OCR group after 2-vax and 3-vax.TNFαproducing central memory CD4+ T cells were increased in OCR group after 2-vax andIFNγandTNFαproducing effector memory and terminally differentiated effector memory CD4+ T cells were increased in FIN group after 2-vax and 3-vax as compared to HC.

Conclusions: MS patients on ocrelizumab and fingolimod had decreased spike antibody responses, but preserved T cell responses compared to HCs after SARS-CoV-2 mRNA vaccination.

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A long term multicenter observational study on the efficacy and safety of alemtuzumab in multiple sclerosis highly active naïve patients

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Introduction: Alemtuzumab(ALEM) is an anti-CD52 monoclonal antibody approved for the treatment of active Multiple Sclerosis(MS) which showed high efficacy also in the subgroup of highly active patients in the clinical trials.
Objectives: To verify if the highly aggressive (HA) naive patient is the ideal candidate of ALEM
Aims: To evaluate efficacy and safety of ALEM-treatment in a population of HA naïve-patients.
Methods: Clinical and radiological parameters were collected from patient's clinical records in 28 MS Centers from October 2015 to August 2021
Results: 138 naïve pts were treated with ALEM: 60,8% females, mean age 36,6 (± 11,6) years, mean disease duration 18,45 (± 24,9)months, mean follow-up(FU) 60,14 (± 12,14)months, median EDSS 3(0-6,5), ARR in the year preceding treatment 1,7 (± 0,9), mean number of brain T2/FLAIR-hyperintense lesions 29,8 (± 20,8) and mean number of Gd-enhancing lesions 3,4(± 5,1).
Regarding ALEM efficacy, we report data obtained after the first complete cycle of treatment (2 ALEM-courses) because the presence of disease activity between the first and second course is not indicative of a therapeutic failure.
117/138 pts have at least 36 months of FU: 77,7%(91/117) were relapse-free, ARR was 0,11 and the mean time to first relapses was 17,96(± 3,75)months; 68% were MRI activity-free; 88% were progression-free with median EDSS of 2,0(IQR 1 - 2). 59,8%pts was NEDA-3; 5,1% needed a third cycle of ALEM, 3 pts shift to ocrelizumab, 1 to natalizumab and 1 to aHSCT.
Overall 74,4% of pts had adverse events. Infusion-reaction and infections occurred respectively in 70,1% and 9,8% of pts (2 cases of listeriosis); regarding secondary autoimmune disease thyroid dysfunctions occurred in 22,2 % of pts; moreover, there were cases of immune thrombocytopenia, agranulocytosis and vitiligo.
Conclusions: In our very active population, after ALEM-treatment a strong reduction of both relapse rate and MRI activity

was achieved. These results strengthen the assumption that aggressive naïve patient is an ideal candidate for immune system resetting, likely due to young age, short disease duration and low disability. Furthermore, absence of previous immunomodulating/immunosuppressant drugs altering the immune system could play a key role in determining effectiveness of this powerful drug. However, longer FU is needed to confirm our data and evaluate whether an early induction therapy could be worthy in this specific population, balancing benefit-risk ratio

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Immunotherapy for people with clinically isolated syndrome or relapsing-remitting multiple sclerosis - treatment response by demographic, clinical, and biomarker subgroups: a systematic review and meta-analysis

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Introduction: Given the large number of available disease modifying treatments (DMTs) in MS, prediction of treatment response based on baseline characteristics before treatment initiation is highly relevant. While subgroup analyses based on possible treatment effect modifiers (TEM) have been performed for single studies, no systematic review across all available possible TEMs has been attempted yet.

Objective: The primary objective of this review is to assess the differential treatment effects of approved DMTs in subgroups of adults with clinically isolated syndrome or relapsing forms of MS.

Methods: We analysed possible TEMs defined by baseline demographic characteristics (gender, age), MRI (T2 lesion load, contrast enhancing lesions) and clinical (i.e. relapses, disability level) measures of MS disease activity. We included all phase-2 and 3 RCTs with a placebo comparator and study duration of at least 12 months. Disability, relapse frequency, quality of live and MRI are analysed as outcomes. Random-effects meta-analyses were used to summarize treatmenteffects within subgroups, and differences in treatment effects between subgroups Results: A systematic literature search yielded 4596studies to be screened, out of which 653full-texts were reviewed, and 43studies were included. Comparative analysis of TEM was available between different interferon-beta and between different sphingosine studies. Preliminary analyses indicate differences in treatment efficacy depending on patient age and presence of Gd+ lesions. In RRMS, larger treatment effects in terms of annualized relapse rates were observed in younger patients (rate ratio (RR) 0.45 vs. 0.64, p=0.0013) and with at least one gadolinium enhancing lesion (RR 0.45 vs. 0.56, p=0.0062). In CIS, no treatment effect modifier could be identified.

Conclusion: This systematic review and meta-analysis supports previous findings that younger age and higher inflammatory disease activity are treatment effect modifiers.

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Therapy - Neuroprotection and Repair

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Neuroprotective effects of RP-101074 in a preclinical, non-inflammatory neurodegeneration animal model

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Introduction: In multiple sclerosis (MS), the chronic disability in patients results from axonal and neuronal degeneration, which is not sufficiently addressed by conventional immunosuppressive or immunomodulatory therapies. Recent trials have demonstrated positive effects of selective sphingosine-1-phosphate receptor (S1PR)-1 and -5 modulators on progressive MS (Kappos et al., 2018). We investigated the effects of RP-101074, a S1PR1/5 modulator, in a non-inflammatory animal model of neurodegeneration to evaluate possible neuroprotective effects.
Aims/Objectives: To investigate whether RP-101074 has neuroprotective properties, its effects will be analyzed in the non-inflammatory model of light-induced photoreceptor loss (Li-PRL).
Methods: For Li-PRL, 6-week-old female C57Bl/6J and CX3CR1^{GFP}transgenic mice were used, which express a green fluorescent protein (GFP) under the control of the CX3C receptor 1 promoter.In these mice, myeloid cells, i.e., monocytes, macrophages and microglia, are fluorescently labeled. Irradiation was performed with an LED cold light source. Inner retinal layer (IRL) thickness and visual function - as indicators of neurodegeneration and neuroprotection (Dietrich et al., 2019) - were measured using optical coherence tomography (OCT), confocal scanning laser ophthalmoscopy (cSLO) and optomotor reflex measurements (OMR) at defined intervals after irradiation and compared with the baseline measurements. Further, histological evaluations were performed as endpoint analysis. The mice are treated daily with RP-101074 (0.3 mg/kg and 1 mg/kg) or vehicle by oral gavage, starting from the day of irradiation until the end of the experiment after 6 weeks. Using the CX3CR1^{GFP}mouse line, the activity as well as the cell morphology of retinal CX3CR1+ myeloid cells was investigated in vivo using cSLO.
Results: Treatment with RP-101074 had a positive effect both on the thickness of the inner retinal layers and on visual function. Furthermore, RP-101074 modulated the activity of microglia. OMR, OCT, cSLO (CX3CR1^{GFP}) data and histological analyzes will be presented.
Conclusions: Therapeutic RP-101074 treatment shows a neuroprotective effect in the preclinical, non-inflammatory Li-PRL animal model.

Disclosure
Nothing to disclose

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Early onset of action and sustained efficacy of MRI outcomes during cladribine tablets treatment in highly active relapsing multiple sclerosis: results of the 2-year MAGNIFY-MS study

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Introduction: With the use of frequent magnetic resonance imaging (MRI), the 2-year MAGNIFY-MS study (NCT03364036) was designed to increase understanding of the onset of action and sustained efficacy of cladribine tablets (CladT) 3.5mg/kg cumulative dose over 2 years in patients with highly active relapsing multiple sclerosis (RMS). Results from the 6-month MRI analysis (primary endpoint) were presented previously (ECTRIMS 2020).

Objectives: Report the 2-year follow-up MRI, clinical, and safety results from MAGNIFY-MS.

Aims: Determine the onset of action and maintenance of effect of CladT over 2 years.

Methods: MRI scans were performed at screening, baseline, and at Months 1, 2, 3, 6, 12, 15, 18, and 24 following the initiation of CladT. Changes in combined unique active (CUA), T1 Gd+, and new or enlarging T2 lesion counts were compared exploratively between baseline and post-baseline visits using a mixed-effects linear model for repeated measures. Annualised relapse rate (ARR) was estimated from a Poisson regression model. Safety endpoints are summarised descriptively.

Results: Overall, 270 patients received treatment (mean age 37.7 years; 66.7% female). Among evaluable patients (n=265), mean CUA lesion counts were significantly reduced from Month 2 onwards (-3.52 lesions/year; 95% confidence interval [CI]: -4.60, -2.43; $p<0.0001$). The maximum mean change was reached at Month 6 (-5.99 lesions/year; 95% CI: -6.18, -5.80; $p<0.0001$) and was maintained until Month 24 (-5.91 lesions/year; 95% CI: -6.15, -5.67; $p<0.0001$). Mean T1 Gd+ and mean annualised new/enlarging T2 lesion counts decreased in a similar manner. ARR was 0.11 (95% CI: 0.09, 0.15) and Expanded Disability Status Scale score remained stable for most patients. Regarding safety, ⩾1 treatment-emergent adverse event (TEAE) was experienced by 227 patients (84.1%); 14 patients (5.2%) had ⩾1 serious TEAE. Most post-baseline lymphopenias were Grade 1-2; 24.4% (66/270) of patients experienced Grade 3 and 0.7% (2/270) experienced Grade 4 lymphopenia. TEAEs leading to temporary discontinuation of study treatment occurred in 4 patients (1.5%). Six patients (7.7%) withdrew due to progressive disease.

Conclusions: Treatment with CladT shows an early onset of action from Month 2 onwards with a sustained reduction in MRI lesion counts (CUA, T1 Gd+, and active T2). Over the 2 years, the benefit:risk profile of CladT remained unchanged and in line with observations made during the clinical development phase.

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The monoselective sphingosine-1-phosphate receptor-1 modulator ponesimod enhances remyelination in the cuprizone model of demyelination

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Background: Sphingosine-1-phosphate (S1P1) receptor modulators are used clinically to treat relapsing forms of multiple sclerosis (MS). Selective functional antagonism of the S1PR1 subtype by ponesimod prevents lymphocyte egression from lymph nodes, hence hampering neuroinflammation in MS. Recent findings suggest a potential additional role for ponesimod in the Central Nervous System (CNS) in the differentiation of oligodendrocyte precursor cells (OPC) into mature myelinating oligodendrocytes, and therefore potentially having some effects on remyelination.
Objective: As the Giα-coupled S1P1 receptor is the most prominently expressed S1PR in OPCs, and the S1P1-monoselective receptor modulator ponesimod promotes OPC differentiation, we hypothesized that functional antagonism by ponesimod can induce remyelination*in vivo*.
Methods: Nine-week-old male C57BL/6J mice were fed a 0.3% cuprizone diet for 6 weeks to induce demyelination. Three days before the stop of the cuprizone diet, mice were treated with a daily gavage of ponesimod (1mg/kg, 3mg/kg, or 10mg/kg) or vehicle (0.1% DMSO) for one week during the remyelination phase. The Y maze spontaneous alternations test was applied to test recovery from demyelination-induced working memory deficits at the end of the treatment period. In parallel, de- and remyelination of the optic nerve axon was evaluated by measuring the latency time of visual evoked potentials both during the de- and remyelination phase. Post-mortem remyelination was quantified in an immunohistogical staining for myelin basic protein (MBP) in the corpus callosum, cortex and hippocampus and by determining g-ratios in transmission electron microscopy (TEM) pictures of the corpus callosum.
Results: Ponesimod (1mg/kg, 10mg/kg) decreased the latency time compared to vehicle conditions, which is indicative of functional remyelination. MBP IHC analysis of the corpus callosum (ponesimod 1mg/kg), hippocampus (ponesimod 1mg/kg, 10mg/kg) and cortex (ponesimod 3mg/kg) revealed an increased MBP-positive area. TEM analyses revealed decreased G-ratios in the groups treated with ponesimod 10mg/kg. In addition, the Y maze spontaneous alternations test revealed restored working memory after treatment with ponesimod (1mg/kg, 3mg/kg).
Conclusion: Ponesimod S1P1-monoselective receptor modulator increased remyelination in the cuprizone model of demyelination.

Disclosure
MS, EW ad TV report no competing interest. MAT is an employee of Janssen and may own stock or stock options in Johnson & Johnson.

P719

Oral administration of a novel small molecule that blocks BMP-signaling ameliorates EAE through oligodendrogenesis and remyelination

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Introduction: Oligodendrocyte precursor cells are present in demyelinated MS lesions. However, their differentiation into functional oligodendrocytes is insufficient, and most lesions evolve into nonfunctional astroglial scars. Parenteral anti-bone morphogenetic protein (BMP) therapy was reported to ameliorate EAE through oligodendrogenesis and remyelination.
Objective: To evaluate the effect of oral administration of a novel anti-BMP small molecule (SM) at different doses in experimental allergic encephalomyelitis (EAE) murine model.
Aims: To measure the effect of SM vs. vehicle on EAE clinical signs, BMP signaling, oligodendrocytes regeneration, and the SM pharmacokinetics
Methods: Different doses of a novel anti-BMP- SM, given daily by oral gavage from day 9 (signs onset) until day 38 to EAE induced SJL mice by $PLP_{139-151}$vs. vehicle (PEG-400), n=12 per group. We analyzed the clinical signs (score 0-5), histopathology by confocal microscopy, and SM pharmacokinetics.
Results: Oral administration at a daily dose of 750 μg or 1500 μg of SM to EAE- induced mice ameliorated the disease scores between days 14-30 ($p<0.05$ for each day) and the cumulative scores (mean±S.E.M) of 44.7±2.9 (p=0.032 and 50.3±6.6 p=0.05, respectively vs. 72.3±12.7 in vehicle). The expression of the BMP-signaling transducer phospho-SMAD1/5/8 was reduced after treatment with oral SM in astrocytes (15.0±4.9 cells/mm^2vs. 43.8±4.2 cells/mm^2 in-vehicle, p=0.001) and in oligodendrocytes (14.5±6.9 cells/mm^2vs. 41.4±4.5 cells/mm^2, respectively, p=0.009). Oral SM

increased the numbers of de novo $Olig2^+PDGFR\alpha^+BrdU^+$ pro-oligodendrocytes (26.0±2.6 cells/mm^2vs. 2.8± 2.3 cells/mm^2 in-vehicle, $p<0.001$) and $Olig2^+CC1^+BrdU^+$ mature oligodendrocytes (25.0±5.2 cells/mm^2vs. 5.2± 2.4 cells/mm^2, p=0.015) in the lumbar spinal cord. A pharmacokinetic study of the SM showed a $T_{1/2}$= 6 hours for both IP and oral administration and IC50 of 1.54μM. Oral bioavailability=68.6%.

Conclusions: Daily administration of oral SM from relapse onset for 30 days has therapeutic potential in demyelinating disorders such as MS, by inducing oligodendrogenesis-mediated remyelination in the affected tissue with comfortable bioavailability and half-life.

Disclosure

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P720

Preservation of myelin in patients with relapsing multiple sclerosis treated with ponesimod compared to teriflunomide

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Background: The Phase III 2 year OPTIMUM study compared ponesimod (20 mg), highly selective S1P1 receptor modulator, with teriflunomide (14 mg). Ponesimod treated MS patients showed greater reduction in annualized relapse rate, difference in Fatigue Symptoms and Impacts Questionnaire-Relapsing Multiple Sclerosis, reduction in active lesions/year, reduction in disability accumulation risk estimates and lower brain volume loss. We compared the impact of treatment on myelination in normal appearing white matter (NAWM) which sustains damage early on in MS.

Objective: Compare ponesimod and teriflunomide treatment effects on changes in myelination.

Methods: Myelination was estimated from T1 and T2-weighted MRI collected at baseline, week 60 and week 108 in 427 patients treated with ponesimod and 428 with teriflunomide. Standardized T1/T2 was used to quantify myelination in non-lesional corpus callosum, cingulum, and remaining NAWM. Average myelination change ($\Delta\mathbf{M}$) from baseline at weeks 60 (w60) and 108 (w108) were compared across treatment arms using two-sided two sample t-tests.

Results: With teriflunomide, myelination decreased significantly ($p<0.001$) across each of the 3 regions of interest and at both visits. Conversely, in the ponesimod arm, cingulum showed preservation of myelination while corpus callosum and remaining NAWM showed a slight decrease at w108 ($p<0.05$). However at both visits, average myelination decreases were significantly larger for teriflunomide compared to ponesimod at all regions: corpus callosum: $_{w60}\Delta\mathbf{M}^{pon}$ - $_{w60}\Delta\mathbf{M}^{ter}$= 0.008, $p<0.001$, $_{w108}\Delta\mathbf{M}^{pon}$- $_{w108}\Delta\mathbf{M}^{ter}$= 0.01, $p<0.001$; cingulum: $_{w60}\Delta\mathbf{M}^{pon}$ - $_{w60}\Delta\mathbf{M}^{ter}$= 0.0028, $p<0.05$, $_{w108}\Delta\mathbf{M}^{pon}$- $_{w108}\Delta\mathbf{M}^{ter}$= 0.004, $p<0.001$; remaining NAWM: $_{w60}\Delta\mathbf{M}^{pon}$ - $_{w60}\Delta\mathbf{M}^{ter}$= 0.0025, $p<0.05$, $_{w108}\Delta\mathbf{M}^{pon}$- $_{w108}\Delta\mathbf{M}^{ter}$= 0.004, $p<0.001$.

Conclusions: Ponesimod patients showed either preservation of myelination or less demyelination compared to teriflunomide treated patients, indicating protection of myelin and tissue microstructure.

Disclosure

Ritobrato Datta, Michael Kutch, Derelle Kirksey, Ibrahim Turkoz, Allitia DiBernardo, Maria Ait-Tihyaty, Ziad S. Saad, Hartmuth C. Kolb are or were employees or contractors of Janssen Pharmaceuticals and may hold stock or stock options in Johnson & Johnson. J. Wuerfel is employee of the MIAC AG Basel, Switzerland. He served on scientific advisory boards of Actelion, Biogen, Genzyme-Sanofi, Idorsia, Novartis, and Roche. He is or was supported by grants of the EU (Horizon2020), German Federal Ministries of Education and Research (BMBF) and of Economic Affairs and Energy (BMWI).

P721

NurOwn (MSC-NTF) phase 2 clinical trial in progressive MS: effects on CSF neuroprotective biomarkers

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Introduction: MSC-NTF cells (NurOwn®) are autologous bone-marrow derived mesenchymal stem cells that are induced to secrete high levels of neurotrophic factors while maintaining their intrinsic immunomodulatory activity. In a phase 2 trial (NCT 03799718) we demonstrated safety and promising functional improvements following intrathecal MSC-NTF cell therapy. CSF neuroprotective biomarkers (VEGF[1], HGF[2], and NCAM-1[3]) have previously shown a relationship to disease progression and treatment response in PMS and therefore were evaluated in this clinical trial.

Objectives: Evaluation of CSF neuroprotective biomarkers following MSC-NTF cell therapy.

Aims: Longitudinal analysis of CSF neuroprotective biomarkers following repeat intrathecal treatment.

Methods: Eligible participants had baseline Expanded Disability Status Scale (EDSS) scores between 3-6.5, no clinical relapses

within 6 months of study enrollment, and able to walk 25 feet in 60 seconds or less. 18 participants were randomized to receive 100-125 x 10^6 MSC-NTF cells by lumbar puncture at weeks 0, 8, and 16 and then were followed to week 28. CSF was collected at weeks 0, 8 and 16 (just prior to each treatment).
Neuroprotective biomarkers (VEGF, LIF, HGF, Follistatin, Fetuin-A, NCAM-1, Clusterin/ApoJ) were detected with a highly sensitive, customized ProcartaPlex multiplex immunoassay (Thermo Fisher Scientific, Waltham, MA). Assays were validated by matrix evaluation, including spike recovery, parallelism, and sample stability. Biomarker data were log transformed for analysis and percent changes were graphed in the original units. We present geometric means and the first (Q1) and third (Q3) quartiles.
Results: At week 16, following 2 intrathecal MSC-NTF cell treatments, we observed % increases [geometric mean, (Q1,Q3)] from baseline of VEGF 90.17 (-9.16, 12.48x10^1), LIF 29.84 (-16.36, 10.41x10^1), HGF 15.16 (0.32,19.44), Follistatin 72.14 (0, 11.31x10^1), Fetuin-A 17.43 (-21.77, 25.65), and NCAM-1 17.43 (-3.61,19.88). CSF Clusterin/ApoJ decreased by -0.25 (-15.97,15.79) % from baseline at week 16.
Conclusions: Intrathecal MSC-NTF cell treatment consistently increased CSF neuroprotective biomarkers, confirming the proposed mechanism of action of NurOwn in PMS. These observations support further investigation to address the important unmet medical need in this disorder.
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Jenny Li: Employed by Brainstorm Cell Therapeutics
Sidney Spector: Employed by Brainstorm Cell Therapeutics
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P722
Acceleration of debris clearance and remyelination by neuroimmune modulation

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Introduction: Multiple sclerosis (MS) is a debilitating disease, characterized by neuroinflammation and extensive demyelination, particularly as patients age. Current therapeutic options for MS are predominantlyimmune modulating, however they do not directly promote remyelination. Recent research has demonstrated that vagus nerve stimulation (VNS) modulates endogenous neuro-immune reflexes that reduce inflammation and are neuroprotective in the CNS and that activation of glial nicotinic receptors accelerate myelination (Immunol Rev. 2012 248(1):188, J Neurochem. 2015 135(6):1086).
Objectives: To explore potential therapeutic effects of VNS on remyelination in a lysolecithin-induced MS model in young and old mice.
Methods: Self-limited demyelinating lesion were induced by injecting spinal cords (SC) of female BALB/c (<6 months) or aged (12-19 months) C57BL/6 mice with 1% lysolecithin (0.5 μL). VNS or sham VNS was performed 4 days post-induction (DPI), on the day of expected peak lesion volume (J Neurocytol. 1995 24(10): 775). Blood-SC barrier (BSCB) leakage was measured by Evans blue (EB) extravasation into the SC. Debris clearance and SC lesion volumes were quantified from oil red-o (ORO) and luxol fast blue-stained 20 μm serial sections, respectively. Remyelination was further visualized in toluidine blue-stained 1 μm sections.
Results: BSCB leakage was significantly reduced in VNS treated animals. On 5 DPI, EB extravasation in the VNS group was reduced 52% as compared to the sham group (n=5/group) and 43% at 4 DPI pre-VNS (n=5/group). Remyelination occurred at a significantly accelerated rate in the VNS treated animals. On 8 DPI, mean lesion volume in the young VNS group was reduced 66% as compared to sham (n=12-13) and the area under the curve from 4 through 21 DPI was reduced by 65%. Similarly, in aged mice, the demyelinated volume in VNS group SC was 50% of the demyelinated the sham group (n=9) on 10 DPI. ORO-stained area was increased in VNS-treated groups of both young and aged mice.
Conclusion: VNS reduced BSCB leakage and accelerated remyelination in this murine model across both strain and age, demonstrating the neuro-protective effect after a single dose of stimulation. This novel approach may provide a non-pharmacologic pro-remyelination treatment option for chronic demyelinating injury in patients with MS.

Disclosure
All authors are full time employees or were full time employees of SetPoint Medical, Inc. when this data was acquired and interpreted.
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Therapy - Long-term treatment monitoring

P723

Long-term efficacy and safety of ocrelizumab in treatment-naive patients with early relapsing multiple sclerosis: 7-year data from the OPERA open-label extension trials

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Background: Long-term safety and efficacy data are required to support evidence-based therapeutic decisions for first-line therapies.

Aims: To assess disease activity, progression and safety in patients with early relapsing multiple sclerosis (RMS; diagnosis ⩽2 years) treated with ocrelizumab (OCR) over 7 years in the Phase III OPERA trials (NCT01247324/NCT01412333).

Methods: During a 96-week double-blind period (DBP), patients were randomised to OCR or interferon (IFN) beta-1a. In the open-label extension, patients continued (OCR–OCR) or switched to OCR (IFN–OCR). Efficacy endpoints were no evidence of disease activity (NEDA) with MRI rebaselining at Week (W)24 (defined as an absence of protocol-defined relapses [PDR], 24W-confirmed disability progression [CDP] and MRI activity). Safety analyses included rates of adverse events (AEs), serious AEs (SAEs) and the relationship between immunoglobulin (Ig)G levels and serious infections (SIs).

Results: Patients (n=756) who met the criteria of MS disease diagnosis ⩽2 years and no previous disease-modifying therapies before enrolment were analysed (OCR–OCR, n=375; IFN–OCR, n=381); 70% remained on treatment for over 7 years (OCR–OCR, 73%; IFN–OCR, 67%). Up to Year 7, a significantly higher proportion of OCR continuers had NEDA compared with IFN–OCR switchers (OCR–OCR, 51% vs IFN–OCR, 28%; $p<0.001$: no 24W-CDP 81% vs 76% [p=0.140]; no evidence of MRI activity 90% vs 56% [$p<0.001$]; no PDR 76% vs 66% [p=0.003]). Rates of AEs, SAEs and SIs over 7 years were similar to the DBP. Rates of SIs were numerically lower in the OCR arm during the DBP (rates per 100 patient years, [95% CI]: OCR, 0.30 [0.04–1.09]; IFN, 1.97 [1.05–3.37]); the overall rate of SIs in OCR-treated patients remained stable over 7 years (1.36 [1.03–1.77]). A small proportion of OCR-treated patients had IgG levels < lower limit of normal (LLN) throughout the study, reaching 9.3% (17/182) at Year 7.3. SIs were uncommon in OCR-treated patients during episodes of IgG<LLN, affecting 0.4% (3/668) of patients; types and outcomes of SIs in this subgroup were consistent with the overall OCR-treated population.

Conclusions: Early initiation and continuous OCR treatment over 7 years was more effective than starting on IFN in maintaining NEDA and was associated with a favourable safety profile without emerging safety concerns. Rates of AEs, SAEs and SIs remained low. These findings support first-line use of OCR in newly diagnosed patients with early RMS.

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G Pardo has served on advisory boards and/or speakers' bureau for Biogen Idec., Celgene/Bristol Myers Squibb, EMD Serono, Greenwich Biosciences, Janssen Pharmaceuticals, Novartis, F. Hoffmann-La Roche Ltd/Genentech, Sanofi-Genzyme, TG Therapeutics and Viela Bio/Horizon Therapeutics; and is a member of the Scientific Advisory Board of Progentec Diagnostics Inc.
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P724

Predictors of infection, hypogammaglobulinemia, lymphopenia and neutropenia in multiple sclerosis patients treated with rituximab

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Introduction, objectives and aims: Rituximab is extensively used off-label to treat multiple sclerosis (MS), and long-term vigilance for adverse events is thus needed. This study aims to determine frequencies and predictors of haematological adverse events, including hypogammaglobulinemia, severe lymphopenia and neutropenia, as well as infections leading to hospitalization.
Methods: This retrospective cohort study included all patients with MS initiating rituximab treatment at the Haukeland University Hospital between January 1st, 2017 and July 1st, 2021. Patients were followed by clinical monitoring and repeated blood sampling every six months. Clinical outcomes and laboratory results were retrieved from the Norwegian MS registry and Biobank and the patient administrative system at Haukeland University Hospital.
Results: A total of 556 patients were included, 515 with relapsing-remitting MS (RRMS) and 41 with progressive MS. Overall, 33 patients (5.9%) had 56 episodes of infections requiring hospital admission. Sixty patients (10.8%) had confirmed hypogammaglobulinemia, 17 (3.1%) had confirmed severe lymphopenia and 10 (1.8%) had confirmed severe neutropenia. Predictors of infection requiring hospital admission were progressive MS (adjusted OR (aOR): 4.81; 95%CI: 1.25-18.48), duration of treatment with rituximab(aOR: 1.52; 95%CI: 1.11-2.09), and confirmed severe lymphopenia (aOR: 13.58; 95%CI: 3.41-54.06) and neutropenia (aOR: 13.40; 95%CI: 2.93-61.25). Of the haematological abnormalities, only hypogammaglobulinemia was associated with treatment duration (aOR: 1.35; 95%CI: 1.09-1.69).
Conclusions: Patients treated with rituximab for up to 4.5 years had a low rate of serious infections and haematological abnormalities. We observed a time-dependent decline in IgG-values, in contrast to neutrophil and lymphocyte count, suggesting a cumulative dose-dependent response. Predictors of serious infection would be useful for clinicians in the assessment and monitoring of MS patients receiving rituximab.

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P725

Infusion-related reactions with ocrelizumab in relapsing multiple sclerosis: Over 9 years of data from OPERA OLE

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Background: Infusion-related reactions (IRRs) were the most common adverse events (AEs) observed in the double-blind period (DBP) of the Phase III OPERA I/II trials. Long-term data on the IRR profile of ocrelizumab (OCR) are useful for clinical practice.

Aims: To characterise the long-term profile of IRRs for over 9 years of OCR treatment, in patients with relapsing multiple sclerosis in the OPERA trials and open-label extension (OLE).

Methods: In the 96-week DBP patients were randomised to OCR or interferon beta-1a (IFN). Patients continued OCR (OCR–OCR) or switched from IFN to OCR in OLE. Frequency, severity and types of IRR were analysed during and 24 hrs post-infusion.

Results: In the OCR–OCR arm (N=825), 13,984 infusions were administered (DBP: 3,901; OLE: 10,083) for over 9 years (up to Nov 2021), corresponding to 4 DBP and up to 19 OLE doses per patient. IRRs were the most common AE; 40.1% (n=331) of patients experienced ⩾1 IRR (840 IRRs in total). IRR incidence was highest at the first infusion (27.5%; 227/825) and decreased with subsequent infusions (<5% for OLE Doses 3–19). IRRs were mild to moderate in the majority of patients (93.4%; 309/331). In the DBP, 20 Grade 3 (severe) IRRs and one Grade 4 IRR (life-threatening; bronchospasm at Dose 1) were reported. In the OLE, one Grade 3 IRR and no Grade 4 or Grade 5 IRRs were reported. Most IRRs occurred during infusion (78.2%; 259/331). IRR incidence decreased 1 hr (13.3%; 44/331) and 24 hrs post-infusion (27.2%; 90/331). Most frequent IRR symptoms were pruritus (28.7%; n=95), rash (27.8%; n=92), throat irritation (25.1%; n=83), flushing (18.1%; n=60) and headache (14.8%; n=49); this pattern remained consistent over time. Infusion slowing/temporary interruption with subsequent completion was experienced by 2.5% (21/825) of patients (DBP: 15/825 [13/15 at Dose 1]; OLE: 6/703). Overall, 99.8% (838/840) of IRRs recovered/resolved and treatment compliance was high: >99% of infusions administered with ⩾80% of total dose. 14 patients (1.7%) permanently withdrew from OCR due to an IRR (DBP Dose 1: 11; OLE: 3). Pooled data including patients who switched from IFN to OCR will also be presented.

Conclusions: In more than 9 years of continuous OCR treatment, IRRs remained the most common AEs, were mostly mild to moderate and decreased in incidence with long-term treatment. As almost all IRRs recovered/resolved and only a small proportion led to temporary discontinuation, IRRs were not treatment-limiting AEs with OCR.

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COVID-19 outcomes in fingolimod- or siponimod - treated patients: clinical trial and post marketing cases

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Introduction: Understanding how immunomodulatory therapies influence COVID-19 outcomes in people living with multiple sclerosis (PlwMS) is vital to patients and physicians alike.

Aims and Objective: Evaluate COVID-19 outcomes in PlwMS receiving either fingolimod or siponimod.

Methods: The Novartis clinical trial (CT) and safety databases were reviewed to identify confirmed (CT: confirmed if patient is SARS COV-2 positive; post-marketing [PM]: considered as reported) or suspected cases of COVID-19 in PlwMS receiving either fingolimod or siponimod (CT cut-off: fingolimod 04-Aug-2021, siponimod 29-Oct-2021; PM cut-off: fingolimod 28-Feb-2022, siponimod 25-Mar-2022).

Results: For fingolimod, there were 1054 cases comprising of 45 suspected (PM=45) and 1009 confirmed cases (CT=9; PM=1,000) of COVID-19 (mean age in years: 17 [CT], 43 [PM]; female: 71% [715/1009; CT=4, PM=711]; male: 25% [254/1009; CT=5, PM=249] and not reported: 4% [40/1009; PM=40]). Of these, 35% (358/1009; CT=8, PM=349) were from Europe, 30% (305/1009; PM=305) from the US and 34% (347/1009; CT=1, PM=346) from the rest of the world (ROW). Hospitalisation was required for 13% of patients (130/1009; PM=130); 1% (13/1009; PM=13) had a fatal outcome; and 43% (437/1009; CT=9, PM=428) recovered or were recovering at the most recent follow-up.

For siponimod there were 321 cases comprising of 6 suspected (CT=1; PM=5) and 315 confirmed cases (CT=53; PM=262) of COVID-19 (mean age in years: 49 [CT], 53 [PM]; female: 68% [214/315; CT=34, PM=180]; male: 28% [88/315; CT=19, PM=69] and not reported: 4% [13/315; PM=13]). Of these, 53% (168/315; CT=6, PM=162) were from the US; 30% (96/315; CT=46, PM=50) from Europe; and 16% (51/315; CT=1, PM=50) from the ROW. Hospitalisation was required for 19% of patients (60/315; CT=15, PM=45); 2% (7/315; CT=3, PM=4) had a fatal outcome; and where information was provided 42% (131/315 CT=50, PM=81) recovered or were recovering at the most recent follow-up.

Conclusions: Available data indicates that most COVID-19 cases among PlwMS treated with fingolimod or siponimod were non-serious. Among PlwMS exposed to disease-modifying therapies (DMTs), the reported hospitalisation and mortality rates are 12.8%–21.5% and 1.62%–3.5%, respectively (Reder et al 2021; Sormani et al 2022). Thus, hospitalisation and fatality rates with siponimod and fingolimod in these series of Novartis reported cases were similar to those observed in PlwMS on other DMTs.

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BJW serves on a scientific advisory board for Novartis and reports personal fees from Novartis for this activity. He is also a medical officer for Medicago Inc and holds parts of patents for vaccines targeting influenza, Clostridioides difficile, and Schistosomamansoni. In the last 5 years, he has held academic industry awards with Medicago, MIT Canada, and Aviex Technologies.

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High adherence and minimal delays of year 2 treatment in people with multiple sclerosis treated with cladribine tablets: results from multi-country patient support programmes

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Introduction: Cladribine tablets (CladT) at a cumulative dose of 3.5 mg/kg over 2 years is used in the treatment of people with multiple sclerosis (pwMS). Depending on country-specific restrictions, some pwMS continue treatment and receive another course of CladT (i.e. course 3).
Objectives: Adveva®, a multinational nurse-/pharmacy-led patient support programme (PSP), collects treatment-related clinical information for pwMS receiving CladT.
Aims: Evaluate the initiation of Year 2 CladT treatment and subsequent treatment course in centres with a PSP in Australia, Canada, the Gulf region, Latin America (LatAm) countries, and the UK.
Methods: Treatment-related clinical data collected from adveva® between 05 Dec 2017 and 23 Feb 2022 were analysed. PwMS were followed from treatment initiation until the cut-off date, loss to follow-up, or treatment discontinuation. Demographics, prior disease-modifying therapy (DMT), treatment initiation in Year 1 and, among patients with ⩾18 months follow-up since Year 1 initiation, Year 2 treatment initiation are reported. In countries with pwMS with ⩾24 months' follow-up since Year 1 treatment initiation (Australia, Canada, and the UK), information on those who received subsequent treatment courses of CladT are also described.
Results: 5639 patients (74.6% female) initiated CladT during the study period (Australia, n=898; Canada, n=2146; Gulf, n=116; LatAm, n=1010; UK, n=1469). Most had been on at least one prior DMT (Australia, 72.2%; Canada, 100%; Gulf, 70.7%; LatAm, 61.9%; UK, 38.9%) and the most common prior DMTs were oral therapies (Australia, 50.2%; Canada, 48.7%; Gulf, 47.6%; LatAm,67.4%). In all countries, >95% of pwMS initiated Year 2 treatment and a delay of ⩾6 months to Year2 initiation was seen in only a minority (4.6% of patients in Australia, 4.3% in Canada, 2.5% in Gulf, 2.3% in LatAm, and 10.3% in the UK). Among those with ⩾24 months' follow-up, a third treatment course of CladT were observed in 7.7% of pwMS in Australia (11/142), 6.4% in Canada (14/219), and 0.5% in the UK (3/656). Course 3 of CladT was initiated, on average, between 29 and 40 months after Year 1 treatment initiation.
Conclusions: Adherence to CladT at Year 2 was consistently high across participating countries with minimal delays in Year 2 treatment initiation. A small proportion of pwMS received a third treatment course of CladT with variable timing in relation to Year 1 treatment with CladT.

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Clinical effectiveness and safety of cladribine tablets for patients treated at least 12 months in the Swedish post-market surveillance study "immunomodulation and multiple sclerosis epidemiology 10" (IMSE 10)

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Introduction: Cladribine is a deoxyadenosine analogue prodrug that selectively induces immune reconstitution by targeting B- and T-lymphocytes. Cladribine tablets (CladT) are administered in two courses, 12 months apart, for patients with relapsing multiple sclerosis (RMS). CladT are included in the Swedish post-market surveillance study "Immunomodulation and Multiple Sclerosis Epidemiology" (IMSE).
Objectives: To assess the safety and effectiveness of CladT with focus on patients treated at least 12 months.
Methods: Data of Extended Disability Status Scale (EDSS), Multiple Sclerosis Severity Scale (MSSS), Symbol Digit Modalities Test (SDMT), Multiple Sclerosis Impact Scale (MSIS-29), European Quality of Life - 5 Dimensions Test (EQ-5D), Visual Analog Scale (VAS), relapses and Adverse Events (AEs) is obtained from the nationwide Swedish Neuro Registry (NeuroReg). Effectiveness measures were assessed using Wilcoxon Signed Rank Test and relapse rates were tested using paired samples T-test.
Results: 208 patients were included in the IMSE 10 study since the Swedish market launch in April 2018 with an overall drug survival rate of 94.2%. 12 patients discontinued treatment, of which 1 later restarted. The most common reason for discontinuation was lack of effect (83%). 21 AEs were reported of which 7 were serious. The most common AE reported were infection and infestation (8 reports).
139 patients were treated for at least 12 months. 29 % of the patients was treated with CladT as their first MS drug. 19 % were treated with natalizumab and 10 % with dimethyl fumarate prior to CladT. The number of relapses decreased significantly from 249 per 1,000 patient years before treatment start to 73 during treatment. 12 patients in this cohort have experienced a relapse during treatment.
Significant improvements in mean values at 12 months of treatment compared to baseline were noted for MSSS *(p=0.005)* and MSIS29 Psychological*(p=0.033)*. MSIS-29 Physical showed a tendency for improvement while all other tests remained stable after one year of treatment.
Lymphocyte levels decreased from a mean of 1.9 x 10^9/L at treatment start (n=80) to 1.1 x 10^9/L after 12 months of treatment (n=71).
Conclusions: CladT treatment demonstrates clinical stability in patients treated 12 months. However, continued follow-up is needed to assess the effectiveness and safety of CladT over a longer time to assess if these results sustain after the final treatment course has been administered.

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Very-early treatment in patients with CIS or early MS: a propensity analysis using a novel magnetic resonance score

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Introduction: Magnetic resonance (MR), an essential tool for treatment decision-making in clinically isolated syndrome (CIS) and early multiple sclerosis (MS), is not usually integrated to construct Propensity Score (PS) when evaluating outcomes. We

assess the association of receiving very-early treatment with the risk of long-term disability accounting for a novel MR Score (MRS) in CIS patients.
Methods: We included 580 CIS patients prospectively collected from the Barcelona-CIS cohort between 1994 and 2021, who received at least one disease modifying treatment (DMT). Patients were classified into tertiles of time from the CIS to first DMT: First (FT) or very-early treatment (6 months; N=194); second (ST) (6.1-16 months, N=192), and third tertile (TT) (16.1 months, N=194). A 5-score MRS was built: ⩾9 brain lesions (1pt); ⩾1 infratentorial lesion (1pt); ⩾1 spinal cord (SC) lesion (1pt); ⩾1 contrast-enhancing (CE) brain lesion (1pt); ⩾1 CE SC lesion (1pt). PS were computed through logistic regression models for the FT vs. ST, and FT vs.TT comparisons, accounting for the MRS and classical MS covariates, for each of the outcomes. Inverse PS-weighted Cox regression or logistic regression models assessed the risk of different outcomes between tertile-groups.
Results: Very-early treatment decreased the risk of reaching EDSS 3.0 (Hazard Ratio, HR [95% Confidence Interval, 95%CI]: 0.57 [95%CI 0.34-0.97]), EDSS 6.0 (HR 0.30 [95%CI 0.10-0.87), secondary progressive MS (HR 0.37 [95%CI 0.18-0.78), and sustained disease progression 12 months after DMT initiation (HR 0.28 [95%CI 0.13-0.57), compared to the TT group. The FT had lower progression rates (Odds Ratio [OR] 0.53 [95%CI 0.29-0.99]), and had a lower risk of high disability measured by the Patient Determined Disease Step (OR 0.19 [95%CI 0.07-0.51]) than the TT group.
Conclusions: After including the novel MRS in PS models, we showed that treatment initiation at very-early stages (6 months from the CIS) robustly prevents long-term disability accrual.

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Early use of high efficacy therapies in pediatric forms of relapsing-remitting multiple sclerosis: a real-life observational study

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Introduction: Pediatric forms of relapsing-remitting multiple sclerosis (RRMS) are more active than those in adults. Yet, the effectiveness of different therapeutic approaches is not well studied in this population.
Objectives: To compare the effectiveness of the early use of high efficacy therapies (HET) vs intermediate efficacy therapies (IET) in children and adolescents with multiple sclerosis.
Methods: This retrospective analysis included patients with RRMS starting before 18 years old from 4 Alsatian centers, diagnosed during a 10-years period (2010-2020). Collected data included age, gender, disease-modifying treatment (IET: beta-1a interferon, glatiramer acetate, dimethyl fumarate, teriflunomide; HET: fingolimod, natalizumab, ocrelizumab, alemtuzumab), relapses, Expanded Disability Status Scale (EDSS), magnetic resonance imaging findings. The primary endpoint was the occurrence of a new relapse.
Results: Sixty four patients were included in the analysis (80% women, mean age 15.5 years, 81% treated with IET) with a median follow-up of 37 months. The cumulative probability of being relapse-free was 0.0% under IET, vs 90.9% under HET (p=0.013). The cumulative probability of no worsening of EDSS was 78.3% under IET, versus 100% under HET (p=0.43).
Conclusions: Patients under intermediate efficacy therapies had a much higher disease activity than those on early high efficacy therapies. Rapid initiation of more aggressive treatment may allow better disease control. However, the effect on EDSS worsening remains uncertain, probably due to the small number of events and the short follow-up duration.

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P731
MRI and clinical outcomes of evobrutinib, a Bruton's tyrosine kinase inhibitor, in relapsing multiple sclerosis over 2.5 years of the open-label extension to a Phase 2 trial

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Introduction: Evobrutinib (EVO), a highly selective Bruton's tyrosine kinase (BTK) inhibitor, was effective at reducing T1 gadolinium-enhancing (Gd+) lesions and new/enlarging T2 lesions in a double-blind, randomised, Phase 2 trial (NCT02975349) in patients with relapsing multiple sclerosis (pwRMS).
Objective: To describe the long-term treatment effect of EVO on magnetic resonance imaging (MRI) outcomes (number of T1 Gd+ lesions and T2 lesion volume) and Expanded Disability Status Scale (EDSS) score in pwRMS up to Week (W) 144 of the open-label extension (OLE) of the Phase 2 trial.
Methods: In the 48W double-blind period (DBP), pwRMS (n=267) received placebo (PBO; switched to EVO 25mg once-daily [QD] at W24), EVO 25mg QD, 75mg QD, or 75mg twice-daily (BID), or open-label dimethyl fumarate (DMF; 120mg BID for the first week and 240mg BID thereafter) in fasted state. At W48, patients could enter the OLE (DMF: 4–8W washout) and received EVO 75mg QD for a mean time of 49.8W, before switching to 75mg BID.
Results: Of 213 DBP patients that entered the OLE, 160 (75.1%) had reached OLE ⩾144W at time of analysis. Mean number of T1 Gd+ lesions per treatment group at DBP BL: PBO, 1.19; EVO 25mg QD, 0.92; EVO 75mg QD, 1.65; EVO 75mg BID, 1.72; DMF, 2.20. At OLE BL, mean number of T1 Gd+ lesions by DBP treatment group: PBO/EVO 25mg QD, 0.92; EVO 25mg QD, 1.63; EVO 75mg QD, 0.71; EVO 75mg BID, 0.48; DMF, 0.25. Some fluctuations occurred when switching from the DBP doses to 75mg QD at OLE W0 and then to EVO 75mg BID. Pooling all patients, during the 75mg QD stage of the OLE, the mean number of T1 Gd+ lesions rose (OLE W0: 0.76, OLE W48: 1.42) before dropping after switching to 75mg BID (OLE W96: 0.55, OLE W144: 0.79). During OLE, overall change of median volume (cm^3) of T2 lesions pooled across treatment groups from DBP BL was low (OLE W48: 0.072, W96: 0.074, W144: 0.119). Mean EDSS score pooled across treatment groups remained stable from DBP BL (3.27) to OLE W144 (3.31) and the overall change in the mean EDSS score from DBP BL was low (OLE W48: -0.04, W96: -0.01, W144: 0.00).
Conclusions: After ⩾144W of OLE, the number of T1 Gd+ lesions remained low compared with DBP BL and were reduced after switching from 75mg QD to 75mg BID, providing supporting evidence that EVO 75mg BID (fasted – equivalent to 45mg BID fed dose in Phase 3) was the optimal dose in this trial. The change in T2 lesion volume from baseline was low across treatment groups. EDSS scores remained stable.

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P732
Safety patterns with ozanimod during phase 3 and open-label extension trials in patients with relapsing multiple sclerosis

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Introduction: Ozanimod is a sphingosine 1-phosphate receptor 1 and 5 modulator approved in multiple countries for treatment of adults with relapsing forms of MS (RMS) or moderately to severely active ulcerative colitis.
Objectives: To describe incidence rates (IRs) of treatment-emergent adverse events (TEAEs) in patients with RMS treated with ozanimod 0.92 mg in phase 3 and open-label extension (OLE) trials.
Methods: In phase 3 trials, adults with RMS were randomised to oral ozanimod 0.46 or 0.92 mg/d or intramuscular interferon β-1a 30 μg/wk for ⩾12 months (SUNBEAM–NCT02294058) or 24 months (RADIANCE–NCT02047734). Completers were eligible to enrol in the ongoing OLE trial (DAYBREAK–NCT02576717) of ozanimod 0.92 mg/d. IRs and 95% confidence intervals (CI)/1000 person years (PY; 100,000 PY for malignancies) were calculated for TEAEs during the pooled phase 3 trials and at yearly intervals during the OLE (2 Feb 2021 cutoff).
Results: In patients treated with continuous ozanimod 0.92 mg (n=882), the IR [95%CI]/1000 PY decreased over time (from phase 3 to OLE >36 months) for overall TEAEs (896.1 [826.8–971.3] vs 259.1 [180.0–372.8]); infections (300.5 [268.9–335.9] vs 144.9 [109.2–192.3]); opportunistic infections (12.0 [7.4–19.6] vs 4.3 [1.4–13.3]); cardiac disorder TEAEs (22.8 [16.0–32.7] vs 4.2 [1.4–13.0]); and hepatic disorder TEAEs (77.0 [63.1–94.0] vs 15.1 [8.1–28.1]). The most common opportunistic infections in phase 3 trials and the OLE were oral herpes and herpes zoster (including varicella zoster virus). IRs remained relatively stable for serious TEAEs (31.2 [23.0–42.4] vs 30.5 [19.7–47.3]), malignancies (372.2 [120.8–868.5] vs 276.7 [33.5–999.6]/100,000 PY), confirmed macular edema (n/N, 1/882; 0.7 [0.1–5.3] vs n/N, 1/687; 1.4 [0.2–9.8]), and pulmonary TEAEs (11.3 [6.8–18.7] vs 0.0 [0.0–9.9]). The IR for serious infections remained relatively stable until OLE >36 months, at which time the IR increased (6.7 [3.5–12. 9] vs 9.8 [4.7–20.6]), which may be partially due to the COVID-19 pandemic. The most common serious infections were appendicitis (n/N, 3/882) and pyelonephritis acute (n/N, 1/882) (phase 3), and pneumonia (n/N, 4/762) and coronavirus infection (n/N, 3/762) (OLE). Most coronavirus infections were nonserious (31/34 [91.2%]).
Conclusions: In this post hoc analysis, IRs of TEAEs in patients with RMS treated with continuous ozanimod 0.92 mg in phase 3 and OLE trials generally declined or remained stable over up to 5 years of observation time.

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P733
The impact of disease modifying therapy on information processing speed in multiple sclerosis

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Introduction: Cognitive impairment (CI) is common in multiple sclerosis (MS). CI has been described at all stages of the disease, including clinically isolated syndrome, and is considered an early marker of disease activity. Processing speed is commonly affected in MS, making it an ideal target for monitoring CI. Whether treatment with disease modifying therapies (DMT) affects cognitive performance longitudinally remains poorly understood.
Objective: To evaluate whether processing speed in MS is significantly affected by DMTs.
Aims: To compare the effect of DMT status and intensity on longitudinal changes in processing speed test (PST) scores over time.
Methods: We performed a retrospective analysis of patients from a single academic MS center using the PST, a digital adaptation of the Symbol digits Modalities Test. Patients with at least two PST assessments during outpatient clinic visits were included. We compared PST scores longitudinally between MS patients on DMT (for a minimum of 2 years) and those off DMT (for a minimum of 2 years). The DMT treated group was further divided into highly effective versus platform therapies. A linear regression model was fitted to evaluate the rate of cognitive change over time amongst cohorts. Propensity score adjustment was conducted

using a multivariable logistic regression for all analyses between cohorts. Significance was set at $p < 0.05$.
Results: 639 patients were included in our analysis, 537 on DMT and 102 off DMT. The median age and disease duration was 49.7 (IQR 42.4-57.9) and 16.6 (IQR 9.3-23.0) in the DMT group, and 58.9 (IQR 52.2-65.3) and 20.0 (IQR 14.1 – 31.4) in the non-DMT group. Both cohorts were predominantly female (75% DMT, 79.6% non-DMT). The mean number of PST assessments in both groups was 4 (IQR 3-5). DMT status and DMT intensity were not found to be significant predictors of PST change over time after adjusting for age, education level, MS phenotype, disease severity and disability level.
Conclusion: Our analysis revealed that neither DMT status nor DMT intensity were significant predictors of cognitive decline. While DMT is effective in controlling acute disease activity, our study reveals similar levels of change in cognitive impairment despite DMT status or intensity, suggesting a possible degenerative process (outside inflammation) driving cognitive decline in MS. Future prospective multi-center trials are necessary to further support these findings.

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P734

Compliance and persistence with ofatumumab treatment in patients with relapsing multiple sclerosis in clinical trials for up to 4 years

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Introduction: Ofatumumab (OMB) demonstrated superior efficacy and a similar safety profile to teriflunomide in the ASCLEPIOS I/II trials in relapsing multiple sclerosis (RMS) patients. Sustained efficacy and a consistent safety profile have also been observed in the long term ALITHIOS open-label extension study for up to 4 years. In ASCLEPIOS I/II, 98.8% of patients had ⩾80% compliance to the study treatment schedule, and 82.9% randomized to OMB completed the study on drug up to 30 months.
Objectives: To evaluate compliance and persistence with OMB treatment in RMS patients for up to 4 years across the OMB core studies and ALITHIOS extension study.
Methods: Patients completing the core ASCLEPIOS I/II, APOLITOS and APLIOS trials could enter ALITHIOS. Compliance was analyzed for up to 4 years (cut-off: 25-Sep-2021) in overall, continuous (OMB in core) and newly switched (teriflunomide core and OMB extension) groups. Compliance was calculated as the duration of exposure to study drug/duration of on-treatment period×100%, with ⩾80% defined as the threshold to indicate patients were compliant. The number of patients continuing OMB (as a measure of treatment persistence) and discontinuing treatment in ALITHIOS, and reasons for discontinuations are also presented.
Results: As of 25-Sep-2021, in the overall (N=1969), continuous (N=1292), and newly switch groups (N=677), 94.9%, 95.1%, and 94.4% of patients were compliant with OMB therapy, respectively. In total, 1715 patients entered the ALITHIOS study; 12 (0.7%) of these were screening failures, and 1703 patients were enrolled in the study and received study treatment; 1508 (87.9%) were ongoing in the study at the time of data cut-off, and 195 (11.4%) discontinued study treatment. The primary reasons for discontinuation in the ALITHIOS study were patient/guardian decision (n=75 [4.4%]); adverse event (n=66 [3.8%]); pregnancy (n=12 [0.7%]); physician decision (n=12 [0.7%]); lack of efficacy (n=12 [0.7%]); lost to follow-up (n=8 [0.5%]); death (n=6 [0.3%]); non-compliance (n=2 [0.1%]); and protocol deviation (n=2 [0.1%]).
Conclusions: Overall ~95% of patients were compliant with OMB treatment across core studies and the open-label extension study, indicating high compliance with monthly subcutaneous OMB therapy. In addition, only a small proportion of RMS patients treated with OMB in the clinical trial setting discontinued treatment, indicating high treatment persistence.

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P735

Flushing and gastrointestinal adverse event analysis from the phase 3 EVOLVE-MS-1 study of diroximel fumarate in patients with relapsing-remitting multiple sclerosis

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Introduction: Diroximel fumarate (DRF), an oral fumarate for the treatment of relapsing-remitting multiple sclerosis (RRMS), has the same active metabolite as dimethyl fumarate (DMF). Flushing and gastrointestinal (GI) adverse events (AEs) are common AEs on DMF. DRF has similar safety and efficacy to DMF but with improved GI tolerability.

Aims: Evaluate flushing/flushing-related and GI AEs in patients who newly initiated DRF in EVOLVE-MS-1.

Methods: EVOLVE-MS-1 (NCT02634307), an open-label, 96-week, Phase 3 study, assessed safety, tolerability, and efficacy of DRF in adults with RRMS between 10Dec2015-11Nov2021. Patients either newly initiated DRF or rolled over from completing EVOLVE-MS-2 (NCT03093324), a randomised, blinded, Phase 3 study of DRF or DMF over 5 weeks. We report outcomes for flushing/flushing-related and GI AEs in patients who newly initiated DRF and were in the de novo group of patients who had not participated in EVOLVE-MS-2.

Results: Of 1057 patients overall, 593 (56.1%) newly initiated DRF (de novo group). Treatment-emergent AEs occurred in 938 (88.7%) patients overall and in 519 (87.5%) patients in the de novo group.

Flushing/flushing-related AEs occurred in 292 (49.2%) patients in the de novo group; most were mild/moderate (n=287, 98.3%) and occurred in the first month on DRF (n=242, 84.0%). Median (10^{th}-90^{th} percentile) duration of flushing/flushing-related events that resolved was 8.0 (1.0-349.3) days. DRF was discontinued due to flushing/flushing-related AEs in 4 (0.7%) patients; most (81.8%) patients with flushing/flushing-related AEs did not receive aspirin.

GI AEs occurred in 200 (33.7%) patients in the de novo group; most were mild/moderate (n=191, 95.5%) and occurred in the first month on DRF (n=117/199, 58.8%). Median (10^{th}-90^{th} percentile) duration of events that resolved was 10.5 (1.0-134.7) days. DRF was discontinued due to GI AEs in 5 (0.8%) patients; 89 (44.5%) patients with GI AEs received transient concomitant therapy for GI symptoms.

Conclusions: Flushing/flushing-related AEs and GI AEs were common in patients who newly initiated treatment on DRF in EVOLVE-MS-1; in most cases these AEs were mild/moderate and occurred in the first month on DRF. Four (<1%) patients discontinued DRF due to flushing/flushing-related AEs and five (<1%) patients discontinued due to GI AEs. These data are consistent with the known safety profile of DRF.

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FB: Employee of and holds stocks/stock options in Biogen.
HC: Employee of and holds stocks/stock options in Biogen.
SL: Employee of and holds stocks/stock options in Biogen.
SE: Employee of and holds stocks/stock options in Biogen.
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Therapy - Risk management for disease modifying treatments

P736

Serological effect of mRNA vaccination against COVID-19 in multiple sclerosis patients treated with immunosuppressive DMTs

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Background: Immunosuppressive therapies may impact immune response to COVID-19 vaccines in persons with multiple sclerosis (pwMS). Accordingly, effects of vaccination in pwMS

treated with disease-modifying therapies (DMTs) need further elucidation.
Aim: To investigate COVID-19 BNT162b2 vaccine effect concerning antibody seroconversion, T cells-associated cytokines production and immunophenotype assessment in pwMS under three different DMTs: cladribine, fingolimod, ocrelizumab.
Methods: Enzyme immunoassay test was used for anti-spike IgG detection in 98 DMTs-treated pwMS completing first vaccination cycle. In a subset of patients (n=47), serum T cells-associated cytokines (GrB, IFN-γ and TNF-α) were quantified using an automatic ELISA (ELLA) and blood immunophenotype was assessed by flow cytometry. ANCOVA followed by post hoc tukey's test was used to compare anti-spike IgG response in the different DMTs, Student's paired t-test was used to evaluate differences between pre- and post-vaccination in pairwise samples and Pearson's correlation was applied to evaluate association between spike-specific IgG antibody titer and lymphocytes count.
Results: More pwMS treated with ocrelizumab (63%) lacked anti-spike IgG compared to patients treated with cladribine (14%) and fingolimod (20%) ($p<0.001$). When present, the anti-spike IgG titer in the ocrelizumab group was lower than in cladribine- ($p<0.001$) and in fingolimod-treated pwMS ($p=0.003$). No significant differences in lymphocytes count and T-cell associated cytokines were observed in cladribine- and in fingolimod-treated pwMS, while in pwMS on ocrelizumab a significant increase in GrB serum levels ($p=0.021$) and a trend of increased $CD4^+$ T cells count were observed after vaccination. Specifically considering non-seroconverted ocrelizumab-treated pwMS, a significant increase of GrB serum levels ($p=0.008$) and of $CD4^+$ T lymphocytes count ($p=0.040$) was foundafter vaccination and a negative correlation was observed between anti-spike IgG production and $CD4^+$T cells count (rho=-0.452, $p=0.014$).
Conclusion: Our data confirmed differences in spike-specific antibodies among different DMTs and provided evidence of T-cell immunity preservation and activations after BNT162b2 vaccination in ocrelizumab-treated pwMS, specifically in pwMS patients lacking anti-spike IgG, suggesting a protective T-cell response that might explain why the ongoing treatment with ocrelizumab is not associated with a higher risk of COVID-19 infection.

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P737
Efficacy and persistence between dimethyl fumarate, fingolimod, and ocrelizumab after natalizumab cessation

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Introduction: Natalizumab therapy is often discontinued to mitigate the risk of progressive multifocal leukoencephalopathy. The optimal DMT following natalizumab cessation has yet to be determined.

Objectives: To compare the effectiveness and treatment persistence of three DMTs (ocrelizumab, fingolimod, and dimethyl fumarate [DMF)] after natalizumab cessation among patients with relapsing-remitting multiple sclerosis (RRMS).
Methods: Using data from MSBase registry, we included 1,386 subjects who had used natalizumab for ⩾6 months and switched to ocrelizumab, fingolimod, or DMF <3 months after natalizumab discontinuation. The primary outcomes were annualized relapse rate (ARR) and time to the first relapse. Secondary outcomes were confirmed disability progression, confirmed disability improvement, and treatment discontinuation. Disability outcomes were limited to comparison between fingolimod and ocrelizumab due to limited DMF numbers. We used negative binomial models to compare ARRs and Cox proportional-hazards models for other outcomes. We used inverse probability weighting based on propensity scores to balance informative covariates. Individual propensity scores were calculated using multinomial logistic regression.
Results: 425 patients switched from natalizumab to ocrelizumab, 823 to fingolimod, and 138 to DMF. The ARR for ocrelizumab was 0.06, fingolimod, 0.26, and DMF, 0.27.ARR ratio (95% confidence interval [CI]) of fingolimod/ocrelizumab was 4.33 (3.12-6.01) and of DMF/ocrelizumab 4.50 (2.89-7.03). Compared to ocrelizumab, the hazard ratio (HR) of time to first relapse was 4.02 (2.83-5.70) for fingolimod, 3.70 (2.35-5.84) for DMF; the HR for discontinuation was 2.57 (1.74-3.80) for fingolimod and 4.26 (2.65-6.84) for DMF. Fingolimod was associated with a 49% higher risk of confirmed disability progression than ocrelizumab. There was no difference in disability improvement rates between fingolimod and ocrelizumab.
Conclusion: Among the three DMTs that the RRMS patients switched from natalizumab to, ocrelizumab use was associated with the lowest ARR and discontinuation rates, and the longest time to first relapse.

Disclosure
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P738

Long-term safety of teriflunomide in multiple sclerosis patients: results of prospective comparative studies in three European countries

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Background: Teriflunomide (TF) is a disease modifying therapy (DMT) indicated for the treatment of remitting-relapsing forms of multiple sclerosis (MS). This post authorisation safety study assessed risks of adverse events of special interest (AESI) associated with TF use.
Methods: The study was based on secondary use of individual data of patients from the Danish MS Registry (DMSR), the French National Health Data System (SNDS), the Belgian national database of health care claims (AIM-IMA) and the Belgian Treatments in MS Registry (BELTRIMS). Study cohorts included treatment-naive patients who started a DMT or switched to another DMT after the date of TF reimbursement. In each data source, hazard rates (HR) and (95% confidence intervals) of AESI were computed by comparing AESI occurrence in patients treated with TF to AESI occurrence in patients treated with a platform DMT other than TF. For non-cancerous AESI, HR were derived from Cox models with time-dependent exposure. For cancerous AESI, HR were derived from Cox model with ever/never exposure. HR were adjusted for gender, age, new or prevalent user status, major comorbidities, and (when available), the expanded disability status scale (EDSS).
Results: 81,620 patients (72% women) were included in the study, of whom 22,324 (27%) were treated with TF. After a median treatment duration with TF of 3.5 years, TF use compared to other platform DMT was not associated with a risk of all-cause mortality, severe infection, pneumoniae, herpes zoster reactivation, pancreatitis, peripheral neuropathy, cardiovascular condition, and cancerous conditions. Results were mostly consistent across data sources. No case of progressive multifocal leukoencephalopathy was identified among TF users. For opportunistic infections, HR for TF vs other platform DMT was 2.4 (1.2-4.8) in the SNDS, which was not bound to a particular type of opportunistic agent. For renal failure, HR was 2.0 (1.1-3.7) in the SNDS, but was not increased in other data sources. Among 187 French patients with history of renal failure and treated with TF prior to cohort entry, none had a renal failure after TF start. Because of few cases, results on interstitial lung disease, psoriasis and peripheral neuropathy were not informative.
Interpretation: This large study conducted in nationwide registers found no evidence that TF use would be associated with an increased risk of AESI. The conflicting results on renal failure are considered inconclusive.

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P739

Safety of shorter ocrelizumab infusion confirmed over multiple administrations: results of the ENSEMBLE PLUS substudy

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Background: Shortening the infusion duration of ocrelizumab (OCR) to 2hrs reduces total site stay (including mandatory premedication/infusion/observation), which lowers patient and staff burden.

Aims: To report final safety and tolerability data of OCR administered over a shorter infusion time in ENSEMBLE PLUS.

Methods: ENSEMBLE PLUS was a randomised, double-blind substudy to ENSEMBLE (NCT03085810). In ENSEMBLE, treatment-naive patients with active, early-stage relapsing-remitting MS (18–55 years; disease duration ⩽3 years; EDSS score 0–3.5) receive OCR 600mg infusions every 24 weeks for 192 weeks. In ENSEMBLE PLUS, OCR (600mg) administered over the approved infusion time (3.5hrs; conventional duration [CON]) was compared with a 2hr infusion (shorter duration [SHORT]); the initial 2×300mg dose infusion duration was unaffected. Frequency and severity of infusion-related reactions (IRRs) were assessed during and 24hrs post-infusion. The primary endpoint was the proportion of patients with IRRs at the first randomised dose (RD).

Results: At first RD, 27.1% patients (n=101/373) in the CON and 28.8% (n=107/372) in the SHORT infusion group had IRRs (difference, stratified estimates [95% CI]: 1.9% [-4.4, 8.2]). Up to 6 consecutive infusions were administered; overall most IRRs (99.4% in the CON and 97.7% in the SHORT infusion group) were mild or moderate (Grade 1 or 2), the remainder were severe (Grade 3: CON 0.6%, n=1; SHORT 2.3%, n=4). IRR frequency decreased over the course of RDs. Most common IRR symptoms were throat irritation and dysphagia during infusion, and fatigue and headache 24hrs post-infusion. IRRs led to infusion slowing/temporary interruption in 39 patients (10.5%) in the CON and 55 (14.8%) in the SHORT infusion group. No IRR-related discontinuations occurred. Overall, >98% of IRRs resolved without sequelae in both groups. No IRRs were life-threatening or fatal, 1 was serious. Adverse events (AEs) and serious AEs were consistent with the known OCR safety profile. On completion of ENSEMBLE PLUS, overall, 98% of patients continued in ENSEMBLE.

Conclusions: The frequency and severity of IRRs were similar between CON and SHORT infusions. None were clinically significant. No new safety signals were detected. Most patients (98%) continued in ENSEMBLE. These results confirm the outcomes of the interim analysis. Revised prescribing guidance now permits 2hr ocrelizumab infusions, thus reducing infusion site stays and potentially easing patient and staff burden.

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T Berger has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Almirall, Bayer, Biogen, Biologix, Bionorica, BMS/Celgene, GW/Jazz Pharma, Horizon, Janssen-Cilag, MedDay, Merck, Novartis, Octapharma, Roche, Sandoz, Sanofi/Genzyme, TG Pharmaceuticals, Teva-ratiopharm and UCB. His institution has received financial support in the last 12 months by unrestricted research grants (Biogen, BMS/Celgene, Merck, Novartis, Roche and Sanofi/Genzyme) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Biogen, BMS/Celgene, Merck, Novartis, Octapharma, Roche, Sanofi/Genzyme and Teva.

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Does routine urinalysis prior to ocrelizumab infusion improve patient safety and experience? Audit of practice at a single centre

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Background: Ocrelizumab is a humanized anti-CD20 monoclonal antibody used in the treatment of Multiple Sclerosis (MS). Infection is a known adverse effect of ocrelizumab treatment and current active infection is a contraindication to infusion. There is concern that proceeding with ocrelizumab in the presence of a urinary tract infection (UTI) may lead to an increased risk of developing urosepsis. Practice on the infusion unit is to routinely dip urine of all patients prior to infusion. A positive dip results in delays to treatment while blood tests are sent for analysis to exclude signs of active infection.
Objectives: We aimed to assess the incidence of a positive urine dip prior to ocrelizumab infusion and whether there is a relationship between a positive urine dip and development of a UTI requiring treatment. We evaluate the incidence of UTI and assess whether we could safely reduce the time taken to proceed with infusion thus improving patient experience.
Methods: Patients who had received ocrelizumab over a 3 year period were identified from a service data base. The medical notes of these patents were reviewed to identify the results of the urine dip and any subsequent urine microscopy. Any subsequent diagnosis of UTI & antibiotic treatment was also recorded. Time taken to start infusion was recorded and a comparison made between those who had a positive urine dip and those who did not.
Results: 119 patients were identified as having attended for a total of 353 infusions during the study period. 85% (299/353) of urine dips were recorded as negative. 15% (54/353) urine dips were recorded as positive. Of 54 positive urine dips 24% (51) were in female patients and 2% (3) were in male patients. Only 1 positive dip resulted in diagnosis of a UTI requiring antibiotics. A positive urine dip resulted in delays to the start of the infusion while bloods were drawn and analysed. Clinical signs and symptoms of infection were not routinely recorded. Further results on time taken to start infusion to be presented.
Conclusions: The results show that a positive urine dip is not a good indicator of a UTI requiring antibiotics in this patient group. There is a very low incidence of UTI requiring treatment at the time of ocrelizumab infusion in our patient group. Results to be presented show a delay to infusion start times as a result of waiting for blood results. Recommendations are made on alternative ways of assessing for infection and improvements to patient pathways.

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P741

OPERA-ting differently: could extending the time-interval between infusions of ocrelizumab maintain efficacy in MS patients while reducing the risk of adverse events? A retrospective study

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Introduction: Ocrelizumab, an anti-CD20 humanized monoclonal antibody, is one of the most effective treatment available for the treatment of Multiple Sclerosis (MS). However, it induces lymphopenia and sometimes hypogammaglobulinemia, thus increasing risk of infections.
To decrease this risk, some MS centres have started extending the period between infusions from 6 months to 9/12, after 2 years of treatment
Objectives: Establish how annualised relapse rate (ARR), progression index (PI) and adverse events incidence are affected by extending the dose-interval
Aim: To assess safety and efficacy of extending Ocrelizumab dose-intervals over 6 months
Methods: 33 MS patients with more than 2 years of Ocrelizumab treatment were recruited at the Hôpital Pitié-Salpêtrière in Paris

from January to May 2022. 22 had an extended period (ExP), defined as an Ocrelizumab infusion interval> 6 months for the last two infusions, 11 followed standard protocol (StP), defined as Ocrelizumab infusions every 6 months . Data including mean ARR, PI, lymphocyte (Ly) count, CD19, infection incidence and IgG levels were collected retrospectively at last patient treatment (mean time under Ocre 2.70±0.48). Lymphopenia was defined as Ly count<1400/mm3, low IgG count as IgG<7.0 g/L, B cells repopulation was defined as CD19 count>80/mm3

Results: No significant differences were found between the two groups concerning disease onset age (p=0.27), sex (p=1), age at Ocrelizumab start (p=0.39), total duration of treatment (p=0.41), conversion to progressive forms (p=0.80), PI (p=0.36) and ARR (p=0.46) before Ocrelizumab start. No patient experienced a clinical relapse after the extension of the time interval and no significant differences concerning ARR (P=1) and PI (P=0.42) were found between groups. Infection incidence was higher in the StP group (p=0.05, β±βS.E. 0.73±0.17). No severe infection occurred in the ExP group, while 1 patient in the StP group had a severe infection (required hospitalization). 27% of patients in the StP group and 36% in the ExP group had their CD19+ levels available before their last infusion: 1 patient of the ExP group showed B cells repopulation versus 0 in the StP group. No significant differences were found concerning incidence of low IgG (p=0.57; OR 0.59; CI 0.10-3.57) and lymphopenia (p=0.55; OR 0.30-9.36)

Conclusions: Extending Ocrelizumab dosing intervals could reduce infectious risk without decreasing efficacy. However, larger studies should be conducted with a longer follow-up to identify late-onset hypogammaglobulinemia

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P742

Effective humoral and cellular immunity in mRNA-COVID-19 multiple sclerosis vaccinees treated with teriflunomide

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Introduction: The National multiple sclerosis (MS) Society and other expert organizations recommended that all MS patients should be vaccinated against COVID-19. The impact of disease-modifying therapies on the efficacy to mount appropriate immune responses is currently under investigation.

Objective: To characterize humoral and cellular immunity in mRNA-COVID-19 MS vaccinees treated with Teriflunomide.

Methods: We prospectively measured (1) SARS-COV-2 IgG response using a quantitative anti-spike protein-based immunoassay (Euroimmun, Lubeck, Germany, cut-off IgG level >35.2 BAU/ml), (2) memory B-cells specific for SARS-CoV-2 RBD, and (3) memory T-cells secreting IFN-g and/or IL-2, in response to SARS-CoV-2 peptides by ELISpot/Fluorospot assays, in MS patients vaccinated with BNT162b2-COVID-19 vaccine before, one and three months after the second vaccine dose. Patients were either untreated (N=31, 21 females) or under treatment with Teriflunomide (N=30, 23 females, median treatment duration 3.7 years, range 1.5-7.0 years). The percent of subjects that developed protective antibodies, the antibody titer, and the cellular B and T cell responses were evaluated.

Results: None of the patients had clinical SARS-CoV-2 or immune evidence for prior infection. Spike IgG titers were similar between untreated and Teriflunomide treated MS patients both at 1 month (median 1320.7, 25-75 IQR 850.9-3152.8 vs. median 901.7, 25-75 IQR 618.5–1495.8, BAU/ml, respectively), and at 3 months (median 1388.8, 25-75 1064.6–2347.6 vs. median 1164.3 25-75 IQR 726.4–1399.6, BAU/ml, respectively), after the second vaccine dose. In untreated and Teriflunomide-treated MS patients specific SARS-COV-2 memory B cells were detected in 41.9% and 40.0% of subjects at 1 month, and in 32.3% and 43.3% and at 3 months following vaccination, respectively. Specific SARS-COV-2 memory T cells were found in 48.4% and 46.7% of untreated and Teriflunomide-treated MS patients at 1 month, and in 41.9% and 56.7% in untreated and Teriflunomide-treated MS patients at 3 months, respectively.

Conclusions: Teriflunomide treatment enabled effective humoral and cellular immune responses to COVID-19 vaccination.

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P743

Multiple sclerosis, rituximab, SARS-CoV-2 vaccination, and COVID-19 severity

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Introduction: Rituximab (RTX) and other B-cell depleting therapies increase the risk of more severe COVID-19 among unvaccinated persons with multiple sclerosis (pwMS) and reduce humoral but not T-cell immune responses to SARS-CoV-2 vaccinations.
Objective/Aims: To determine whether RTX increases the risk of hospitalization for COVID-19 compared to pwMS who were untreated or treated with disease-modifying therapies (DMTs) that do not reduce vaccine efficacy (interferon-betas, glatiramer acetate, natalizumab or dimethyl fumarate) and identify modifiable factors among RTX-treated pwMS (RTX-MS).
Methods: We conducted a retrospective cohort study in Kaiser Permanente Southern California from 1.1.2020 to 15.2.2022. Logistic regression models were adjusted for age, sex, race and ethnicity, Elixhauser comorbidly index and advanced MS-related disability (requiring a walker, wheelchair or worse). Analyses restricted to RTX-MS were additionally adjusted for cumulative dose, dose at last infusion and time since last infusion.
Results: Among SARS-CoV-2 vaccinated pwMS, RTX-MS (n=1495) were more likely to be hospitalized (n=16) but not die (n=0) compared to the 2682 pwMS on no or other DMTs (no/other DMT, n=5 and n=0, respectively; adjusted odds ratio, AOR=6.27, 95% confidence interval CI=2.09-18.85). Receiving a SARS-CoV2 vaccine type other than mRNA (AOR=5.06, p=0.001) and not receiving a booster vaccination (AOR=2.85, p=0.026) were independent predictors of COVID-19 severity. The absolute risk of hospitalization for COVID-19 was low in both groups (RTX-MS 1.4 per 100 person-years and 0.21 among no/other DMT). Among vaccinated RTX-MS, receiving the first vaccination dose more than 6 months after the last RTX infusion significantly reduced the risk of COVID-19 hospitalization (AOR=0.08, 95%CI=0.02-0.35) and advanced MS-related disability increased it (AOR=3.71, p=0.045). Unvaccinated RTX-MS (n=573) were at significantly higher risk of COVID hospitalization (n=30 including n=2 deaths) compared to vaccinated RTX-MS (AOR=5.56, $p<0.0001$).
Conclusions: Rituximab-treated pwMS should be strongly encouraged to receive mRNA SARS-CoV-2 vaccination series and boosters, ideally >6 months since their last RTX infusion. While the absolute risk of severe COVID-19 is low among vaccinated RTX-MS, the odds of hospitalization is significantly higher compared to no/other DMT. The marginal benefits of B-cell depleting therapies in persons with advanced MS-related disability should be weighted against the additional increased risk of severe COVID in this group.

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P744

Longitudinal humoral response in MS patients treated with Cladribine tablets after receiving the second and third doses of SARS-CoV-2 mRNA vaccine

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Introduction: Multiple sclerosis (MS) patients receive immunomodulatory treatments, which can influence their ability to maintain vaccine specific serological response overtime. MS patients treated with Cladribine tablets developed a positive serology response following two doses of mRNA COVID-19 vaccine. However, there is only limited data regarding the effect of cladribine tablets on long-term humoral response after the second and the third booster.
Methods: Serology response to SARS-CoV-2 was tested in healthy controls (HCs) and MS patients treated with cladribine tablets 3 weeks, and 6 and 9-12 months after the second dose, and 1 and 3-6 months following the third booster-dose of the BTN162b2 mRNA vaccine.
Results: HCs (n=27) and MS patients treated with cladribine (n=24) had 100% positive serology response against the SARS-CoV-2 spike protein 3 weeks following the second vaccine dose (13041±9411 AU/mL and 10554±11405 AU/mL respectively). Thirty-five out of 36 MS patients treated with cladribine tablets and 100% (46/46) of HCs had a positive serology response up to 10 months after the second vaccine dose. In addition, all cladribine tablets -treated MS patients (22/22) and HCs (24/24) had a positive robust serology response following the third vaccine with a positive humoral response sustain up to 6 months. One month after the third vaccine dose IgG levels were significantly lower in patients treated with cladribine tablets compared to HCs (15598+11313 vs 26394+11335, $p<0.01$). Six-month post second vaccine and 3-6 months post third vaccine there was no difference in IgG levels between the groups (1088.0±1072.0 vs 1153.0±997.1, p=0.79; 5234+4097 vs 11198+14679, p=0.4).
Conclusion and relevance: MS patients treated with cladribine tablets have sustained positive vaccine specific serology response following the second and third SARS-CoV-2 vaccine dose.

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P745

Management of ocrelizumab in MS patients during the COVID-19 pandemic: an observational registry-based study

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Introduction: Concerns have emerged during Covid-19 pandemic about management of Disease Modifying Therapies (DMTs) in patients with Multiple Sclerosis (pwMS). In particular, Ocrelizumab (OCR)-treated pwMS faced possible delays of scheduled infusions due to disruption of MS Centers activities as well as safety worries during lockdown periods.
Objective: To assess changes of OCR infusion schedule in Italian pwMS during the first wave of COVID-19 pandemic (observation period: February-June 2020) and to investigate predictive factors determining delaying of OCR infusions.
Materials and methods: Data were extracted from the Italian MS Register database. pwMS with an OCR infusion scheduled during the observation period and at least two previous OCR infusions were selected. Demographics (age, gender), disease characteristics (MS phenotype, disease duration, Expanded Disability Status Scale score, number of previous OCR infusions) and location of MS Centers among three Italian macro-regions (North, Center, South) were tested as potential predictors for treatment delay using univariable and multivariable linear model analyses.
Results: Five-hundred ninety-nine pwMS (343 F/256 M; 411 Relapsing MS/188 Progressive MS) from 65 MS centers were included in the analysis. Mean interval between two OCR infusions was 28.1 weeks (SD 2.72) before the observation period compared to 30.8 weeks (SD 5.45) during the observation period, with a mean delay of 2.7 weeks ($p < 0.001$). No clinico-demographic factors emerged as predictors of infusion postponement, except for location of MS centers in the North of Italy (4.7 weeks vs 1.5 in the Center and 1.6 in the South). Such a difference was confirmed in multivariate analysis ($p < 0.001$) adjusting for pre-lockdown mean OCR infusion schedule.
Conclusions: This large registry-based study shows that OCR infusions were significantly delayed during the first wave of COVID-19 pandemic in Italy. The location of the MS Centers in Northern Italy was the only predictor of OCR infusion postponement. This geographical area corresponds to the region in Italy that was hit first and more strongly by Covid-19 pandemic. The observed delay in OCR infusions disruptions of MS centers activities due to a drastic reduction of healthcare workers availability (because of infection/quarantine and/or reallocation in Covid Units) and concerns about using an immunosuppressive DMT like OCR during a new virus pandemic with many uncertainties.

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P746

Natalizumab, a valuable strategy for immunisation to avoid delays of treatment onset in highly active MS patients

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Background: Vaccination during immunosuppression can result in impaired vaccine responses. In highly active patients requiring a rapid treatment initiation, vaccination can delay treatment onset. Natalizumab (NTZ) is a high-efficacy agent with potential low interference in vaccination responses, and could be a bridge therapy to achieve an adequate immunisation before starting another treatment.
Objectives: To assess the safety and immunogenicity of inactivated vaccines administered during NTZ treatment.
Methods: Self-controlled study based on an ongoing prospective cohort that included adult MS patients with complete immunisation schedules for hepatitis B vaccine (HBV), hepatitis A vaccine (HAV) and/or COVID-19 vaccine during NTZ treatment, between September 2016 and February 2022. Seroprotection rates were calculated for each vaccine. Demographic, clinical and radiological characteristics were collected the year before (pre-exposure period) and after vaccination (post-exposure period). Differences in annual relapse rate (ARR), contrast-enhancing lesions (CELs), new T2 lesions (NewT2) and changes in Expanded Disability Status Scale (EDSS) during pre and post exposure period were evaluated. Patients were also categorised according to time on NTZ exposure before vaccination (long-term exposure >1 year and short-exposure $\leqslant 1$ year) and according to JCV status.
Results: From 248 patients treated with NTZ, 60 were vaccinated during NTZ exposure: 44 (73%) women, mean age 45 years, mean disease duration 17 (SD 8.7) years. Thirty (50%) patients bridged to anti-CD20 after immunisation, because of high titers of JC virus. Between the pre and post-exposure period, we observed a decrease in both the AAR (0.28 vs 0.01; p=0.004) and newT2 (0.8 vs 0.02; p=0.1) and no changes in disability accumulation (EDSS 3.5 vs 3.5 p=0.6). The global seroprotection rate was 93% (91.6% (IC95% 73-99) for HAV (n=24), 92.6% (IC95% 76- 99) for HBV (n=27), 100% (IC95% 84-100) for Covid-19 (n=23)).
No differences were seen between short and long term NTZ exposure or between JCV positive or negative patients, in terms of safety and immunogenicity.
Conclusions: Immunisation with inactivated vaccines during NTZ treatment is safe and effective, both for short and long term NTZ exposure. In highly active PwMS who need immunisation, NTZ could be a valuable strategy to avoid delays in the onset of high-efficacy DMD, even in JC virus positive in which it could be used as a bridge therapy strategy.

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P747

Severe COVID-19 outcomes following vaccination in persons with multiple sclerosis: a real-world evidence study

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Background: Recent research has demonstrated that persons with MS (pwMS) treated with disease-modifying therapies (DMTs) may have a reduced immune response to SARS-CoV-2 vaccination. To date, limited research has examined the rate of severe breakthrough infections after vaccination, particularly during the Omicron wave, among pwMS, including those treated with ocrelizumab (OCR).
Objective: To describe the rate of severe breakthrough infections following SARS-CoV-2 vaccination in pwMS overall and by DMT. This study provides an update on previously presented research to include the Omicron wave.
Methods: The sample included all fully vaccinated pwMS in the deidentified Optum COVID EHR database (study period, 11 December 2019–17 March 2022). All pwMS who had COVID-19 prior to the index date or any non-OCR B-cell–depleting therapy, were pregnant or had cancer during the study period were excluded. The index date was 14 days after the last dose of the primary vaccine series. DMT status was based on the last DMT used in the 6 months prior to the index date (i.e. index DMT), and pwMS without any DMT were classified as having "no DMT recorded." Severe breakthrough infections, including COVID-related hospitalisations, hospitalisations for severe COVID and deaths occurring after the index date, were described overall and by the index DMT. The data use agreement required counts <10 to be suppressed.
Results: A total of 4720 fully vaccinated pwMS were included in the study; 740 pwMS (16%) were treated with OCR, 327 (7%) with S1P receptor modulators, 49 (1%) with interferons and 1421 (30%) with other DMTs, and 2183 (46%) had no DMT recorded. Following full vaccination, 57 pwMS (1.2%) had a COVID-related hospitalisation, 25 (0.5%) had a severe COVID–related hospitalisation and <10 COVID-related deaths occurred. COVID-related hospitalisations were low across all DMT subgroups. Compared with all pwMS, hospitalised pwMS tended to be older, male, covered by Medicare and nonambulatory and to have no booster/additional dose recorded. Full results will include severe breakthrough events by DMT based on data through June 2022.
Conclusions: COVID-related hospitalisations, hospitalisations for severe COVID and deaths following vaccination were low among all pwMS, including those treated with ocrelizumab. Characteristics of pwMS with a severe breakthrough event suggest their risk factors were similar to the general population's.

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P748
Impact of extended interval dosing of ocrelizumab on immunoglobulin levels in multiple sclerosis

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Background: Long-term B cell depletion with ocrelizumab in multiple sclerosis (MS) is associated with severe side effects such as hypogammaglobulinemia and infections. Individualized treatment regimens might provide a tool to increase treatment safety, but there is not sufficient evidence to allow for general recommendations.
Objective: To assess immunoglobulin levels under treatment with ocrelizumab and implement an extended interval dosing (EID) scheme.
Methods: Immunoglobulin levels of 51 patients with ⩾24 months of treatment with ocrelizumab were analyzed. After ⩾4 treatment cycles, patients chose to either continue on the standard interval dosing (SID) regimen (n=14) or switch to B cell-adapted EID (n=12, next dose at CD19+ B cells >1% of peripheral blood lymphocytes).
Results: Levels of IgM declined rapidly under ocrelizumab treatment. Risk factors for IgM and IgA hypogammaglobulinemia were lower levels at baseline and more previous disease-modifying therapies. B cell-adapted EID of ocrelizumab increased the mean time until next infusion from 27.3 to 46.1 weeks. Immunoglobulin levels declined significantly in the SID group over 12 months but not in the EID group. Previously stable patients remained stable under EID as measured by Expanded Disability Status Scale (EDSS), neurofilament light chain, timed 25-foot walk, 9-hole peg test, symbol digit modalities test and Multiple Sclerosis Impact Scale (MSIS)-29.
Conclusion: In our pilot study, B cell-adapted EID of ocrelizumab prevented decline of immunoglobulin levels without affecting disease activity in previously stable MS patients. Based on these data, we propose a new therapeutic algorithm for long-term ocrelizumab treatment.

Disclosure
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P749
Infusion related reactions during shorter infusion of ocrelizumab: a real-world single centre experience

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Introduction: Ocrelizumab is an anti-CD20 antibody approved for multiple sclerosis, administered intravenously as two initial doses of 300 mg infusions of about 2.5 hours 2 weeks apart, with subsequent doses every 6 months as single 600 mg infusions of at least 3.5 hours. The ENSEMBLE PLUS study showed that shortening the 600mg infusion time to 2 hours does not impact the rate and severity of infusion related reactions (IRRs)
Aim: We compared the rate, severity and type of IRRs during shorter infusion (SI) versus conventional infusion (CI) of ocrelizumab in clinical practice
Methods: We enrolled 45 patients who received both CI and at least one SI of 600mg ocrelizumab from 2016 to April 2022, according to current recommendations. IRRs were defined as adverse events occurring during or up to 24h after the infusion and judged as related to drug administration. Data are presented as descriptive statistics with no formal hypothesis testing
Results: We observed 274 infusions (90 300mg infusions, 135 600mg CI, 49 600mg SI). The median number of infusions per patient before the SI was 4 (range 2-11). We found an overall IRRs rate of 0.22 (60/274). At the first treatment cycle, we found a higher rate of IRRs during the first 300mg administration (19/45, 0.42) compared to the second one of 300mg (7/45, 0.15)($p<0.01$). The rates of IRRs at CI and SI were similar (0.18 and 0.20 respectively; OR 1.175, 95% CI 0.46 - 2.85). 50% of IRRs at SI and 30% of IRRs at CI were classified as grade 1; 50% of IRRs at SI and 70% of IRRs at CI were reported as grade 2. No IRRs^{3}grade 3 occurred and all resolved without sequalae. Throat irritation was the most recorded IRR (32/60, 53%), and the most frequent at both CI (14, 58%) and SI (7, 70%).40% of IRRs during SI and 70% of IRRs at CI led to an infusion intervention (slowing downor temporary interruption). Symptomatic treatment was administered in 50% for IRRs at SI and for 70% of IRRs at CI with the most frequent being antihistamines (80% at SI, 88% at CI), most commonly in combination with i.m. steroid at SI.No IRR led to infusion or treatment discontinuation
Conclusions: In our single centre experience, shorter infusion of ocrelizumab did not lead to an increased rate of IRRs, neither changed the type of symptoms and their severity, nor the management strategy, compared to the conventional one. As in clinical trials, shorter infusion proved to be safe and convenient to optimize ocrelizumab administration in a real-world setting

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Dr.Confalonieri acted as an Advisory Board member of Biogenand Novartis; received funding for traveling fromBiogen, Merck,Teva, Novartis; received honoraria for speaking or writing fromBiogen- and Novartis. He received support for research project by Novartis and Merck
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P750

StratifyJCV™ serum anti-JCV antibody assay for natalizumab patients: Unilabs global cohort data descriptive analysis and Unilabs customer satisfaction survey results

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Background: Natalizumab (Tysabri®) is a highly effective therapy for relapsing-remitting multiple sclerosis but is also associated with an increased risk of progressive multifocal leukoencephalopathy (PML) in patients who are anti–JC virus (JCV) seropositive. Biogen developed and validated StratifyJCV™, an antibody assay to detect the presence of anti-JCV antibodies in serum and to quantify antibody index values, which are correlated to PML risk in natalizumab-treated patients. On behalf of Biogen, Unilabs (Copenhagen, Denmark) has been conducting the analysis of the StratifyJCV assay since 2011 for over 70 countries (excluding North America), having analysed over 1 million StratifyJCV tests to date.
Objective: To provide an overview of the utilisation of StratifyJCV testing in natalizumab patients conducted by Unilabs and to highlight results from the 2021 Unilabs Customer Satisfaction survey.
Methods: Aggregated data of the results of 845,450 StratifyJCV tests received and assessed by Unilabs from January 2015 to December 2021 were analysed. The anti-JCV antibody index outcomes of retests were compared over time to explore the patient type (low risk or high PML risk) that healthcare professionals (HCPs) are treating with natalizumab.
The Unilabs Customer Satisfaction Survey was sent to 8640 users of the Unilabs StratifyJCVdigital platform worldwide, requesting feedback on the user friendliness of the StratifyJCVweb portal, turnaround time for test results, courier services and Unilabs help desk support.
Results: The percentage of anti-JCV antibody-negative index outcomes in retests was 66% in 2015 (n=91,278 total) in comparison with 72% in 2021 (n=14,8975 total), a 6% increase. There was a decrease in percentage of JCV-positive index results >1.5, from 15% in 2015 to 9% in 2021.
Of the 1010 responders to the Unilabs Customer Satisfaction survey (response rate of 11.7%), 98% were either very satisfied (56.7%) or satisfied (41.2%) with the services provided by Unilabs. Of the responders, 59% were neurologists and 33.2% nurses.
Conclusions: The decrease in percentage of JCV-positive antibody index results >1.5 demonstrates that HCPs are currently treating with natalizumab more patients with a lower PML risk than in 2015, indicating safer use of natalizumab. Overall, users of the StratifyJCV tests are very satisfied with the service provided by Unilabs on behalf of Biogen.

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P751

Post-vaccination SARS-Cov-2 spike-specific memory T-cell repertoires in patients with multiple sclerosis and related disorders

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Introduction: Some MS DMTs, such as anti-CD20 antibodies and sphingosine-1-phosphate (S1P) receptor modulators, decrease post-infection and post-vaccination SARS-Cov-2 humoral responses. However, humoral immunity is only one component of the adaptive response, and T cell responses, which may be preserved in anti-CD20 treated patients, play an important role.
Objectives: To characterize SARS-Cov-2 spike specific memory T-cell receptor repertoires in patients with MS and related conditions post-vaccination with mRNA vaccines.
Aims: To characterize SARS-Cov-2 vaccine-mediated responses for people using MS DMTs.
Methods: Patients without prior COVID-19 infection provided a whole blood sample >3 weeks and <6 months after vaccination with two doses of Pfizer-BioNTech or Moderna mRNA vaccines. Sequencing of the complementary determining region within T-cell receptors (TCRs) was performed. Antigen recognition activates unique TCRs and results in expansion of antigen-specific T-cell clones. Sample TCR sequences were cross-matched with sequences known to react to SARS-CoV-2 using "Multiplex Identification of T-cell Receptor Antigen Specificity (MIRA)", allowing for characterization of SARS-CoV-2-spike-specific TCR frequency (clonal depth) and diversity (clonal breadth). Humoral responses were compared.
Results: 39 patients were recruited: age 25-77; 27 female; 37 with MS, 2 with NMO, and 1 with another neuroimmune condition. DMTs included anti-CD20 (N=13), natalizumab (N=9), fumarates

(N=8), S1P receptor modulators (N=3), and controls (2 glatiramer acetate, 4 no DMT). Mean time interval between 2nd vaccination dose and TCR testing was 13.3+6.0 weeks.
Humoral responses (Roche) were absent in all anti-CD20 and S1P treated patients but preserved in all others. SARS-CoV-2-spike-specific clonal depth and breadth did not differ across all treatment classes except S1P modulators. Despite lack of antibody production, patients treated with anti-CD20 therapies demonstrated comparable TCR depth and breadth to all other groups in univariable assessment. No spike-specific TCRs were found in patients treated with S1P modulators. TCR breadth and depth did not vary with time since vaccination even up to 24 weeks following vaccination.
Conclusion: TCR repertoires were preserved except for in those treated with S1P receptor modulators.Humoral responses were diminished with both anti-CD20 and S1P DMTs. These findings may help guide counseling of patients with regards to DMT choice.

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Therapy - Tools for detecting therapeutic response

P752

Assessing treatment response to oral drugs for multiple sclerosis in real world setting: a MAGNIMS study

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Introduction: The assessment of treatment response, currently based on the integration of clinical and magnetic resonance imaging (MRI) measures, is necessary in patients with relapsing-remitting multiple sclerosis (RRMS) on disease-modifying therapies (DMTs). However, previousstudies have reported responsetoinjectable DMTs. So far we do not know if, we can use the same tools to predict response to oral DMTs.
Objective and Aims: To explore the significance of clinical and MRI measures, alone and combined into the MAGNIMS score, to evaluate response to oral DMTs.
Methods: A multicenter clinical dataset was collected within the MAGNIMS network from 12 centers across Europe. We retrospectively evaluated data of RRMS patients who started dimethyl fumarate (DMF), fingolimod (FNG) or teriflunomide (TNF) according to the following criteria: treatment-naive or switching from injectable DMTs; at least 1 year treatment duration; brain MRI scan collected at baseline and year 1; at least 3 years of clinical follow-up. We explored the association between one-year clinical and MRI activity and (i) the risk of confirmed disability worsening (defined on the basis of the Expanded Disability Status Scale [EDSS]); (ii) the switch to another treatment for efficacy reason by Cox regression adjusted for baseline demographic, clinical and MRI variables.
Results: Data from 1.200 patients (69% women; mean ± SD age 39.3±10.7 years; median EDSS score 1.5 [range 0 to 7.0]; 34.8% treatment naïve) were collected. Of them, 598 were treated with DMF, 308 with FNG and 294 with TNF.
Between year 1 and year 3, 13.3% of the patients experienced confirmed disability worsening, 20% switched to another DMTs due to lack of efficacy and 11% had one or more relapses. In the whole cohort, confirmed disability worsening at year 3 was predicted by

the occurrence of relapses in the first year (HR=2.11, p<0.001) and the fulfillment of MAGNIMS score 1 and 2 (HR=2.06, p=0.001; HR= 2.56, p=0.018 respectively). Patients experiencing relapses during the first year as well as those with 3 or more new T2 lesions at year 1 MRI scan, had a higher probability to switch to other DMTs (HR= 1.52, p=0.015; HR=2.21, p<0.001).

Conclusions: In a multicenter study we report that early relapses and MRI activity in the first year of treatment with oral DMT are associated with an increased risk of short-term confirmed disability worsening and treatment failure in patients treated with oral DMTs.

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P753
Effect of ocrelizumab on leptomeningeal inflammation and humoral response to Epstein Barr-Virus in multiple sclerosis

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Background: Ocrelizumab is an effective treatment for relapsing and primary-progressive multiple sclerosis (MS). However, the effect of ocrelizumab on leptomeningeal (LM) inflammation is unknown.
Objective: To investigate whether ocrelizumab reduces LM inflammation and gray matter (GM) pathology by reducing the exposure to Epstein-Barr virus (EBV)-infected B cells in relapsing-remitting (RR) MS.
Methods: This was a Phase IV, prospective, open-label, single-center, observational, longitudinal pilot study of RRMS patients who started treatment with ocrelizumab (NCT03025269). Clinical, MRI and EBV-antibodies outcomes at baseline, 12- and 24-month of the study were evaluated. The MRI outcomes included T2, T1 and T1-contrast enhancing (CE) lesion counts and volumes, LM CE count, and percentage brain volume changes.
Results: 27 RRMS patients started ocrelizumab and 24 remained on the treatment for whole duration of the study. Most patients remained stable (74.1%) or improved (18.5%) in their disability status. At baseline, 42.3% of patients showed LM CE lesions. The majority of patients remained stable in their LM CE status over the follow-up (72.7%). A significant decrease in percentage volume loss of cortex (p=0.009), GM (p=0.01) and thalamus (p=0.038) was detected, while T1-LV increased (p=0.02). A significant decrease of EBNA-1 IgG (p=0.013) was evidenced. An infusion-related allergic reaction led to discontinuation of the medication in one patient at first dose.
Conclusions: Treatment with ocrelizumab was safe and clinically effective. Brain volume loss and accumulation of T1-LV occurred. While ocrelizumab decreased humoral response to EBV possibly by reducing B cells, it did not reduce LM inflammation and associated GM pathology.

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P754
Better coping with multiple sclerosis is associated with enhanced compliance to early immunomodulatory treatment

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Introduction: Receiving the diagnosis of multiple sclerosis (MS) is a difficult mental burden to the newly diagnosed patients, their families, and close surroundings. Training workshops by targeted coaching can facilitate the process of accepting the diagnosis, which is often entangled by mourning, a sense of loss, and shattering personal life and plans.
Objective: Evaluate the effect of targeted MS management coaching program on coping with the disease in newly diagnosed patients.
Methods: Newly diagnosed MS patients were offered to participate in a targeted MS management coaching program for eight consecutive weekly meetings of two-hours duration. Each coaching program included 8 to 12 patients and was conducted by two trained coachers. During the meetings, the coachers presented various coping strategies such as positive reframing, enhancing self-control, acceptance, and self-compassion and offered social support to achieve better attitudes towards the disease.
Results: Fifty-five newly diagnosed MS patients, 36 females, mean age of 28.2 years, disease duration of 4.8 months, participated in the targeted MS management coaching program. The majority 46/55 (83.6%) initiated immunomodulatory treatment within 2.6 months. In comparison, of 50 newly diagnosed patients, 33 females, mean age of 29.6 years, disease duration of 4.5 months, that did not participate in the coaching program, only 15/50 (30%) initiated immunomodulatory treatment within 6.3 months.

Conclusions: Our findings suggest that better coping with the disease during the early period after the diagnosis is associated with a higher rate of compliance to immunomodulatory treatment.

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P755
Soluble vascular cell adhesion molecule-1 and natalizumab plasma concentration as potential biomarkers for monitoring treatment of multiple sclerosis patients with natalizumab

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Introduction: Natalizumab (NTZ) is an established treatment for highly active relapsing-remitting multiple sclerosis. Since rare occurrence of progressive multifocal leukoencephalopathy (PML) has been recognized and extended interval dosing (EID) has been introduced as an option for reducing PML risk, biomarkers for monitoring treatment with NTZ and allowing personalized therapy are required.
Objectives/Aims: To investigate NTZ plasma concentration (NTZ PC) and sVCAM-1 as potential biomarkers in patients treated with NTZ.
Methods: In a retrospective study at the Medical University of Innsbruck, Austria, we identified patients treated with NTZ and chose samples longitudinally collected during routine follow-ups for measurement of NTZ plasma concentration (NTZ PC) and sVCAM-1 by ELISA. We correlated these with clinical and demographic variables and clinical outcome. Furthermore, we analyzed stability of NTZ PC and sVCAM-1 during treatment.
Results: 137 patients were included. We found a strong negative correlation between NTZ PC and sVCAM-1. Both showed significant association with body mass index, infusion interval, sample age and anti-drug-antibodies. NTZ PC was reduced in EID, but not sVCAM-1. Only sVCAM-1 showed a weak association with relapses during treatment, while there was no association with disease progression. Both, NTZ PC and sVCAM-1, showed a wide inter-individual distribution while levels in single patients were stable on treatment.
Conclusion: sVCAM-1 is a suitable pharmacodynamic marker during treatment with NTZ which is significantly reduced already after the first dose, remains stable in individual patients even on EID and strongly correlates with NTZ PC. Due to high inter-individual range absolute levels of sVCAM-1 and NTZ PC are difficult to introduce as treatment monitoring biomarkers in order to predict disease activity in single patients.

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AB reports no conflicts of interest.
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DR reports no conflicts of interest.
HH has participated in meetings sponsored by, received speaker honoraria or travel funding from Bayer, Biogen, Celgene, Merck, Novartis, Sanofi-Genzyme, Siemens and Teva, and received honoraria for consulting Biogen, Celgene, Novartis and Teva.
GB has participated in meetings sponsored by, received speaker honoraria or travel funding from Biogen, Celgene/BMS, Lilly, Merck, Novartis, Roche, Sanofi-Genzyme and Teva, and received honoraria for consulting Biogen, Celgene/BMS, Novartis, Roche, Sanofi-Genzyme and Teva. He has received unrestricted research grants from Celgene/BMS and Novartis.
FDP has participated in meetings sponsored by, received honoraria (lectures, advisory boards, consultations) or travel funding from Bayer, Biogen, Merck, Novartis, Sanofi-Genzyme, Teva, Celgene and Roche.
KB has participated in meetings sponsored by and received travel funding from Roche, Biogen and Teva.
AZ has participated in meetings sponsored by, received speaking honoraria or travel funding from Biogen, Merck, Sanofi-Genzyme and Teva.
TB has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for MS: Allergan, Bayer, Biogen, Bionorica, Celgene, MedDay, Merck, Novartis, Octapharma, Roche, Sanofi-Genzyme, Teva. His institution has received financial support in the past 12 months by unrestricted research grants (Biogen, Bayer, Merck, Novartis, Sanofi Aventis, Teva and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Bayer, Biogen, Merck, Novartis, Octapharma, Roche, Sanofi-Genzyme, Teva.
MR reports no conflicts of interest relating to the present manuscript.
FD has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker for Alexion, Almirall, Biogen, Celgene, Merck, Novartis, Roche and Sanofi-Genzyme. His institution received scientific grants from Biogen and Sanofi-Genzyme.

P756
Pharmacogenomic predictors of fingolimod response in relapsing-remitting multiple sclerosis

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Introduction: Genetic predictors of treatment response are key in reducing time from diagnosis to effective treatment, therefore reducing the risk of long-term disability for people with multiple sclerosis (MS). Fingolimod (FTY) is an efficacious oral disease-modifying therapy (DMT) and has been prescribed for over 299,000 individuals worldwide since 2010. The ability to predict response to fingolimod will benefit the global RRMS population.
Objective and aims: To identify single nucleotide variants (SNVs) that predict time to failure (TTF) on FTY.
Methods: Participants were recruited from eight study sites across Australia and Europe based on: participation in MSBase Registry, RRMS diagnosis, European ancestry, ⩾3-months FTY exposure and ⩾1 relapse-independent EDSS recorded after FTY initiation. Treatment failure was defined as the first of either an on-treatment relapse or three-month confirmed disability progression (CDP) and used to determine per-patient TTF. Genotyping was performed on customised Illumina MegaEx BeadChip arrays, and raw data was cleaned in PLINKv1.9 using standard filters. Cox-proportional hazards models were used to test the association between SNVs and TTF, followed by fixed-effects meta-analyses to account for data coming from three distinct populations. Bonferroni deflation was used to assess significance ($p<9x10\text{-}8$).
Results: The discovery cohort consisted of 204 RRMS patients with European ancestry from Australia, Spain and the Czech Republic. 108 of 204 (53%) patients failed on FTY (72 by relapse, 36 by CDP) over a median follow-up time of 34.6 months (IQR=17.8-53.3 months). 638,419 SNVs were tested for association with TTF. No SNVs passed genome-wide significance thresholds, but 15 were strongly suggestive of association with TTF ($p<1x10\text{-}5$). The combinatory risk of treatment failure using the top two SNVs was significant at the genome-wide level (HR=3.25, 95% CI=2.28-4.64, p=7.54x10-11). Here, the median time to failure for risk allele carriers at both, one or none of the SNVs was 5.9, 10.4 and 42.0 months, respectively. Notably, these SNVs did not predict TTF on natalizumab. Validation results from an independent cohort of 500 patients are pending and will be presented.
Conclusion: Time to failure on FTY is mediated by polygenic mechanisms in RRMS patients of European descent. A polygenic risk score may have clinical utility in identifying FTY (non-) responders.

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Therapeutic efficacy of MRI: association between MRI utilization and DMT switch among people with MS in the United States

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Introduction: Disease modifying therapies (DMT) are pharmacologic interventions to treat multiple sclerosis (MS), but the effect that magnetic resonance imaging (MRI) has on the choice to change a DMT remains unmeasured.
Objectives: To assess the therapeutic efficacy of MRI in people with MS (pwMS) on DMT.
Aims: To measure the association between MRI utilization and DMT switches in pwMS in the United States in 2018 using de-identified insurance claims data.

Methods: This retrospective cohort study identified pwMS in 2018 from Optum®Clinformatics®Data Mart–a de-identified national claims database. After excluding those without an MS-related clinical encounter or history of DMT use, 11,972 patients were selected. PwMS who received MRI in 2018 were compared to pwMS not receiving any MRI in 2018. MRI utilization was measured by number of central nervous system (CNS) locations imaged. Patients were observed for six months following MRI or first clinical encounter for MS to assess the incidence of a DMT switch. Unconditional logistic regression modeled the association between MRI utilization and DMT switches, adjusted for age and clinical disease activity.

Results: 4,616 (38.6%) pwMS received at least one MRI in 2018. Overall, imaging one or more CNS locations increased the odds of switching DMT (OR [95% CI] = 1.43 [1.21–1.69], 1.79 [1.48–2.16], and 3.09 [2.50–3.81] for 1, 2, and ⩾3 locations imaged). Those on injectable platform DMT receiving MRI of one CNS location had 1.53 (95% CI: 1.16–2.03) times the odds of switching DMT compared to those who did not receive an MRI. The odds ratio increased to 2.26 (95% CI: 1.69–3.02) and 3.63 (95% CI: 2.62–5.04) when 2 and ⩾3 locations were imaged. For those on oral DMT, only receiving MRI of 2 or ⩾3 locations significantly increased the odds of a DMT switch (OR [95% CI] = 1.22 [0.94–1.58], 1.70 [1.27–2.27], and 2.46 [1.76–3.42] for 1, 2, and ⩾3 locations). Finally, for pwMS on high-efficacy infusion therapies, MRI utilization did not significantly change the odds of DMT switch.

Conclusion: Among pwMS on injection or oral DMT, imaging more CNS locations increased the odds of switching DMT. These findings suggest imaging multiple CNS locations for pwMS on low to moderate efficacy DMT as it may better detect subclinical disease activity to inform changes in therapy. For pwMS on high-efficacy infusion DMT, MRI did not change the odds of switching DMT but remains essential for safety monitoring.

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Transcriptome alterations in peripheral blood B cells of patients with multiple sclerosis under immune reconstitution therapy

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Introduction: Therapies for MS that have immunomodulatory effects or affect the proliferation or migration of immune cells need to be given continuously to maintain their therapeutic efficacy. The goal of so-called immune reconstitution therapies (IRTs) is to achieve long-term disease remission by eliminating the pathogenic immune repertoire through short-term immune cell depletion (Lünemann et al., 2020). B cells are major targets for effective immunotherapy in MS.

Objectives: The aim of this study was to analyse the gene expression pattern of B cells before and during IRT (i.e. before B-cell depletion and after B-cell repopulation) to better understand the therapeutic effects and to identify biomarker candidates of the individual clinical response to therapy.

Methods: B cells were obtained from blood samples of patients with relapsing-remitting MS (n=50), patients with primary progressive MS (n=13) as well as healthy controls (n=28). The patients with relapsing MS received either monthly infusions of natalizumab (n=29) or a pulsed IRT with alemtuzumab (n=15) or cladribine (n=6). B cell subpopulation frequencies were determined by flow cytometry, and transcriptome profiling was performed using Clariom D arrays. Differentially expressed genes (DEGs) between the patient groups and controls were examined with regard to their functions and interactions. We also tested for differences in gene expression between patients with and without relapse following alemtuzumab administration.

Results: Patients treated with alemtuzumab or cladribine showed on average a >20% lower proportion of memory B cells as compared to before IRT. This was paralleled by profound transcriptome shifts, with >6,000 significant DEGs after adjustment for multiple comparisons. The top DEGs were found to regulate apoptosis, cell adhesion and RNA processing, and the most highly connected nodes in the network of encoded proteins were *ESR2, PHB* and *RC3H1*. Higher mRNA levels of *IL13RA1* and *SLC38A11* were seen in patients with relapse despite IRT, but these differences did not pass the false discovery rate correction.

Conclusions: We show that B cells circulating in the blood of patients with MS under IRT present a distinct gene expression signature, and we delineated the associated biological processes and gene interactions. Moreover, we identified candidate genes whose expression may be an indicator of relapse risk, but further studies are needed to substantiate their potential predictive value.

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Therapy - Symptomatic treatment

P759

Rapid discontinuation of baclofen as a treatment for spasticity among MS patients with incident and prevalent diagnoses

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Introduction: Baclofen is the first line drug choice for spasticity; a common MS feature influencing function and quality of life. Its prescription and discontinuation patterns among persons with MS (pwMS) are described incompletely.
Objective & Aim: To characterize baclofen prescription patterns in a nationwide cohort study of people with prevalent (pMS) and incident (iMS) MS.
Method: Data was linked from the Swedish MS register and national health registers for PwMS aged 18-65 years at diagnosis. Baclofen initiation was identified using the Prescription Drug Register excluding prescriptions from 1 July 2005—30 June 2006 (1st year of the register) and before MS diagnosis, to identify new prescriptions. Follow-up was from first dispensation until discontinuation, 31 Dec 2014 or death. Discontinuation was defined as no renewed prescription within gaps of 90, 150, or 180 days from last dispensation. Failure functions were plotted and Cox regression estimated hazard ratios.
Results: A total of 188 (10%) of iMS (N=1826) and 628 (19%) of pMS (N=3519) received a new baclofen prescription. Discontinuation among iMS and pMS was similar using different time gaps: 49% (CI 0.42-0.57) iMS and 51% (CI 0.48-0.56) pMS discontinued within 150 days and approx. 90% discontinued overall. Approx. 65% of individuals discontinued within 1-year and 80% by 2-years. iMS with progressive course were treated for longer than relapsing course, and though similar among pMS differences between courses were less evident. Stratifying by EDSS (0-2.5, 3.0-5.5 and 6+) at baclofen initiation showed that PwMS with higher EDSS persisted longer than EDSS 0-2.5 but discontinuation was high among all groups. Cox regression showed EDSS associated with discontinuation, with iMS of EDSS 3-5.5 and 6+ 72% (CI 0.44-1.16) and 61% (CI 0.35-1.05); pMS 78% (CI 0.59-1.03) and 65% (CI 0.49-0.85) less likely to discontinue. No other MS characteristics (duration, age, course, sex, diagnosis/onset age), depression or seizures were associated. Though not statistically significantly associated, females and those with a progressive course were less likely to discontinue.
Conclusions: Baclofen has similarly high discontinuation rates among patients with iMS and pMS, possibly reflecting low tolerability or efficacy. Only increased disability indicated by higher EDSS was associated with longer baclofen persistence highlighting the need for more tolerable and efficacious pharmacological treatments for spasticity in PwMS.

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Botulinum toxin trial treatment for MS- tremor: a randomized, double-blinded study

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Background: Tremor affects about half of people with Multiple Sclerosis (MS), most often including the upper limbs and dominant arm. MS tremor is associated with worse quality of life, but no efficient treatment has been established. A previous double-blind, randomized study showed improvement in tremor-affected tasks (e.g., writing, drawing) following injection of botulinum toxin type A (BT-A). The present study sought to confirm those findings as well as estimate the permanence of treatment effect after 12 weeks.
Methods: We sequentially enrolled 58 people with MS-related tremor who were randomly and double-blindly allocated to receive either placebo or BT-A. An experienced neurologist, guided by electroneuromyography, injected the most affected upper limb according to the participant. We recorded demographics, disease and tremor characteristics (duration, type and severity), medication, as well as clinical scores, blinded (Bain) tremor ratings, and

electromagnetic tracking of upper limbs during a standard battery of tremor-eliciting tasks.

Results: Thirty participants received placebo (21 females, mean age 47.9 years, mean disease duration 17.6 years, mean EDSS 4.7) and 24 received BT-A (19 females, mean age 47.9 years, mean disease duration 14.4 years, mean EDSS 4.5). Tremor severity at baseline varied widely between individuals in both groups, with a mean Bain score of 3.2 for the placebo group (SD=3) and 3.1 for the BT-A group (SD=2.3) while the predominant type of tremor in both groups was coarse distal action tremor in 46.7% and 54.2% of participants, respectively. Mean total injection dose was 70.2 (SD=28.4). Six and twelve weeks after injections, Bain scores improved on average by 0.3 and 0.4 for the placebo group (SD=1.21 and 1.4); and by 0.46 and 0.29 for the BT-A group (SD=1.35 and 1.2). Bain change differences between placebo and BT-A groups were negligible at six (p=0.66) and twelve weeks (p=0.76). Changes were also non-significant for self-reported weakness, clinician-tested strength, and electromagnetic metrics. Treatment responders were not associated to a particular tremor type.

Conclusion: Tremor was alleviated for some people with MS-related tremor in both placebo and BT-A groups. This similarity between treatment groups contradicts with previous results and thus require further confirmation.

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Therapy - RWE and MS registries

P761

Eculizumab use in neuromyelitis optica spectrum disorders: real-world evidence from Germany and Austria

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Introduction: Neuromyelitis optica spectrum disorders (NMOSD) are characterized by relapsing attacks to the optic nerves and spinal cord. Attack prevention is key to avoid disability accumulation. Eculizumab (ECU), a monoclonal antibody inhibiting the terminal complement cascade, was highly effective in attack-prevention in a Phase III trial and is approved for the treatment of relapsing aquaporin-4 (AQP4)-IgG seropositive (+) NMOSD.

Objectives: To evaluate the effectiveness and safety of ECU in a real-world NMOSD patient cohort.

Methods: Annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS), MRI activity, adverse events and tolerability of meningococcal vaccinations were retrospectively evaluated in 55 ECU treated patients with AQP4-IgG+ NMOSD (n=52), MOG-IgG-associated disease (MOGAD, n=2), and double-seronegative NMOSD (n=1) in Germany and Austria between August 2019 (ECU approval in Germany) and April 2022.

Results: Patients (median age at ECU start 55.2 years; IQR 46.8-67.7) received ECU for 14.6 months (median; IQR 7.4-21.2). For AQP4-IgG+ patients, the median ARR decreased from 1.0 (range 0-3.0) in the 2 years before ECU start to 0 (median, range 0-1.7; $p<0.001$) under ECU. During ECU, 86% of all patients were relapse-free (87% for AQP4-IgG+). Similar EDSS scores (median 6.0; p=0.058) before and during ECU treatment indicated clinical stabilization. Under ECU, inflammatory MRI activity decreased in AQP4-IgG+ NMOSD in brain ($p<0.05$) and spinal cord ($p<0.01$). Adverse events included urinary tract infections, sepsis (meningococcal sepsis in 1 patient), infusion-related reactions, edema, diarrhea, ileus, and intracerebral hemorrhage (ICH). 5 patients (median age 53.7 years; IQR 50.2-67.7) died during ECU treatment, 3 presumably related to the treatment (sepsis) and 2 rather unrelated to ECU (myocardial infarction; ileus). 5/55 (9%) patients experienced relapses shortly after meningococcal vaccination (median 10 days; 8.0-11.0). 12/55 (22%) patients discontinued ECU due to diarrhea, ileus, infections, ICH, and meningococcal sepsis. Add-onimmunosuppressants in 13/55 (24%) patients showed no advantage in ARR compared to ECUmonotherapy.

Conclusions: This real-world study confirms that ECU is highly effective in relapse-prevention in AQP4-IgG+ NMOSD patients. Adverse events and an increased relapse risk after vaccination must be considered and can lead to treatment discontinuation. Final results of the study will be presented at ECTRIMS.

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Real-world use of cladribine tablets (Completion rates and treatment persistence) In patients with multiple sclerosis in England: the CLARENCE Study

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Introduction: Cladribine tablets (CladT; 3.5 mg/kg cumulative dose over 2 years) have been available in England for the treatment of highly active relapsing multiple sclerosis (MS) since

2017. As a compulsory requirement of National Health Service (NHS) reimbursement, all disease-modifying therapies (DMTs) prescribed for MS within NHS England must be registered via the Blueteq® high-cost drug database.
Objectives: To evaluate real-world use of CladT in England using data collected by the Blueteq® platform, as part of the CLARENCE study.
Aims: To describe baseline characteristics, treatment completion rates (full course of CladT received) and treatment persistence (no need for switching/discontinuation) in patients treated with CladT in the real-world setting.
Methods: NHS England collect data on CladT use via the Blueteq® platform, and provided the associated anonymised patient-level data to the study sponsor on a quarterly basis. Longitudinal data were collated for patients prescribed CladT between November 2017 and September 2021. Treatment history and Expanded Disability Status Scale (EDSS) scores were recorded at CladT initiation. Change in EDSS score, treatment completion, and persistence were evaluated over the length of the study. Data were analysed descriptively.
Results: In total, 1934 patients prescribed CladT had a completed Blueteq form®; at treatment initiation, median (minimum; maximum) EDSS score was 2.5 (0; 8.5) and 691 (36%) patients were treatment naïve. Over the 2-year treatment course, 505 (83%) patients had a stable EDSS score (defined as no change or decrease). At the point of data cut-off, 1020 (53%) patients had completed the full course of CladT, 742 (38%) had received the first course with <18months of follow-up, and 172 (9%) discontinued treatment before completing the second course of CladT. Overall, 78 (4%) patients switched to another DMT; of these, 45 (58%) received one treatment course of CladT and 33 (42%) received two courses.
Conclusions: Patients treated with CladT in England showed high rates of treatment completion and persistence (low switching rate of 4%), with stable EDSS scores across the planned 2 years of treatment. These findings highlight the real-world effectiveness of CladT in patients with highly active relapsing MS.

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Differences between clinical trials and "real-world" use of disease modifying therapies: insights from the UK OPTIMISE:MS pharmacovigilance study

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Introduction: Clinical trials of disease modifying therapies (DMT) in MS are used to inform risk:benefit discussions, yet trial populations do not fully reflect the range of people with MS treated in clinical practice. Most clinical trials have age restrictions and exclude people considering pregnancy or with significant comorbidities alongside inequity in access to research at a population level.
Aims: The OPTIMISE:MS pharmacovigilance study collects real-world data in the UK. Participating sites are encouraged to approach all eligible people with MS for enrolment. We sought to understand similarities and differences between the OPTIMISE:MS cohort and populations enrolled in pivotal clinical trials.
Methods: All participants enrolled in OPTIMISE:MS with complete baseline data on 1st April 2022 were considered (n=2507). All second generation DMT with >=100 patient months of follow-up (n=765) were compared against trial populations . Data regarding participants were compared to publicly available data from pivotal trial cohorts.
Results: Overall 1831 (73%) participants in OPTIMISE:MS are female with age range 18-82 (median 43.6, mean 43.8, SD 10.96). The majority are of White race (1951, 78%). 2346 (94%) have RRMS with a mean time since diagnosis 8.5 years (SD 7.62).
Across most DMT, there are a higher proportion of females in the OPTIMISE:MS cohort than trial populations (OPTIMISE:MS 63-83% F; trials 64-72%). The OPTIMISE:MS population is older (OPTIMISE:MS mean age 37.4-43.4; trials 31.9-40.6 years) and more racially diverse across all DMT (OPTIMISE:MS 70-84% White; trials 78-97%). Second generation DMT were more likely to be used as second line treatment in OPTIMISE:MS than clinical trials, with a wide range of disease duration prior to

treatment in all cohorts (OPTIMISE:MS mean range 5.2-10.7 years; trials 2.1-10.4). People receiving DMT in OPTIMISE:MS tended to have higher EDSS than those enrolled in clinical trials (OPTIMISE:MS mean EDSS 2.6-3.6; trials 1.9-2.9). Overall the OPTIMISE:MS cohort had fewer relapses in the year prior to DMT initiation than trial populations.

Discussion: Real world data incorporates a more diverse cohort than clinical trials. This highlights the care that must be taken when applying findings directly patient cohorts, particularly around treatment-associated risks. Prospective real world studies such as OPTIMISE:MS have the potential to aid understanding of risks and benefits across the spectrum of DMT use.

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Evaluating the effect of disease duration in high efficacy versus mid efficacy disease modifying therapies: could this help in deciding when to de-escalate?

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Introduction: Our previous studies demonstrated higher effectiveness with infusible disease modifying therapies (DMTs) (rituximab, natalizumab) over oral DMTs (fingolimod, dimethyl fumarate) in multiple sclerosis (MS) patients. However, many patients do well on oral DMTs, especially as they get older. The effect of disease duration is less understood and may help in identifying patients who may benefit in de-escalating their treatment in clinical practice, which still remains a challenge.

Objective: Identify baseline characteristics associated with future disease activity in MS patients comparing oral and infusible disease modifying therapies(DMTs) to inform treatment decisions.

Methods: Relapsing-remitting MS (RRMS) patients prescribed fingolimod, dimethyl fumarate, natalizumab or rituximab at the Rocky Mountain MS Center at the University of Colorado were followed for 24 months or until drug discontinuation. Patients receiving oral (fingolimod, dimethyl fumarate) and infusible (natalizumab, rituximab) DMTs were evaluated for disease activity, defined as experiencing a clinical relapse, new T2 lesion and/ or gadolinium enhancing lesion (GdE). Logistic regression was used to compare disease duration and DMT groups.

Results: Of the 1004 RRMS patients analyzed, 509 received oral DMTs and 495 received infusible DMTs. Among those receiving oral DMTs, 36.4% experienced disease activity versus 21.2% in among those receiving infusible DMTs. Disease duration was similar between patients on infusible (10.67 years) and oral (10.15 years) DMTs (p=0.215). In the oral DMT group, those with a disease duration $\leqslant$12 years had greater odds of experiencing disease activity overall (OR=2.19, $p<0.001$) and new T2 lesions (OR=1.91, $p<0.011$) compared to those $>$12 years. There was no significant difference between disease duration groups for GdE lesions or clinical relapses. In the infusible DMT group, there was no significant difference when comparing those with a disease duration $\leqslant$12 years to those $>$12 years for disease activity overall, new T2 lesions, GdE lesions or clinical relapses. The odds of experiencing disease activity with oral versus infusible DMTs is greater in patients with a disease duration $\leqslant$12 years (OR=2.69, $p<0.001$) than patients with a disease duration of $>$12 years (1.12, p=0.689).

Conclusions: In addition to age, future disease activity is associated with disease duration.Higher efficacy therapies appear to have a disproportionately larger effect among those with a disease duration $\leqslant$12 years. Additional predictive modeling will be presented.

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Real world evidence for cladribine and fingolimod: comparative effectiveness study after 2 years of follow-up

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Introduction: fingolimod (FTY) and cladribine (CLD) are oral disease-modifying treatments (DMT) for multiple sclerosis (MS) with similar labels that are used in comparable populations.
Objective: to compare the effectiveness of FTY and CLD after first two years of treatment in a real-world setting.
Methods: this is a multicenter and retrospective study that include all relapsing MS patients who initiated treatment with CLD or FTY before 1st of April 2020. We analyze naïve patients or switchers from other moderate efficacy treatments. Patients are followed every 6 months, and presence of relapses and EDSS score is collected. MRI scans at baseline and after 2 years treatment is recorded. Baseline characteristics and frequency of treatment discontinuation are described. The primary endpoint compares the annualized relapse rate (ARR) at 2 years. Other secondary clinical and radiological outcomes are analyzed.
Results: A total of 168 patients are included [Age, mean: 29 years; % women: 74,4%; EDSS, median: 2 (range: 0-4)] of which 146 patients initiated FTY (86,9%) and 22 CLD (13,1%). There are no significant differences at baseline characteristics between both treatment groups including age, MS disease duration, EDSS, AAR in the prior 2 years of treatment initiation, % baseline MRI with gadolinium-enhancing lesions and % of naïve or switcher from one DMT). After 2 years of treatment no significant differences in the AAR between both groups are observed (FTY: 0,14; CLD: 0,09; p= 0,531). FTY patients showed a non-significant shorter time to first relapse (p=0,335). Confirmed EDSS disability progression at 6 months is observed in 15,2% of overall patients without significant differences between groups (p=0,74). Follow-up 2 years MRI showed new T2 lesions in 36.7% patients in the overall group without differences (p=0,818). Treatment discontinuation during the first 2 years did not differ between groups (FTY: 15, 97%; CLD: 15;79% p=1).
Conclusion: This population-based real-world study reports similarities in treatment outcome effectiveness between FTY and CLD during the first 2 years of follow up.

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Early MRI activity predicts subsequent disease activity in multiple sclerosis patients treated with cladribine

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Introduction: Cladribine is one of the latest incorporations to our therapeutic arsenal for multiple sclerosis (MS). Real-world evidence regarding its effectiveness and safety is rapidly growing, but MRI data are still scarce.
Objectives: First, to describe the MRI evolution from baseline to yearly scans after Cladribine start. Second, to identify predictors of MRI activity during follow-up (FU) in a real-world setting.
Methods: We present a retrospective study including MS patients, who started Cladribine between Aug 2018 and May 2020, in two university hospitals in Castilla-La Mancha (Spain). We recorded clinical (age, sex, MS duration, prior disease-modifying treatments (DMT), prior disease activity, FU relapses, and FU disease progression) and radiological data (baseline T2 load, FU activity -new T2 lesions and/or gadolinium-enhancing lesions- in year 1 (Y1), year 2 (Y2) and year 3 (Y3). For univariate statistical analysis, we applied Chi-squared test, Fisher exact test, independent samples T-test, and Mann-Whitney U test as appropriate. Binomial logistic regression was used for the multivariate analysis.
Results: 36 MS patients were identified, 25 of whom had MRI results available. Mean age was 40.5±10.2 years, median baseline EDSS was 2, and median MS duration was eight years. Prior high-efficacy DMT (HE-DMT) was noted in 27.8%, and 11.1% were naïve. 82.9% had an active baseline MRI, which drops to 52% after Cladribine initiation (Y1 42.4%-n=25-, Y2 28.6%-n=21-, Y344.4%-n=9-). Early MRI activity (Y1) was significantly associated with late (Y2 or Y3) MRI activity (OR 14, 95%CI 1.86-105, p 0.01), and treatment discontinuation due to relapses (3/4 after the full dose was completed, p 0.024). Late MRI activity was higher in younger patients (p 0.006). Logistic regression model (including age, sex, baseline EDSS, HE-DMT, and early MRI activity) revealed that an early active MRI is an independent predictor of late radiological activity.
Conclusions: Even though the full dose of Cladribine consists of two-yearly courses, our findings suggest that patients with an active MRI after one year of treatment are at risk of subsequent MRI and clinical activity, and we should closely monitor them.

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P767
Assessing the impacts of persistency for disease modifying therapies in a German registry for multiple sclerosis

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Background: Multiple sclerosis (MS) is an uncurable progressive disease, with numerous disease modifying therapies (DMTs) available. Treatment persistency is an important factor for disease management.
Aim: To identify, characterize, and compare outcomes of patients with high persistency (HP) and low persistency (LP).
Methods: Study data came from MS disease registry of the doctors-run German NeuroTransData(NTD) network of neurologists and psychiatrists capturing demographic, clinical history, and clinical variables during outpatient visits. Inclusion criteria were patients with RRMS, treatment naïve or 1 switch, and with one future visit after therapy start. Only patients with an index date (i.e., therapy start) after 1 January 2009 were retained.From patient distribution, HP was defined as continuous exposure time of at least two years, while LP was less than two years. Propensity Score Matching was performed on age, sex, relapses, baseline EDSS, and time since MS manifestation for 1 year pre-index. Cox regression was used to compare time to first relapse and time to 12-week confirmed disability progression (CDP).
Results: In total, 2,367 patients were matched for HP and LP cohorts. The mean [standard deviation (SD), interquartile range (IQR)] for age was 38.3 (10.7; 29.9-46.4) years, 0.7 relapses in the past year (0.8; 0-1), mean baseline EDSS was 2.0 (1.5;1-3), and symptoms manifestation time was 6.6 years (sd:7.2; 0.96-10.3); 76.2% were females. Mean (SD; IQR) DMT exposure time in years was 0.78 years (0.57;0.29-1.2) for the LP cohort and 4.7 (2.2;2.9-6.2) for the HP cohort.The use of DMTs was: 49.1% on injectables, 40.5% on orals, 2.2% on infusions (excluding monoclonal antibodies) and 8.2% on monoclonal antibodies. Using Cox Regression, the hazard ratio (95% CI) on time to relapse for LP versus HP cohort was 1.4 (1.3-1.5) (Wald p value: < 0.001). For time to first CDP, it was 1.2 (1.0-1.3) (Wald p value: 0.011).
Conclusion: HP had better outcomes on time to first relapse than matched LP cohort. The minor difference in CDP risk between two cohorts may be due to 2 years limited follow-up. These findings support the importance of identifying appropriate DMTs for individual patients with due consideration to their underlying disease characteristics in maintaining treatment persistency and improved outcomes.

Disclosure
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Horizontal versus vertical switch of treatment in patients with relapsing-remitting multiple sclerosis in Austria

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Introduction: Studies matching the clinical efficacy between horizontal and vertical switch after a platform therapy (interferon beta (IFN-beta) or glatiramer-acetate (GLAT))provided conflicting results.These discrepancies ask for further investigations to confirm or rebut the published findings, especially by real-life experiences.
Objectives: To compare the efficacies, frequencies and reasons for treatment interruption ofdimethylfumarate (DMF) andteriflunomide (TERI) (horizontal switcher) versus alemtuzumab (AZM), cladribine (CLAD), fingolimod (FTY), natalizumab (NTZ), ocrelizumab (OCR) and ozanimod (OZA) (vertical switcher)in a nationwide observational cohort.
Methods: Twocohorts of patients with relapsing-remitting multiple sclerosis (RRMS) having switched either to DMF and TERI or AZM, CLAD, FTY, NTZ, OCR and OZA after a treatment with IFN-beta and/or GLAT documented in the Austrian MS Treatment Registry (AMSTR) since 2014 and staying on therapy for at least three months. The horizontal switch cohort included 669 and the vertical switch cohort 800 RRMS patients. We used multinomial propensity scores for inverse probability weighting in generalized linear (GLM) and Cox proportional hazards models to correct for the bias of this non-randomised registry study.
Results: Estimated mean annualized relapse rates (ARR) were 0.23 for horizontal switcher and 0.18 for vertical switcher. The incidence rate ratio (IRR) in the GLM model for relapses showed an increased relapse probability of 86% for the horizontal versus the vertical switcher (IRR = 1.859 95% CI (1.383 to 2.502), $p > 0.001$). Analysing the time to the first relapse by Cox regression a hazard ratio of 1.584 (95% CI (1.238 to 2.025, $p > 0.001$) indicated an increased risk of 58% for the horizontal switching cohort.
Regarding sustained Expanded Disability Status Scale (EDSS) progression for 12 and 24 weeks no significant differences were found, although a trend towards higher probability for sustained EDSS regression for 12 and 24 weeks were reported within the vertical switchers ($p = 0.089$).
Conclusions: A horizontal switch after a platform therapy revealed a higher relapse probability and a trend towards less EDDS improvements comparing to a vertical switch in Austrian RRMS patients. Therefore, switching to a higher efficacy treatment should be preferred in the case of treatment failure.

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Predictors of treatment switching in the big multiple sclerosis data network – an update

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Objective: The objective of this study was to identify independent predictors of treatment switching in the Big MS Data Network
Aims: The aim of this study was to characterize drivers of treatment sequences in Big MS.

Methods: We merged information on 269,822 treatment episodes in 110,326 patients from 1996 to 2016 from five clinical registries in this cohort study. Associations between baseline clinical and demographic factors and the switching end-point were analysed using a shared frailty survival model

Results: Every 1 point increase in EDSS at treatment start was associated with 1.08 times the rate of switching adjusting for age, sex and calendar year (adjusted Hazard Ratio (HR) 1.08: 95% CI 1.07-1.08). Female sex was associated with 1.11 times the rate of switching relative to males (95% CI 1.08-1.14) whilst older age was also associated with an increased rate of switching. DMT's started between 2007-2012 were associated with 2.48 times the odds of switching relative to DMTs started between 1996-2006 (HR 2.48; 95% CI 2.48-2.56) controlling for age, sex and EDSS. DMTs started from 2013 onwards were even more likely to switch relative to the earlier treatment epoch (HR 8.09; 95% CI 7.79-8.41; reference=1996-2006). Across the full 1996-2016 observation period, higher EDSS at treatment start (HR 1.09; 95% CI 1.08-1.11), female sex (HR 1.17: 95% CI 1.11-1.24), older age (HR 1.01; 95% CI 1.00-1.01) and year (HR 1.15: 95% CI 1.14, 1.15) were all associated with increased rates of switching from IFNβ. Associations were similar when the analysis was confined to 2007-2012. Higher EDSS (HR 1.10; 95% CI 1.09-1.11), female sex (HR 1.11; 95% CI 1.07-1.16), older age (HR 1.01: 95% CI 1.00-1.01) and later calendar years (HR 1.24; 95% CI 1.22-1.25) were all associated with a significantly increased rate of treatment switching. When the modelling was limited to the most recent treatment epoch (2013 onwards), EDSS was associated with a significant, albeit smaller, increase in switching rate (relative to the 1996-2006 and 2007-2012 epochs) with every 1 point increase in EDSS being associated with 1.02 times the rate of switching (HR 1.02: 95% CI 1.01-1.03). Older age, female sex and later calendar years were all associated with increased rates of switching within the 2013+ epoch.

Conclusions: Treatment switching has become an increasingly common phenomenon since DMTs were first used in 1996. EDSS, female gender and older age were the key drivers of treatment switching.

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Trajectories of disease-modifying therapies and associated sickness absence and disability pension among people with multiple sclerosis

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Background: Multiple sclerosis (MS) is the most common disabling neurological disease of working-aged people. In the last decades, disease-modifying therapies (DMTs) have ameliorated this impact. However, how DMTs are used over time and their associations with sickness absence (SA) and disability pension (DP) are not well studied. We aimed to identify trajectories of DMT use among people with MS (PwMS) in Sweden and their associations with SA/DP.

Methods: A longitudinal register-based cohort study was conducted assessing DMT use among PwMS for 10 years following MS onset. Among those with an MS onset in 2007-2010, 1923 fulfilled the inclusion criteria. Treatment options were categorized as: before treatment, high-efficacy, non-high-efficacy, and no DMTs for each 6-month period until the end of follow-up. Sequence analysis was performed to identify sequences of treatment and cluster them into different DMT trajectories. Multinomial

logistic regression analysis was used to predict cluster membership by demographic and clinical characteristics. The association of SA/DP net days with the trajectories was assessed using generalized estimating equations.
Results: Four trajectories of treatment use were identified: *long-term non-high-efficacy DMTs* (38.6%), *escalation to high-efficacy DMTs* (31.2%), *discontinued/no DMTs* (15.3%), and *delayed start and escalation to high-efficacy DMTs* (14.9%). Age, MS type, expanded disability status scale score, and the number of DMT switches were associated with cluster membership. In the final years of follow-up, PwMS using non-high-efficacy DMTs showed lower mean SA/DP net days, whereas the *escalation to high-efficacy* and *discontinued/no DMT* clusters showed higher mean SA/DP net days. PwMS in the*delayed start and escalation to high-efficacy DMTs* cluster showed increasing mean SA/DP net days over time.
Conclusions: This study adds a description of the long-term trajectories of DMTs among PwMS in Sweden and their association with SA/DP net days, sociodemographic and clinical characteristics.

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Ocrelizumab in patients with early-stage RRMS – results from the phase IIIb ENSEMBLE trial and the matched real-world NTD MS registry cohort

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Background: Early treatment of multiple sclerosis (MS) with high efficacy disease-modifying therapies (DMTs) can provide long-term benefits on disease outcomes. Our understanding of ocrelizumab (OCR) effectiveness in early-stage MS is still limited.
Aims: To assess treatment effectiveness of OCR in patients with early-stage relapsing-remitting MS (RRMS) from ENSEMBLE (NCT03085810) compared with commonly used first-line DMTs in a real-world setting, using the German NeuroTransData (NTD) MS registry as an external control arm.
Methods: Treatment-naive patients with early-stage RRMS (age 18–55 years; disease duration ⩽3 years; Expanded Disability Status Scale [EDSS] ⩽3.5; with ⩾1 signs of MRI activity or ⩾1 relapses in the prior 12 months) from the multicentre, open-label, single-arm Phase IIIb ENSEMBLE study, received OCR 600 mg every 24 weeks for 192 weeks. The matched NTD cohort was selected using ENSEMBLE inclusion criteria, with interferon β-1a/1b, glatiramer acetate, dimethyl fumarate and teriflunomide as comparators. NTD patients were matched to ENSEMBLE using 1:1 propensity score matching adjusted for age, EDSS score, prior relapses, baseline (BL) T1-weighted contrast-enhancing lesions (T1w-CELs) and time since first MS symptom. NTD patients had sufficient on-therapy data to assess no evidence of disease activity (NEDA)-2 (no relapses and no 24-week confirmed disability progression [CDP]) up to Week 48 and Week 72. Sensitivity analyses with varying matching factors were performed.
Results: BL characteristics for ENSEMBLE (N=1,050 with sufficient data [BL MRI, Week 48 MRI, Week 72 EDSS]) and NTD (N=601) were similar (ENSEMBLE/NTD: Median age, 32.0/33.9; female, 63.4/66.7%; median duration since first MS symptom, 0.75/0.43 years; median duration since RRMS diagnosis, 0.22/0.16 years; BL EDSS score, 1.79/1.06). The odds ratio (95% CI) for ENSEMBLE vs NTD (462 vs 278 patients) for NEDA-2 was 1.68 (1.04–2.72; p=0.047) at Week 48, and 1.99 (1.29–3.07; p<0.001) at Week 72. Week 72 NEDA-2 did not change substantially when duration since first MS symptom or (T1w-CELs) were excluded from matching. NEDA-3 results (including no MRI activity) up to 48 weeks will also be presented.
Conclusions: Treatment with ocrelizumab in patients with early RRMS was associated with significantly lower risk of relapses or CDP compared with first-line treatment with other DMTs in the

real-world. Sensitivity analyses of NEDA-2 and NEDA-3 and its components support robustness of results.

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Treatment emergent adverse events experienced early and transiently in the treatment course with cladribine tablets: data from the CLEVER real-world study

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Background: Cladribine tablets are a short-term treatment approach for patients with highly active relapsing multiple sclerosis (RMS) administered in 2 treatment courses in 2 consecutive years (with a maximum of 20 days of oral treatment).

Little is known about the occurrence of treatment-emergent adverse events (TEAEs) over time reported in patients treated with the oral pulsed therapy regime of cladribine tablets and the associated short periods of drug exposure.

Objective: To investigate the dynamics of safety reporting in a real-world setting and identify TEAE patterns that occur early in the course of treatment.

Method: The analysis of the adverse event (AE) occurrence pattern over the observation time of 6 months revealed an accumulation of AE reports early after treatment initiation. To further stratify the background of AEs, the number of TEAEs was assessed and subgroups based on the last previous MS medication were formed: naïve, platform (Interferon beta, Dimethylfumarate, Teriflunomide) and high efficacy (Alemtuzumab, Fingolimod, Natalizumab).

Results: In the CLEVER study 185 (37,7%) patients reported 310 AEs in total. For most of the patients (62,1%) AEs were reported within 45 days after first cladribine tablet intake.

To better understand the relevance of this early time period after treatment initiation, the AE analysis was extended to include TEAE and last previous therapy of the affected patients.

74 (52,5%) of 141 patients reported 97 AEs out of which 32 (22,6%) patients had 38 TEAEs. No treatment related serious adverse events (SAE) have been reported. The most frequent TEAEs were headache (9 patients), skin and subcutaneous tissue disorders (5), gastrointestinal disorders (5), fatigue (4), lymphopenia (3).

The analysis by last previous MS medication within the 45 days' time interval suggested that lymphopenia occurred more frequently in the high efficacy treatment group, gastrointestinal symptoms in treatment naïve patients, nervous system related symptoms (e.g. headache, dizziness) in platform therapy treated patients.

Conclusion: Cladribine tablets were well tolerated during the first 45 days of treatment as suggested by a relatively low incidence of TEAEs. Following this 45-day time period the rest of the AEs were distributed over the remaining observation time with proportionally less AEs and affected patients. This is in line with the post hoc analysis of CLARITY and ORACLE-MS safety.

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Experience with cladribine in multiple sclerosis patients in the third and forth year of treatment

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Introduction: Oral cladribine is used for the treatment of Multiple Sclerosis (MS). An important issue is what happens in the years 3 and 4 after the treatment.
Objective: Our objective is to evaluate the effectiveness and safety of Cladribine in our clinical practice and to evaluate the efficacy in long term.
Methods: Retrospective, longitudinal study. We analyze safety and effectiveness: relapses, Expanded Disability Status Scale (EDSS) and new MRI lesions during treatment with cladribine during 4 years.
Results: We present 75 patients: 25 with less than 1 year of treatment,50 patients with the 2cycles of treatment, and 32 patients with more than 3 years of treatment. The average age was 43,4 (SD10,1) the duration of MS was 9,5 (SD 7,4) years. The 66% of the patients had previous relapses. The EDSS was 2,5. The majority of patients came from platform treatments.30%were naive patients.92%of patients were naive o first switch patients. We observe a reduction of rate relapses of 75% after starting cladribine. The rate relapses decreased along the years. We study the rate relapses according the previous DMT. The reduction in rate relapses was higher in naive patients (90%). The reduction in patients with previous DMT was lower. The EDSS remained stable in naive and first switch patients, however in patients with previous high efficacy treatment we observe an increase of EDSS. At the baseline40%of patients presented activity on MRI. After the first dose the reduction was around a 50%. In the years 2 and 3 the patients presented a small number or none enhanced lesions. We observe a higher reduction of gadolinium lesions in naive patiens.75% of patients didn't need additional treatments in years 3 and 4. 2 patients needed an additional cycle of Mavenclad in the third year of treatment due to mild activity of the disease.3 patients switch to another DMT,2 of them after the first cycle and the other one after the second cycle of treatment.3 patients presented progression. We observed as small number of adverse events, the majority of them were mild.
Conclusions: Cladribine has shown clinical benefit and good tolerability through the follow-up with an important reduction in rate relapses and MRI activity. The EDSS remained stable in the majority of patients The early treatment seems to show more benefit in the evolution of the patients if we compare with delayed treatment. A small number of patients who need new treatment after cladribine. Few patients discontinued the treatment due to adverse events

Disclosure
Nothing to disclosure

P774

Maven4: Phase IV non interventional, prospective, Spanish multicenter study to evaluate Cladribine tablets long term effectiveness on real-world clinical practice

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Introduction and objectives: From the pivotal studies of cladribine tablets is expected that clinical efficacy of two annual courses over two years can last for at least 4 years.We aimed to assess the proportion of patients that after two full annual cycles did not require additional therapy for the, at least, next 2 years in real-world clinical practice.
Material and Methods: This is a prospective, multicenter, non-interventional study in Spain, in which patients that had initiated at least the first course of cladribine tablet were invited to participate, within the first year of treatmment. Collected data included baseline clinic-demographic features, history of previous disease-modifying therapies (DMTs), disability measured by the Expanded Disability Status Scale (EDSS), and Magnetic Resonance Image (MRI) data. Patients were prospectively followed-up on a regular basis and efficacy and safety outcomes were recorded almost every 6 months according to the normal clinical practice of the sites.
Results: Between June 2019 and February 2022, a total of 450 patients from 39 Spanish sites were recruited. This first interim analysis includes data from 443 patients, 76.5% female, mean (standard deviation) age 39.1 (9.95) years. Sample baseline characteristics: annual relapse rate 1.2 (0.9), EDSS score of 1.9 (1.41); 20% were naïve patients, and 80% switches from other DMTs (26.5% injectables, 51% oral platform, 22.6 % high efficacy),143 patients (32,3%) came from a first switch. Of the 273 (62%) patients that completed the first year of follow up, 238 (87%) were relapse free, the EDSS score had remained stable [2.1 (1.58)]. No evidence of Disease activity (NEDA) was observed in 183 out of 240 patients (73%), evaluable by clinical and MRI criteria after 1 year of treatment. After a mean follow-up of 18 (9.34) months, only 5 (1.1%) required additional therapy. The most frequent adverse event was lymphopenia reported on 28 patients (6.3%); no grade IV recorded until now, and no new safety findings were reported.
Conclusion: These real-world data support the clinical trial findings on the short-term efficacy and safety outcomes of cladribine tablets.

Disclosure
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2. Y. Aladro reports compensation for consulting services and speaker honoraria Merck, TEVA, Biogen, Novartis, Roche, Sanofi, BMS.
3. L.Costa-Frossard reports compensation for consulting services and speaker honoraria from Biogen, Bristol-Myers Squibb,Janssen,Merck Serono,Novartis,Sanofi, Roche y Teva.
4. Sánchez Magro is a MERCK KGaA employee
5. Rodriguez-Antigüedad reports compensation for consulting services and speaker honoraria Merck, Biogen, Novartis, Roche, Sanofi, Janssen y BMS

Therapy - Symptoms Management (including cognition, fatigue, imbalance)

P775
Patient education for fatigue in people with multiple sclerosis: cochrane systematic review and meta-analysis

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Introduction: Fatigue is one of the most common and disabling symptoms in patients with Multiple Sclerosis (MS). In the absence of convincing pharmacological treatment options, non-pharmacological approaches have shown potential to reduce fatigue, including educational interventions informing patients about fatigue and applying strategies to better manage and cope with fatigue.
Aim: To systematically review the current best evidence on patient education programmes for MS-related fatigue.
Methods: Systematic review and meta-analysis following the Cochrane Handbook of Systematic Reviews. We included all randomized controlled trials evaluating patient education programmes for people with MS with the primary aim of reducing fatigue. On March 16, 2022, we conducted a systematic search in eight databases. We also searched reference lists and trial registers, and contacted experts in the field.
Results: 1079 studies were identified and assessed by two independent raters and 15 studies with a total of 1623 participants were included. 11 studies were included in the meta-analyses. All interventions provided information and education about different aspects about MS-related fatigue, applying different psychological interventions. Most frequently cognitive behavioural therapy (CBT) (n=5) and energy conservation (n=4) approaches were applied. Delivery of interventions differed e.g. with group vs. individual and direct vs. remote application. Studies differed markedly, e.g. for number of participants (n=23 to 275) and length of follow-up (10 to 52 weeks). Interventions effectively reduced fatigue severity (SMD -0.28; 95%CI -0.53 to -0.03; low certainty) and fatigue impact (SMD -0.21; 95%CI -0.42 to -0.00; moderate certainty) directly after the intervention. Mixed results were found for long-term effects on fatigue, for secondary endpoints (depression, quality of life, coping), and for sub group analyses.
Conclusion: Educational interventions for patients with MS-related fatigue are effective in reducing fatigue in the short term. More research is needed on the importance of specific intervention components and aspects of delivery and context.

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Declarations of interest:
Andrea Giordano: nothing to disclose.
Maria Janina Wendebourg: nothing to disclose.
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Sascha Köpke: nothing to disclose.

P776
Employment and cognitive improvements in ocrelizumab-treated patients with relapsing-remitting multiple sclerosis: 96-week CASTING study data

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Background: Multiple sclerosis (MS) affects mainly adults of working age, impacting employment and quality of life (QoL). Employment enhances QoL and is a gauge of overall functioning in people with MS (PwMS), hence ensuring work participation is beneficial to both PwMS and society. Cognitive impairment is a key symptom in PwMS and is associated with unemployment and lower QoL.
Aims: To report employment status by baseline demographic, disease history and cognitive function, and changes in status over 96 weeks in patients with relapsing-remitting MS in the Phase IIIb CASTING trial (NCT02861014).
Methods: Patients (Expanded Disability Status Scale score [EDSS] $\leq$4.0) with suboptimal response to 1 or 2 prior disease-modifying

therapies received intravenous ocrelizumab 600 mg every 24 weeks for 96 weeks. Work Productivity and Activity Impairment (WPAI) questionnaire was used to determine employment status at baseline (BL), Weeks 24, 48 and 96. Symbol Digit Modalities Test (SDMT) was measured at BL, Weeks 48 and 96. Scores were also translated to z-scores with a cut-off of −1 to define cognitive impairment; BL z-score ⩽ −1 defined the cognitively impaired subgroup and BL z-score > −1 in the minimally impaired subgroup.

Results: At BL, 427 patients were employed (EMP) vs 230 unemployed (UNEMP): unemployment was slightly higher in patients who were younger (UMEMP 78.7% ⩽40 vs EMP 72.6% ⩽40), and female (UNEMP 67.8% vs EMP 61.4%), and associated with higher BL EDSS (UNEMP 2.38 vs EMP 1.95), and greater cognitive impairment (mean SDMT score: UNEMP 48.7 vs EMP 56.6), whereas disease duration since MS onset was similar (UNEMP 4.9 vs EMP 5.0 years). At Week 96: 32.2% of BL UNEMP patients shifted to EMP status, while 12.9% of BL EMP patients shifted to UNEMP status; the probability of being EMP was 52% in the minimally cognitively impaired and 31% in the cognitively impaired subgroups. From BL to Week 96: EDSS increased in UNEMP (from 2.38 to 2.48) and decreased in EMP (from 1.95 to 1.91) patients; SDMT score improved by an average of 1.4 points both in UNEMP and EMP patients.

Conclusions: Over the two years of the CASTING study, patients treated with ocrelizumab showed a greater shift towards employment than towards unemployment. The increased SDMT score, evident in both ocrelizumab-treated employed and unemployed subgroups, may contribute to the factors causing and explaining employment status.

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P777

Memory rehabilitation for people with multiple sclerosis

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Introduction: Problems with cognition, particularly memory, are common in people with multiple sclerosis (MS) and can affect their ability to complete daily activities and can negatively affect quality of life. Over the last few years, there has been considerable growth in the number of randomised controlled trials (RCTs) of memory rehabilitation in MS. To guide clinicians and researchers, this review provides an overview of the effectiveness of memory rehabilitation for people with MS.

Aims: We conducted an update of a Cochrane systematic review to determine whether people with MS who received memory rehabilitation compared to those who received no treatment, or an active control showed better immediate (within one month), intermediate (1-6 months), or longer-term (6 months plus) outcomes in their: memory functions, other cognitive abilities, and functional abilities.

Methods: We systematically searched all available databases using relevant search terms to identify studies that assessed the effectiveness of cognitive rehabilitation in MS.

Results: 2903 records were retrieved, and data were extracted from 29 new studies, combined with the 15 studies included in the previous update. We found a significant effect at immediate follow-up for subjective memory, verbal memory, visual memory, working memory, information processing, quality of life and depression measures; at intermediate follow-up for subjective memory, verbal memory, information processing, and quality of life; at longer-term follow-up for subjective memory and quality of life. We found no significant effect for activities of daily living or anxiety measures.

Conclusions: A significant effect was seen in both subjective memory and quality of life measures at each follow-up point, suggesting that the improvements as a result of memory rehabilitation are evident, meaningful and sustainable.

Disclosure

RdN, JMM, KJP and NBL have conducted memory rehabilitation studies in MS that have been included in this review.

RdN and NE have been funded by NIHR for a programme grant on cognitive screening and rehabilitation.
NE has received lecture fees from Biogen and participated in paid advisory board for Biogen, Roche and Merck where cognition was discussed.
RdN is the Chair of the NIHR Research for Patient Benefit East Midlands Research Advisory Committee. He has received funding to prepare and deliver lectures (speakers bureau) on cognitive rehabilitation in multiple sclerosis from Novartis, Merck, and Biogen.
LT, DW, and LS have nothing to declare.

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Polypharmacy, anticholinergic medication burden, and objective cognitive performance in adults with multiple sclerosis (MS)

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Introduction: Polypharmacy, or the use of ⩾5 daily medications, is relatively common in adults with multiple sclerosis (MS), due in part to the range of physical, cognitive, and emotional manifestations of the disorder. However, there is a dearth of research regarding the association between polypharmacy and cognitive outcomes in MS. Furthermore, individuals with MS often use medications with anticholinergic properties, which are often associated with cognitive impairment and other central adverse effects. Currently, the utility of scales measuring anticholinergic burden in MS is unknown.
Objectives: We assessed the bivariate and multivariate relationships between polypharmacy and objective cognitive performance in a sample of adults with MS. We also examined whether commonly used anticholinergic burden scales can explain additional variance in cognitive performance above and beyond factors known to be relevant in this population.
Aims: Examine associations between polypharmacy and cognition in MS.
Methods: We recruited 90 individuals with MS during routine visits at an MS specialty clinic in the midwestern region of the United States. Participants completed questionnaires about their health and a brief virtual assessment of cognition, from which we computed a cognitive composite score. We also gathered participants' medication lists to assess for polypharmacy and calculate scores on several anticholinergic burden scales. The relationships between polypharmacy and cognitive outcomes were assessed with Spearman's correlation analysis and linear regression models.
Results: Approximately 44% of the study sample met criteria for polypharmacy. The nonparametric partial correlation between number of daily medications and cognitive performance was $r^s = -0.31$, $p < .01$, after accounting for age, education, MS disease duration, and comorbidities. In a stepwise linear regression model, the Drug Burden Index (DBI) accounted for additional variance in cognitive performance beyond that explained by age, education, disease duration, and comorbidities, $\Delta R^2 = .12$, $F(5, 84) = 7.84$, $p < .001$.
Conclusions: Polypharmacy may adversely affect cognitive function. Clinicians and researchers should consider polypharmacy when addressing cognitive concerns in people with MS. Anticholinergic burden scales such as the DBI may be valuable in this regard. Future investigations could explore behavioral and pharmacological interventions aimed at reducing polypharmacy in this population.

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Jade Robichaud: nothing to disclose
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Therapy - Neurobiology & Rehabilitation

P779

The insula modulates the effects of aerobic training on cardiovascular function and ambulation in multiple sclerosis

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Introduction: In multiple sclerosis (MS), impairment of the autonomic control of cardiovascular function is very common (7-60%). Insula of Reil represents a key grey matter region involved in the regulation of this function with some differences between the left and right hemisphere. Lesions and atrophy of the insula are a frequent finding in MS. Aerobic training (AT) directly targets the cardiopulmonary system and is proposed as a neuroprotective strategy in several neurological conditions.
Aim: To understand the effects of AT, focusing on the role of insula (differentiating in right and left) in establishing cardiovascular fitness (CF) and AT responses in MS patients.
Methods: 61 MS patients were enrolled and randomized in two groups (MS-A and MS-C) to perform 24 training sessions of

30-40 minutes for 2-3 times per week. MS-A performed moderate AT, while MS-C underwent non-specific motor training. All patients had a baseline and follow-up evaluation after the training period, including assessment of maximal peak of oxygen consumption (VO2max), heart rate reserve (HRR), 6-minute walk test (6MWT) and a MRI scan to quantify lesion volumes (LV), global and regional brain atrophy. Two age- and sex-matched healthy control (HC) groups were enrolled to have reference data for the analysis of CF and brain volumetry data.
Results: At baseline, MS patients showed impaired values of VO2max, HRR and 6MWT ($p<0.001$) and a widespread pattern of atrophy compared to HC, including bilateral insula. In MS, higher left insula LV correlated to higher HRR ($R=0.27$, $p<0.05$). After training, MS-A experienced an improvement in 6MWT compared to MS-C, independently from the presence of focal T2 lesions in the insula. At follow-up, MS-C showed a reduction of left anterior insula volume compared to baseline ($p<0.001$). In MS-A, increase of the left anterior insula volume correlated to 6MWT improvement ($R=0.65$, $p<0.001$).
Conclusions: AT improves CF and walking capacity in MS. It showed a neuroprotective effect, especially for the left insula that has a stronger relationship with CF, compared to the contralateral region.

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Therapy - Others

P780
Progressive multifocal encephalopathy in the first patient with relapsing-remitting multiple sclerosis treated with ocrelizumab

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Introduction: Progressive multifocal encephalopathy (PML) is a rare but often fatal complication of multiple sclerosis (MS) treatment, mainly related with natalizumab, but it has also been described with the use of other immunotherapies.
Objectives: To report a case of PML in a patient with relapsing-remitting multiple sclerosis (RRMS) treated with Ocrelizumab and without the previous use of natalizumab.
Methods: A 57-year-old woman diagnosed with RRMS treated with glatiramer acetate until February, 2017 (this treatment was withdrawn due to radiological activity in brain MRI). On March 27, 2017, she was enrolled in the CASTING clinical trial. Once the trial was completed, she continued treatment with Ocrelizumab, receiving a total of 10 doses. The last dose was delivered in August 2021.
In November 2021, she presented a subacute and progressive left hemiparesis. The MRI showed an extensive subcortical lesions highly suggestive of PML, with foci of gadolinium enhancement compatible with immune reconstitution inflammatory syndrome (IRIS). The JCV DNA study in the cerebrospinal fluid (CSF) analysis detected 882 copies/ml and the diagnosis of PML was confirmed.
Results: During the following days she presented a progressive worsening developing left visual extinction, severe left hemiparesis and anosognosia. Treatment with methylprednisolone 1 gram a day for 3 days was administered, achieving clinical stability for three weeks. Two doses of Pembrolizumab were given and a control brain MRI showed resolution of the foci of gadolinium enhancement.
A second lumbar puncture performed four weeks after the first dose of pembrolizumab showed an increase of the JCV DNA copies (up to $>$ 300.000 copies/ml) in CSF, twelve weeks after the diagnosis the patient presented a refractory status epilepticus which finally caused her death.
Conclusion: To our knowledge this is the first case of RRMS treated with Ocrelizumab, without previous use of natalizumab or other immunosuppressants drugs who developed a PML/IRIS.

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González-del-Río M: nothing to disclose.
Salavedra-Pont J: nothing to disclose.
Miguela A: nothing to disclose.
Gich J: has received speaking fees from Novartis, Teva, Sanofi and Merck.
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Boix-Lago Almudena: nothing to disclose.
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P781

COVID-19 humoral and T-cell mediated vaccination responses in people with multiple sclerosis

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Background: For people living with MS (pwMS) the impact of disease modifying treatments (DMT) on vaccine efficacy has been a growing concern.
Methods: We used remote sampling to assess humoral response using dried blood spot (DBS) and ELISA for anti-SARS-CoV-2 IgG and performed T-cell analysis on a selection of participants. Compliance rates were maintained at ~70% post each vaccination time-point and DBS quality rates improved across the time frame of the study.
Results: The cohort consisted of 184 participants who could be grouped by DMT into; anti-CD20 (40%), fingolimod (8%) and all other DMT/no DMT (52%).The primary vaccination course was Oxford/AstraZeneca for 61% and Pfizer-BioNTech for the remainder. Post-v2 76/110 (69%) of participants had seroconverted, increasing to 131/173 (76%) post v3.
Vaccine response was influenced by DMT. After v2 13/38 (34%) of participants on anti-CD20 and 1/9 (11%) on fingolimod seroconverted compared to 63/63 (100%) of those on other/no DMT. Lower vaccine responses were seen post-v2 in those on anti-CD20; 6.6 BAU/ml (IQR 63) and fingolimod; 9.9 BAU/ml (IQR 9) compared to all other/no DMT; 326.7 BAU/ml (IQR 535), $p<0.001$.
In v2 responders successive vaccinations further increased response. A median of 313 BAU/ml (IQR 440) was found post v2, increasing to 936 BAU/ml (IQR 1362) at v3 and 1559 BAU/ml (IQR 1374) at v4, $p<0.001$.
Amongst v2 non-responders third vaccinations increased seroconversion. 9/32 (28%) of v2 non-responders seroconverted after v3; 3/23 (13%) of these were on anti-CD20 and 5/9 (56%) were on fingolimod.
T-cell responses were found in the majority of individuals regardless of seroconversion status. All 14 anti-CD20 participants tested had a positive T-cell response at v3. Preliminary evidence suggests that T-cell response is sustained for at least 6 months post vaccination.
Conclusions: DMT influences both seroconversion and antibody titre in response to vaccination. Additional vaccination courses post-v2 result in increased titre, and even in those who failed to seroconvert after v2, increase chance of seroconversion. Amongst those who fail to show a humoral response, a T-cell response is evident in the majority.

Disclosure
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P782

Wearing-off effect reports of people with multiple sclerosis treated with ocrelizumab in Canada: a descriptive summary of real-world data

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Introduction: Ocrelizumab (OCR) is a humanized monoclonal antibody selectively targeting CD20+ B cells and is approved in Canada for the treatment of relapsing-remitting and primary progressive multiple sclerosis (MS). Persons with MS (PwMS) receiving monoclonal antibodies have reported increased fatigue and other MS symptoms prior to the next dose, described as "wearing-off effect". This effect is important to investigate as a minimum interval of 5 months should be maintained between each OCR dose.
Objectives: To evaluate reports of wearing-off effect in PwMS in Canada treated with OCR.
Methods: Canadian cases with the preferred term (PT) "therapeutic response shortened" were identified from the Roche Global Safety Database cumulatively from November 5, 2008 until November 30, 2021. These cases were linked to information on infusion dates and therapy status within the Canadian Roche Patient Support Program (COMPASS). The results only included safety reports from persons receiving OCR via COMPASS.
Results: A total of 7,949 PwMS in Canada received at least one dose of OCR via the COMPASS program as of November 30, 2021. 89 unique patient cases (1.12%) reported an adverse event (AE) coded to the PT, therapeutic response shortened. The majority of patients (87.6%, 78/89) continued on therapy and discontinuation

of OCR was rarely reported among cases that reported therapeutic response shortened (0.14%,11/7,949). Of the 89 cases, 4 (4.5%) discontinued OCR by recommendation of a physician, 1 (1.1%) due to an adverse event, 1 (1.1%) due to financial concerns, and 5 (5.6%) for unknown reasons. Of cases reporting the event of interest, those with relapsing-remitting MS more frequently remained on therapy (92.9%,65/70) as compared to those with primary progressive MS (68.4%,13/19 of which 1/19 discontinued after an AE). Additional data will be presented at the congress.

Conclusions: Wearing-off effect events are rarely reported in the COMPASS program, which differs from some published literature. This may be due to the self-reported nature of COMPASS data, limitations inherent to post-market safety data, and varying study methodologies. Importantly, however, the majority of patients reporting wearing-off events did not discontinue OCR after event occurrence. Repeated cumulative reviews of the Roche Global Safety Database for cases related to lack of efficacy did not identify new safety concerns.

Disclosure

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SA Morrow has, in the past 3 years served on advisory boards/had speaking engagements for: Biogen Idec; BMS/Celgene; EMD Serono; Greenwich Bio; Novartis; Roche ; Sanofi Genzyme; Teva Neurosciences; and has received Investigator Initiated Grant Funds from Biogen Idec; Novartis; Roche; Sanofi Genzyme; and has acted as site PI for multi-center trials funded by BMS/Celgene; EMD Serono; Novartis; Genzyme; Roche

V Gitman is an employee and shareholder of Hoffmann-La Roche Limited

J Rassi is an employee and shareholder of Hoffmann-La Roche Limited

N Pasquarelli is an employee and shareholder of F. Hoffmann-La Roche Ltd

K Fitovski is an employee and shareholder of F. Hoffmann-La Roche Ltd

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P783

Patient's experience and quality of care when moving to at home natalizumab: a prospective evaluation of multiple sclerosis patients (TYSAD-35)

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Introduction: The patient's care experience is a crucial factor to consider in order to improve the quality of care and the quality of life in multiple sclerosis (MS). In the context of COVID-19 pandemic, the French health authorities allowed the administration of natalizumab at home by at-home health service.

Objectives: The main objective was to evaluate the quality of care from the point of view of the patients when moving from hospital to at home natalizumab administration.

Aim: Improve quality of care and quality of life in multiple sclerosis.

Methods: Thirty relapsing remitting MS patients treated with natalizumab since more than 6 months were prospectively recruited to benefit from an at home procedure that was evaluation during 1 year by using the following questionnaires: MusiCare, the first specific MS patient's experience, was filled out at baseline, 6 and 12 months ; MusiQol (to assess quality of life), ExPerf (adapted from the PPE15 to assess practice experience) and a satisfaction scale were filled out every months. The primary endpoint was the mean difference of MusiCare scores between Baseline and 12 months.

Results: From June 2020 to November 2021, 306 infusions were performed at home. Three patients stopped the study (one loss of follow-up, two preferred to move back to hospital's procedure). No worsening of patients experience or quality of life was observed. One dimension of MusiCare was significantly improved at 12 months compared with baseline (91.5 versus 81.8, p=0.0203): relationship with healthcare professionals. The MusiQol global score remained stable (75.5 vs 72.4) but coping and friend's relationship dimensions were significantly improved at M12 versus baseline (respectively p=0.0491 and p=0.0478). Answers to the ExPerf questionnaire show some pain during infusion (21.8%) and some contradictions between health professionals (17.2%). The mean satisfaction about the care was 9.1/10. MS activity remained low. There was no serious adverse event.

Conclusion: Positive patient's experience of at home natalizumab administration gives an important opportunity to improve patient's quality of care.

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P784

Cladribine protects SH-SY5Y neuron-like cells from oxidative stress conditions in vitro

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Background: Cladribine is a synthetic purine nucleoside analogue with immunosuppressive functions demonstrating beneficial effects in patients with RRMS. The effect of cladribine on cells of the central nervous system is not well understood, nor its capacity to protect neurons and oligodendrocytes from damage.
Aim: To analyse the direct effect of cladribine on neurons and oligodendrocytes upon inflammatory, excitotoxic or oxidative stress stimuli.
Methods: SH-SY5Y human neuroblastoma cell line was differentiated into neuron-like cells, and stimulated with 800 μM tert-butyl-hydroperoxide (TBHP, oxidative stress stimulus), 100 ng/ml IFNγ and TNFα (inflammatory stimulus) or 150 mM glutamate (excitotoxic mediator) in the presence of cladribine (0.02 μM or 0.002 μM, concentrations reflecting the mean estimated brain exposure) or combined with deoxycytidine as a competing substrate for deoxycytidine kinase (evaluation of cladribine as an agonist of adenosine receptors). Cell toxicity was assessed by flow cytometry, LDH release or measurement of morphological parameters of immunocytochemistry-stained cells. MO3.13 human glial cell line was differentiated into mature-like oligodendrocytes, and then stimulated with 100 μM H_2O_2 (oxidative stress damage) or 100 ng/ml IFNγ and TNFα (inflammatory stimulus) in the presence of 0.02 μM and 0.002 μM or combined with deoxycytidine (DC). Cell toxicity was evaluated by LDH release measurement. Statistical analysis was performed with mixed models to account for correlated measures with Dunnett's as post-hoc test.
Results: The concentration reflecting the mean estimated brain exposure of cladribine enhanced neuron-like cell survival under oxidative stress conditions (TBHP-stimulated: 44.76%±16.92 dead cells; 0.02 μM: 21.94%±11.86 dead cells; 0.002 μM: 22.22%±12.65 dead cells; $p<0.05$) even if cladribine was in its prodrug form (0.02 μM + DC: 18.01%±10.82 dead cells; 0.002 μM + DC: 23.25%±9.69 dead cells; $p<0.05$). However, cladribine did not exert a neuroprotective effect on neuron-like cells challenged with cytokines or glutamate. In addition, cladribine did not protect mature-like oligodendrocytes from oxidative stress and inflammatory damage.
Conclusion: In vitro, mean estimated brain concentration of cladribine enhances SH-SY5Y neuron-like cell survival under oxidative stress conditions, but has no direct protective effect on either SH-SY5Y neuron-like or MO3.13 mature oligodendrocyte-like cell death induced by other stimuli.

Disclosure
H Eixarch, L Calvo-Barreiro, N Fissolo and C Espejohave nothing to disclose.
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X. Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS
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P785
Prevalence and characteristics of MS patients with COVID-19 infection at Karolinska University Hospital, Stockholm, Sweden

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Introduction: Multiple sclerosis (MS), an immune-mediated neurodegenerative disorder, is commonly treated with disease-modifying therapies (DMTs). DMTs affect the immune system, and some are associated with an increased risk of infections, potentially rendering MS patients vulnerable during the COVID-19 pandemic.
Objectives/aims: To determine the proportion of MS patients followed at Karolinska University Hospital (KS) that tested positive with COVID-19 between September 1st 2019, and September 1st 2021, determining proportion of MS patients that tested positive with COVID-19 depending on MS treatment, and estimating risk of contracting COVID-19 and risk of severe COVID-19 illness (hospitalization), depending on MS treatment.
Methods: A retrospective chart review was performed of all living MS-patients included in the Swedish MS registry and cared for at KS. Clinicodemographic, DMT and COVID-19 variables were recorded. DMTs were pooled into first-line (teriflunomide, interferons, glatiramer, fingolimod, siponimod and dimethylfumarate) and second-line (natalizumab, cladribine, ocrelizumab and haematopoietic stem cell transplantation) treatments. Rituximab was analysed seperately. Risk of contracting COVID-19 and risk of severe illness (hospitalization) was analysed with Chi-squared test. P-values of <0.05 were considered significant. P-values were adjusted according to Holm. Statistical analyses were performed using R version 4.1.1.
Results: Of 1120 patients, 177 COVID-19 infections were identified (15.8%). Among treatments, rituximab accounted for the greatest proportion of infections (n=74, 41.8%), followed by no treatment (n=39, 22%) and dimethylfumarate (n=22, 12.4%). Compared to no treatment, rituximab (RR=3,36; 95% CI 2.34-4.83, p=0.001,p_{adj}= 0.001), pooled first-line treatments (RR=3.55; 95% CI 2.43-5.20,p=<0.001,p_{adj}=<0.001) and second-line treatments (RR=2.65; 95% CI 1.43-4.88,p=0.002,p_{adj}=0.013) were associated with increased risk of contracting COVID-19. Rituximab was also associated with an increased risk of hospitalization (RR=2.29; 95% CI 1.03-5.13,p=0.037,p_{adj}= 0.112), although non-significant after adjustment.
Conclusions: This project confirms reports of an increased susceptibility for COVID-19 while treated with common DMTs, as well as an increased risk of hospitalization while treated with rituximab. However, some results are not significant after adjustment and should be interpreted with caution.

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P787

Barriers to access multiple sclerosis disease-modifying therapies in middle east and north africa: a regional survey-based study

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Background: Multiple sclerosis (MS) management varies markedly between different countries of the Middle East and North Africa (MENA) region based on disease-modifying therapies (DMTs) availability, accessibility, and reimbursement. In general, introduction of novel DMTs in most MENA countries is usually delayed. To our knowledge, there are no published studies assessing the accessibility to DMTs across different countries of the region.
Objectives: To evaluate the accessibility to originators and off-label DMTs in each MENA country and identify barriers to MS treatment.
Aims: To gain better understanding of treatment accessibility and explore potential common areas of need in our MENA region.
Methods: This is a descriptive, survey-based study whereby we extracted data collected, between October 2019 and April 2020, for countries in the MENA region by the Multiple Sclerosis International Federation (MSIF) through their Atlas of MS online survey.
Results: 16 out of 19 countries in the MENA region were included in this study. Bahrain, Jordan, and Somalia were excluded as they did not contribute data to the Atlas of MS. Two countries did not have any originator DMTs approved (Sudan and Syria). Among low efficacy originator DMTs, interferons were the most widely approved DMTs (75-88%). As for the moderate-efficacy DMTs, fingolimod was approved in 12 out of 16 countries (75%) followed by dimethyl-fumarate and cladribine, each approved in 8/16 countries (50%). Three countries (19%) did not have any high efficacy DMTs (natalizumab, ocrelizumab, alemtuzumab) approved. On the other hand, follow-on DMTs (generic or copy) were approved in half (50%) of the MENA countries. More than half (56%) of MENA countries reported issues with continuing treatment due to irregular supply (n=9), lack of monitoring tests that determine treatment continuation (n=3), need for regular renewal of reimbursement (n=2) or time-limited supply of DMTs (n=1).Overall, 9 countries (56.2%) reported barriers to treatment. Cost of treatment, which refers to cost for the government, healthcare provider, or insurance provider, was the most important one, reported in nearly half (47%) of the MENA region countries.
Conclusion: Most MENA countries have access to DMTs, including high-efficacy DMTs. However, more than half of them report problems with treatment continuation with cost being the major barrier to treatment.

Disclosure

Competing Interests: The authors have no competing interests to declare that are relevant to the content of this study.
Funding: No funding was received for conducting this study.

P788

A randomized, double-blind controlled clinical study to determine the effectiveness, safety and tolerability of actoferon® compared to betaferon® in subjects with relapsing remitting multiple sclerosis (RRMS)

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Introduction: Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by inflammation, demyelination, gliosis, and neuronal loss. The most common type of the disease is relapsing remitting multiple sclerosis (RRMS).The production of Biosimilar disease modifying therapies is a scientific goal in some countries with lower economic income and relatively high prevalence of MS.
Aims and Objectives: This study is designed to investigate the efficacy, safety, and tolerability of Actoferon® versus Betaferon® in patients with relapsing RRMS.
Methods: 140 patients aged 18-55 with a confirmed clinical diagnosis of RRMS and EDSS (Expanded Disability Status Scale) 0-5.5 were randomized to receive Actoferon®(a biosimilar interferon beta-1b)250 mcg subcutaneous (SQ) every other day or Betaferon® 250 mcg SQ every other day for 12 months. The subjects were examined in days 28, 90, 180, 270, and 365. In each visit, relapse rate, EDSS, flu-like symptoms, injection site reactions, and tolerability of patients were recorded. Laboratory assessments including CBC and liver function tests levels were measured at months 6 and 12.
Results: The subjects were randomly allocated into two groups of 70 with mean age of 35.24±9.25 in Actoferon®group and 33.17±7.79 in Betaferon® group. Mean baseline EDSS in Actoferon® and Betaferon® arms were 2.54±1.67 and 2.00±1.47 respectively. At the end of the study, EDDS change in Actoferon®group was 0.123 higher than that in the Betaferon® group (CI: -0.088 to 0.334). The percentages of patients with relapses for Actoferon® and Betaferon® were 28.6% and 21.4% respectively (p-value: 0.329). In radiologic assessment, during one year 48.5% of Betaferon® and 65.4% of Actoferon®patients developed new T2 lesions on MRI (p-value: 0.194) and 19.2% of Actoferon® and 3% of Betaferon® subjects developed new Gadolinium enhancing lesions (p-value: 0.078). Flu-like symptoms frequency was 42.4% for Actoferon®and 39.1% for Betaferon® group (p-value: 0.697). There was no significant difference between the two groups in systemic adverse events,

except in fever where incidence of fever in Actoferon®patients was less (p-value: 0.046). Laboratory test results and injection site reactions in both groups were similar.
Conclusion: There was no significant difference between Betaferon®and Actoferon®in aspects of efficacy, safety and tolerability. This study showed the non-inferiority of Actoferon®to Betaferon®.

Disclosure
There is no conflict of interest in this study.

P789
Do multiple sclerosis drugs decrease the risk of a severe SARS-CoV-2 infection?

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Introduction: Multiple sclerosis drugs (DMTs) were expected to increase the incidence and risk of severe infection for SARS-CoV-2 and to decrease the response to the vaccine, but has it been the case?
Objectives: 1) To evaluate the relationship between the use of DMTs and the incidence and severity of SARS-CoV-2 infection. 2) To evaluate the relationship between the use of DMTs and the incidence and severity of SARS-CoV-2 infection after vaccination.
Aims: To demonstrate that treatment with DMTs does not increase the incidence and risk of severe illness or the response to vaccination due to SARS-CoV-2 infection.
Methods: Retrospective cohort study of 472 adults with MS in a MS Unit between March, 2020 and March, 2022. All DMTs were prescribed prior to COVID-19 testing. Variables: Demographics data, DMTs, SARS-CoV-2 test results, severity of the infection (hospitalized and death), infection after vaccination.
Results: Among 472 patients with MS, 120 patients (25.4%) had SARS-CoV-2 infection (Incidence in the general population of Catalonia: 22.7%); 83 (26%) were women; mean age: 49 years (44.5 yrs for infected; 50.6 yrs for not infected); there was no significant difference in the incidence of infection between 66 (29.3%) of the 213 treated and 52 (21.8 %) of the 259 untreated patients (p=0,059). There was also no significant difference in hospitalization between the 4 treated (5.9 %) and 3 untreated (2.5 %) patients. None of them died. There wasn't a significant difference between post-vaccination incidence of infection between the 26 treated (41.3%) and 16 untreated (36.4%) patients either.
Conclusions: The use of DMTs was not associated with an increase in incidence or severity of SARS-CoV-2 infection, and a favorable vaccine-induced SARS-CoV-2 response was observed. Further research is needed to determine the possible protective role of MS drugs on risk and severity of SARS-CoV-2 and the mechanisms that underlie these findings.

Disclosure
Nothing to disclose.

RIMS - Physical exercise and lifestyle changes

P790
The impact of COVID-19 pandemic on physical activity in persons with multiple sclerosis: an international RIMS-SIG Mobility study

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Introduction: Restrictions aiming to slow down the spread of COVID-19 had consequences on the amount and content of physical activity in persons with multiple sclerosis (PwMS).
Objectives & Aims: To investigate the impact of the COVID-19 pandemic on physical activity in PwMS.
Methods: An online survey was distributed during May - July 2021 in 11 countries. The survey gathered various metrics of physical activity (e.g. type, intensity, use of technology) performed prior to (2019) and during the pandemic (2021). Factors associated with stopping physical activity were also investigated.
Results: The survey was completed by 3725 PwMS. Pre-pandemic 83% of the respondents reported being physically active, whereas during the pandemic 75% reported being physically active. Concern of contracting COVID-19 and loss of support were highly predictive factors associated with stopping physical activity. The decrease in physical activity was significant for both moderate and high intensity physical activity ($p<.0001$). Prior to the pandemic, 66% of the respondents reported physical activity behaviour indicating that they met the physical activity guidelines, while during the pandemic the respondents meeting the physical activity guidelines was 50%. The proportion of respondents meeting the guidelines decreased with increasing disability (Pre/during-pandemic: mild: 64%/ 55%; moderate: 52%/ 43%; severe: 39%/ 30%). Walking was the most frequent activity pre-pandemic (27%) and during the pandemic (33%). Of the 25% respondents who were inactive during the pandemic, 31% reported no interest in changing their physical activity behaviours, and 44% expressed a preference for a face-to-face format to conduct physical activity after the pandemic. During the pandemic, the most used technology (24%) were wearables (e.g. smart watch).

Conclusions: Physical activity was reduced in PwMS from before to during the pandemic. Concerns of contracting COVID-19 and a loss of support were highly associated with reduced physical activity. There is a need to support PwMS aiming to increase physical activity. Physical activity programmes which address walking (the most frequent), disability and the use of wearable technology may be preferable.

Disclosure
Authors have nothing to disclose.

P791
Changes in sedentary behaviour and physical activity in response to an exercise intervention in persons with multiple sclerosis

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Introduction: A substantial body of evidence supports the beneficial effects of exercise for persons with Multiple Sclerosis (PwMS). However, recent systematic reviews indicate that current exercise interventions only increase self-reported exercise participation, but fail to increase objective measures of total physical activity (PA). This could indicate that PwMS compensate for exercise training (i.e. by decreasing their non-exercise PA or increasing sedentary behaviour [SB]), which might blunt exercise effects.
Objective: To assess physical activity changes of PwMS during a structured exercise intervention, in order to optimise exercise prescription guidelines and exercise benefits.
Aim: In this non-randomised pilot study, the effects of a running exercise intervention on whole-week PA, non-exercise PA and SB are compared between PwMS and healthy controls (HC).
Methods: Twenty-nine mildly-disabled PwMS (EDSS 0-4) and 26 HC completed 10 months of home-based, periodized exercise in which high-intensity interval training and moderate-intensity continuous training sessions were alternated. PA (stand time, low-intensity PA [LIPA] and moderate-to-vigorous PA [MVPA]) and SB (total SB and time in sedentary bouts of ⩾60min) were measured by accelerometry (activPAL3) for 7 consecutive days at baseline, and after 5 and 10 months of exercise. PA and SB were calculated as percentages of waking time/day for the whole week and for exercise (EX) and non-exercise (NONEX) days separately. Secondary outcomes included changes in fatigue, cardiorespiratory fitness, blood pressure, resting heart rate and fat percentage.
Results: There were no differences in baseline PA and SB between groups. During the intervention, both groups trained at a similar mean exercise intensity (mean±SEM: 79±1% of their maximal heart rate) for a total exercise duration of 62.2±1.5h. Interestingly, whole-week MVPA only increased in HC (MS: +0.2±0.4% *vs.*HC: +1.9±0.5%, p=0.035). Moreover, on NONEX days at both 5 and 10 months, PwMS significantly increased their total SB (MS: +2.8±1.2% *vs.*HC:-0.4±1.3%, p=0.029) and time in sedentary bouts of ⩾60min (MS: +0.7±0.2h*vs.*HC: +0.1±0.2h, p=0.003), while HC did not. Fatigue, cardiorespiratory fitness, resting heart rate and fat percentage improved similarly in both groups.
Conclusion: In contrast to HC, PwMS did not show a net increase in MVPA during a structured exercise training intervention due to increases in sedentary behaviour on non-exercise days.

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P792
Can a seated 6-minutes knee antiphase movement test help understand walking fatigability in moderately disabled people with MS through a movement control perspective? Preliminary results

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Introduction: People with multiple sclerosis (pwMS) present often abnormal walking fatigability (prevalence among moderately disabled patients ~50%). Recent findings indicated that a seated 6-minute knee flexion/extension antiphase movement test (6AMT), which minimizes muscle and balance effort compared to the 6-minute walking test (6MWT), is a promising test to "isolate" and investigate central driven mechanisms. However, the feasibility and performance of moderate pwMS presenting walking fatigability on the 6AMT is not known.
Objectives: To investigate the performance in the 6AMT in moderate pwMS with and without walking fatigability and healthy people.
Methods: Twenty-four pwMS were divided into walking fatigability (MSWF: 55±7 years, EDSS 4.9±1, n=17) and non-walking fatigability (MSNWF: 58±11 years, EDSS 5.3±0.9, n=7) groups, using the distance walking index ($DWI_{6\text{-}1}$, cut-off of 10% of decline in distance), derived from the 6MWT, for allocation. Seventeen healthy people (HC- 51±6 years, n=17) composed the healthy control group. The participants performed the 6MWT at their maximum self-selected speed, recording the distance walked minute-by-minute and the total distance. After resting for 30 minutes, two trials (30 minutes apart) of a seated 6AMT were performed. Participants were asked to perform the 6AMT as fast as possible, simulating a walking pattern. Movement variability,

amplitude, and frequency were calculated. Group comparisons (one-way ANOVA) were applied for the 6MWT and 6AMT outcomes.
Results: MSWF (DWI_{6-1}= -15±4%) presented a significantly larger DWI_{6-1} ($p<0.001$) compared to MSNWF (DWI_{6-1}= -2±5%) and CG (DWI_{6-1}= 1±7%), with no difference between MSNWF and HC. Both MSWF (316±129m) and MSNWF (291±110m) walked shorter distances in the 6MWT than HC (572±63m) ($p<0.001$), with no difference between MSWF and MSNWF. During the 6AMT, the MSWF presented higher movement variability and lower amplitude ($p<0.01$) than HC. Both pwMS were similar in terms of 6AMT performance. Movement frequency was similar among groups.
Conclusion: The higher variability and lower amplitude during the 6AMT in the MSWF group may indicate impairments in programming and executing the antiphase movement compared with HC. The findings during the 6AMT may relate to the 6MWT, underlying walking fatigability. We propose the next steps to relate the 6AMT outcomes with gait biomechanics (e.g., stride length) to identify the possible causes of walking fatigability in pwMS.

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P793
COVID-19 and multiple sclerosis: a thematic analysis of the unique experiences of people with multiple sclerosis during the COVID-19 pandemic

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Introduction: The impact of the COVID-19 pandemic on people living with multiple sclerosis (MS) is expected to be significant. Whilst quantitative research in this area has been undertaken, there is a paucity of qualitative research; this study will therefore provide valuable insights into individual experiences and perceptions of people with MS (PwMS) in the United Kingdom (UK) during this unique period.
Objective: The ongoing global health crisis leaves us all in a state of uncertainty that requires constant adaptation to the new 'normal' we are living in, and it is important that the challenges faced by the MS community are recognised and addressed as part of this learning process. We explore self-reported data gathered during the pandemic to reach conclusions regarding the impact of the crisis on PwMS.
Aim: To enhance understanding of
the experiences of PwMs during the COVID-19 pandemic and identifying potential areas where further support could be beneficial.
Method: Between March 3 and October 29, 2020, 1,685 free-text comments regarding the
unique experiences of PwMS were collected online by the UK MS Register (UKMSR).
Thematic analysis of 1,000 randomly selected responses made by 682 individuals was used
to investigate the perceived impact of COVID-19 on the participants, following a
constructivist approach.
Results: Five main themes were identified in the data: connectedness, attitudes towards
change, mental health, stigma, and information and advice. Results of the thematic analysis were varied, with significant numbers reporting positive experiences of the pandemic.
Conclusions: Individual levels of connectedness and attitude towards change significantly influence how PwMS experience life during the COVID-19 outbreak. The data showed the impact of COVID-19 on mental health to be mixed among PwMS. The pandemic hashighlighted that some PwMS remain fearful of being stigmatised in the workplace because of their condition.

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P794
Short- and long-term perceived improvement in self-efficacy of people with multiple sclerosis participating in an individualised physiotherapy outdoor-group and digital intervention, emphasising trunk control and high intensity physical activity

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Introduction: Trunk control and physical activity are reduced in people with MS (PwMS) even when disability is mild and moderate (Expanded disability status scale (EDSS) 0-3.5). Trunk control is essential for optimal physical function and individualised, group-based physiotherapy and digital support may be beneficial.
Aim: To explore the user perspectives of a new intervention (CoreDISTparticipation) which combine these components.
Objective: What are the short- and long-term experiences of PwMS (mild-moderate) participating in a 4-week individualised, group-based physiotherapy and digital intervention emphasising trunk control and outdoor high intensity physical activity (CoreDISTparticipation)?
Methods: This interview study was nested within a randomized controlled trial. A total of 30 in-depth interviews of all participants in the intervention group (n=15; 12 woman; age 38-66 years old; EDSS 0-3.5) were conducted (week 6 and 24). Systematic Text Condensation analysis is performed, informed by a Dynamic Systems Theory and Enactive theoretical framework.

Results: Preliminary themes indicate: 1) Perceived positive changes in movement control and increased exercise intensity during group-sessions were associated with improved self-efficacy of physical activity. 2) Individualised support by the physiotherapist optimised physical performance and perceived safety of exercises. 3) Fluctuations in functions and adverse effects of exercises were reported to reduce compliance. 4) The group setting enhanced meaning of and experienced adherence to exercise. 5) Exercise videos served as a reminder of executing exercises correctly but did not improve perceived adherence to exercise. 6) Advantages of externally initiated and structured exercise program were augmented when perceiving fluctuations and impairments in bodily functions. Data analysis will be completed during first half of 2022.
Conclusion: Our study indicates that individualisation within a group emphasizing trunk control and high intensity physical activity may provide perceived changes in bodily performances and short- and long-term improvement in self-efficacy of physical activity. Adverse experiences may occur and safeguarding by physiotherapy supervision were reported as essential. These findings contribute to the knowledgebase of how to improve trunk control and physical activity in PwMS with mild to moderate disability.

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P795
A pilot study examining the feasibility and acceptability of a weight loss and healthy lifestyle intervention in people with multiple sclerosis

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Introduction: Obesity is associated with greater disease severity in multiple sclerosis (MS). However, all research to date examining the link between obesity and MS has been observational or cross-sectional.
Objectives: Examine the feasibility and acceptability of a 6-month telehealth, behavioral weight loss intervention for people with MS (pwMS) who are overweight or obese.
Aims: The aims of this pilot study were to: (1) Develop and assess the feasibility and acceptability of a comprehensive behavioral weight loss program; (2) Examine the primary outcome variable, percent weight loss, at 6-months; and (3) Assess the association between weight loss, minutes of physical activity, and daily servings of fruits and vegetables in pwMS.
Methods: Participants received Fitbit devices and a subscription to the Lose It! application. Program guidelines included eating 1200 – 1500 calories a day and working up to 150 minutes of physical activity per week. Group members met weekly to discuss topics related to weight loss and healthy lifestyle changes in MS. Changes in diet and physical activity were monitored at baseline and follow-up via questionnaires and Lose It! and FitBit accounts. Percent weight loss was calculated at follow-up.
Results: On average, participants (n=8) attended 17 of the 24 weekly meetings (SD = 7.1). Average percent weight loss at 6-months was 10.6% (SD = 7.2). Self-reported physical activity increased at follow-up, but this was not significantly related to percent weight loss (r =.17, p = .68). Average weekly active minutes in FitBit was significantly associated with weight loss (r= .91, p = .002). Fruit, but not vegetable or combined fruit and vegetable consumption increased significantly (M_{diff}= -.54, p = .03). Average calories logged per week in Lose It! was significantly related to percent weight loss at 6-months (r = .81,p = .02).
Conclusions: The behavioral weight loss program was largely feasible and acceptable for pwMS and resulted in clinically meaningful weight loss for two-thirds of participants. Research examining planned weight loss in pwMS and obesity may help clarify whether treating this comorbidity can reduce MS symptom severity. A larger randomized controlled trial is currently underway to further examine the efficacy of this intervention.
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P796

Sustained attention during prolonged walking in persons with multiple sclerosis

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Introduction: Walking is a cognitively demanding activity, as has been shown in long-distance assessments. It is known that there is often a decrease in walking speed during long-distance walking in persons with multiple sclerosis (pwMS) which could be related to reduced sustained attention while performing simultaneously performing a prolonged motor task (i.e., long distance walking task).
Objective: This study investigated sustained attention during prolonged walking in pwMS withdifferent levels of disabilityand compared it with healthy controls (HC).
Methods: Thirty pwMS with mild disability (EDSS<4.0), 16 pwMS with moderate to severe disability (EDSS 4.0-6.5), and 27 age-gender matched HC performed the 6-Minute Walk Test (6MWT) with an auditory vigilance task. Participants were auditory provided a letter every 2.5s through a headphone and were instructed to say "yes" as fast as possible when they heard one of two selected letters (L and R) and asked to not respond on other letters to assess vigilance. The number of errors and average reaction time in the vigilance task, and distance walked per minute were measured. Distance Walked Index (DWI; change in walking distance between min 1 and min 6) was calculated to determine walking fatigability. Repeated measures ANOVAs (RMANOVAs) were conducted on each outcome variable with post-hoc corrections.
Results: Significant group*time interaction effects were found for reaction times.Reaction times significantly increased in persons with mild disability and moderate to severe disability groups, with greater increase in pwMS with moderate to severe disability (13.22%). There was no change in reaction time between min 1 to min 6 in HCs. Significant time effects were found for walking distance and number of errors, but there was no group*time interaction. The DWI was not different between mildly disabled pwMS and HC (-10.22% vs. -6.54%), but those with moderate to severe disability showed a significantly greater change (-20.59%) than mildly disabled pwMS.
Conclusion: Our findings showed that attention and walking speed deteriorated over time during the six minutes of walking, especially in pwMS with higher disabilities. Change in sustained attention may explain the decrease in walking speed, and it should be further examined.

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RIMS - (Tele)Rehabilitation (physical, neuropsychological and psycho-social approaches)

P797

Sleep quality and fatigue is independent phenomena and show different treatment response to multidisciplinary rehabilitation - The Danish MS Hospitals Rehabilitation Study

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Introduction: Sleep disturbances and fatigue are highly prevalent symptoms in patients with multiple sclerosis (MS) known to have detrimental effects on overall functioning and health-related quality of life. However, the multifactorial relationship between these phenomena is not fully understood and effective treatment strategies counteracting the disabling consequences are warranted.
Objectives: To investigate the relationship between sleep quality and fatigue and the treatment response to multidisciplinary rehabilitation (MDR) in an appropriate sample of patients with MS.
Aims: To optimise treatment of some of the most prevalent and disabling MS symptoms.
Methods: As part of The Danish MS Hospitals Rehabilitation Study 405 patients with MS were included in a randomized controlled partial crossover design. Patients were randomly assigned to 4 weeks of inpatient MDR or a waitlist group. Following the 6-month follow-up, the waitlist group received the 4 weeks of inpatient MDR, and all patients were followed up at month 12. Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) and fatigue impact by the Modified Fatigue Impact Scale (MFIS). Principal Component Analysis (PCA) were conducted to investigate component loadings andrepeated measurement linear mixed effects models were applied to get estimates of difference-in-difference at 6- and 12-month follow-up (MFU).
Results: PCA loadings revealed two separate components of sleep issues and fatigue with limited overlap, suggesting that sleep quality and fatigue are independent phenomena. 4-weeks of inpatient MDR decreased the perception of fatigue-impact when compared to control (6 MFU mean (95 % CI): -2.3 (-0.4;-4.1),p=0.02, and 12 MFU mean (95 % CI): –2.3 (-4.7,-0.1),p=0.04), while a pattern of improvement was observed for sleep quality (6MFU mean (95 % CI): -0.49 (-1.0;0.02),p=0.06, and 12MFU mean (95 % CI):-0.44 (-1.07,0.17),p=0.15). The latter was however driven by the one sub-component of the PSQI that loaded into the fatigue principal component, suggesting that sleep quality may not be specifically improved by the MDR.
Conclusions: Sleep quality and fatigue seem to be independent phenomena with different treatment responses to a pragmatic inpatient MDR intervention, suggesting that specificity is important in order to optimise treatment of these disabling MS symptoms.

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P798

The impact of the COVID-19 pandemic on physiotherapy services for people with multiple sclerosis: a multicentre survey study of the RIMS network

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Introduction: The COVID-19 pandemic has placed a strain on healthcare services worldwide with a highly heterogeneous impact. Therefore, the Special Interest Group for Mobility (SIG Mobility) of the European Network for Best Practice and Research in Multiple Sclerosis Rehabilitation (RIMS) decided to examine the impact of the COVID-19 outbreak on physiotherapy services in people with multiple sclerosis (pwMS).
Objective: To describe the impact of the pandemic on physiotherapy practice from the perspective of physiotherapists (PTs) by investigating changes in rehabilitation methods, organizational framework, and technology usage.
Methods: An online survey was developed by RIMS SIG Mobility and distributed to PTs in 9 countries (Australia, Belgium, Czech Republic, Ireland, Israel, Italy, Norway, Spain, and Turkey) from December 2020 to July 2021.
Results: 215 PTs participated in the study. The therapy most affected during the pandemic was aerobic training/conditioning exercises; 33.5% reported that these activities were either reduced or unavailable. In contrast, 15% reported increased use of relaxation/mind-body techniques and/or fatigue management programs. Frequency, total number, and duration of sessions decreased significantly during the pandemic compared to before the pandemic ($p<0.001$). Physiotherapy service delivery (accessibility) and effectiveness for pwMS were significantly decreased ($p<0.001$). There was a 10% decrease in the use of hands-on techniques and a 10% increase in the use of oral instructions when treating pwMS having moderate or severe disability during the pandemic compared to before. PTs increased use of telerehabilitation applications during the pandemic ($p<0.001$): app usage increased significantly from 37% to 56%, use of recorded videos from 38% to 55%, use of physiotherapy exercise websites from 33% to 52%, and use of exercise classes on TV from 7% to 20%. The top 4 challenges faced in telerehabilitation were limitations of assessment (54%), difficulties with equipment (43%), difficulties with understanding the patient's body language (35%), and not being able to use proprioceptive cues (35%).
Conclusions: The COVID-19 pandemic has notably affected physiotherapy services for pwMS internationally in terms of content, frequency of use, format, accessibility, and effectiveness. The long-term consequences of these changes should be investigated.

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P799

A multiple sclerosis training using the kinect-based MS-FIT exergame. An Italian multicenter feasibility study

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Introduction: Balance impairments are common in multiple sclerosis (MS). Pilates is a popular alternative method for balance performance maintenance and improvement that may reduce the rapid symptoms worsening frequently associated with physical inactivity. An Italian network of fifteen experts in MS rehabilitation developed through a User-Centered Design approach the MS-FIT exergame, a Kinect-based tool, to autonomously train balance through Pilates exercises. The MS-FIT user executes the exercises shown by a teacher's avatar and improves the performances through the feedbacks on the execution correctness.

Aims: This study (Clinical.Trials.gov, NCT04011579) aims at evaluating the feasibility of an at-home intervention with MS-FIT.

Methods: Feasibility was investigated in terms of adherence (sessions number), usability (usability items of Tele-healthcare Satisfaction Questionnaire, u-TSQ, satisfaction (Client Satisfaction Questionnaire, CSQ-8), safety (adverse events), and physical effectiveness (Timed UP-&-GO, TUG; Timed 25-Foot Walk, T25FW; 2-Minutes Walking Test, 2MWT).

Results: Forty-five people with MS (PwMS) were enrolled and randomized into the experimental (EXP, n=23) and control (CTRL, n=22) groups. During the 6 weeks of the study, only the usual physical activities were admitted (rehabilitation excluded) and, in addition, EXP had to practice MS-FIT at least three times a week. Due to organizational consequences of COVID pandemic, 8 subjects dropped-out (EXP, n=17; CTRL, n=20). The sample analysed showed the following characteristics: gender (EXP: 6M; CTRL: 7M), age (EXP: 41.9±9.6y; CTRL: 43.3±10.5y), course (EXP: 94.4% and CTRL: 95.0% relapsing-remitting), disease duration (EXP: 9.9±7.2y; CTRL: 12.5±9.8y) and EDSS (EXP: 2.6±0.8; CTRL: 2.6±0.8).

EXP highly adhered to the MS-FIT training (23.6±6.1 sessions); the tool was usable (u-TSQ: 3.01/4); satisfaction was medium-to-high (CSQ-8: 25.1/32); the training with MS-FIT was safe (no adverse events).

The groups did not differ in TUG, T25FW and 2MWT. An analysis separate for each group showed a significant improvement only in EXP (TUG: pre 7.5±1.2s, post 7.0±1.2s, $p<0.05$; T25FW: pre 6.1±1.5s, post 5.0±1.2s, $p<0.01$; 2MWT: pre 175.4±51.0m, post 194.1±56.9m, $p<0.01$).

Conclusions: MS-FIT is well-accepted and effective and could be a complement of traditional MS interventions. Based on the results and participants' feedbacks MS-FIT has been refined and is used in an ongoing randomized controlled trial.

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P472

The effect of sex and race on delays in multiple sclerosis evaluation and diagnosis: final analysis from a prospective cross-sectional study

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Introduction: Sex and race appear to influence multiple sclerosis (MS) prognosis. Prior observations suggest poorer clinical outcomes in men and Black patients with a more aggressive disease course. However, the possibility that delays in evaluation or diagnosis in these populations could contribute to worsened outcomes remains underexplored.
Objectives/Aims: To evaluate if men or Black patients have delays in being evaluated by a neurologist or in being diagnosed with MS.
Methods: This is the final update of our 2-year analysis in this prospective survey-based study of adult patients with a confirmed diagnosis of MS at our center in Washington, DC from November 2019 to November 2021. We surveyed patients to recall 3 events: their initial *symptom onset*, *first neurology visit*, and eventual *MS diagnosis*. Statistical analyses were done using R 4.1.2 software.
Results: A total of 245 surveys were included in this analysis (99.3% participation rate). Roughly equal numbers of respondents self-identified as Black (50.2%) or White (49.8%), and 76.3% of respondents were women. There was no difference in mean age at *symptom onset*, *first neurology visit*, or *MS diagnosis* between Black and White patients, but there was a trend for an older age at diagnosis in men (38.3±13.1 years) versus women (35.0±10.4 years, p=0.08). There was a significantly increased median delay from *symptom onset* to *MS diagnosis* in men (16.5 months) versus women (5 months, p=0.015), an effect seen among both Black and White patients. Men were more likely to have a delay of at least 6 months in being evaluated by a neurologist or diagnosed with MS after symptom onset compared to women (all $p<0.05$). Black patients were also more likely to have a delay of at least 6 months from *symptom onset* to *first neurology visit* compared to White patients (p=0.03), though there appeared to be no difference in time from *first neurology visit* to *MS diagnosis*. Men and Black patients were more likely to have an impaired gait at the time of diagnosis (all $p<0.05$).
Conclusions: Men have a significant delay in being evaluated for possible MS and in being diagnosed with MS. Black patients were more likely to have a delay of at least 6 months in being evaluated by a neurologist after symptom onset, but once they see a neurologist, there was no overall delay in being diagnosed with MS compared to White patients. Both men and Black patients tend to present with more disabling symptoms at the time of MS diagnosis.

Disclosure
All authors have nothing to disclose.

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Use of COVID-19 prevention therapy Evusheld in patients with multiple sclerosis: a retrospective observational study

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Introduction: Patients with multiple sclerosis (MS) on certain disease modifying therapies may not be able to mount an adequate immune response to the COVID-19 vaccine. AstraZeneca's Evusheld, tixagevimab co-packaged with cilgavimab, was introduced as pre-exposure prophylaxis against COVID-19 for patients unable to be vaccinated or mount adequate responses to vaccines. This is the first study to describe the experience of MS patients receiving Evusheld.
Objectives/Aims: To describe the characteristics and outcomes of MS patients who receive Evusheld under Emergency Use Authorization from the U.S. Food and Drug Administration (FDA).
Methods: We performed an IRB-approved retrospective chart review of MS patients from our center who received Evusheld from December 2021 to April 2022. Only adult patients (≥18 years) with a confirmed diagnosis of MS were included.
Results: Twenty-two patients were analyzed. All were above 50 years old (mean 60.9 ± 8.7 years) and mostly female (N=15, 68.2%). Racial groups included White (N=18, 81.8%), Black (N=3, 13.6%), and Asian (N=1, 4.5%). Patients had primary progressive MS (N=4, 18.2%), secondary progressive MS (N=6, 27.3%), and relapsing-remitting MS (N=12, 54.5%). Most patients (N=19; 86.4%) were on a B-cell therapy. Five patients (22.7%) had a prior COVID-19 infection. Twenty-one patients (95.5%) received at least 2 doses of COVID-19 mRNA vaccines. Of these, 19 (90.5%) received a third vaccine dose. None had a side effect to the first 2 doses of mRNA vaccines, but 1 patient had a pseudo-relapse after a third dose. All patients were administered Evusheld. Nine (40.9%) were given the 150mg tixagevimab/150mg cilgavimab dose prior to the FDA revision of the recommended dosing to 300mg tixagevimab/300mg cilgavimab. All 9 of these patients received catch up dosing. While there were no major complications to Evusheld, one patient experienced mild bradycardia to 48 bpm within 1 hour of receiving the 150mg tixagevimab/150mg cilgavimab dose. When that patient returned for catch up dosing, there was no complication with a second 150mg tixagevimab/150mg cilgavimab dose. No patients reported an MS relapse or pseudo-relapse after receiving Evusheld.
Conclusions: Evusheld was well tolerated in our cohort of MS patients without major complications or signs of relapse or pseudo-relapse. A longer term follow-up is needed to evaluate the efficacy of Evusheld in protecting against symptomatic COVID-19 infection in this population.

Disclosure
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