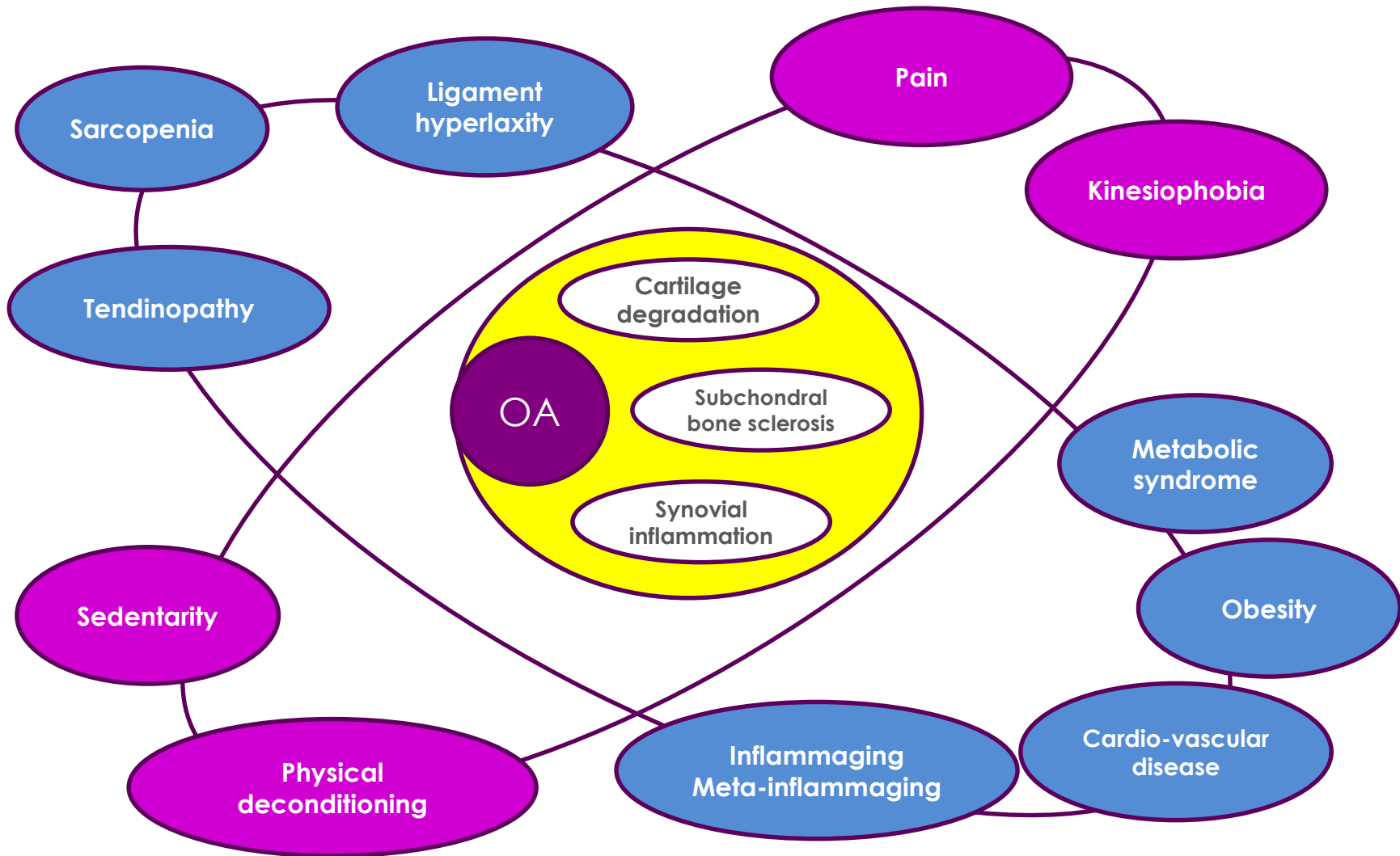




HA INTRAARTICULAR INJECTION: THERAPEUTIC AND ECONOMIC CONSIDERATIONS

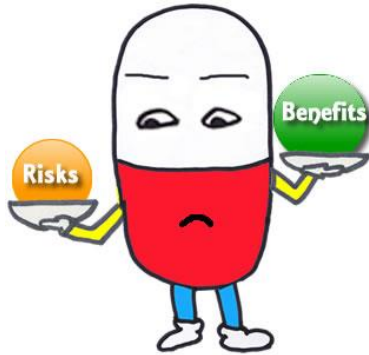
Osteoarthritis

A complex and severe disease

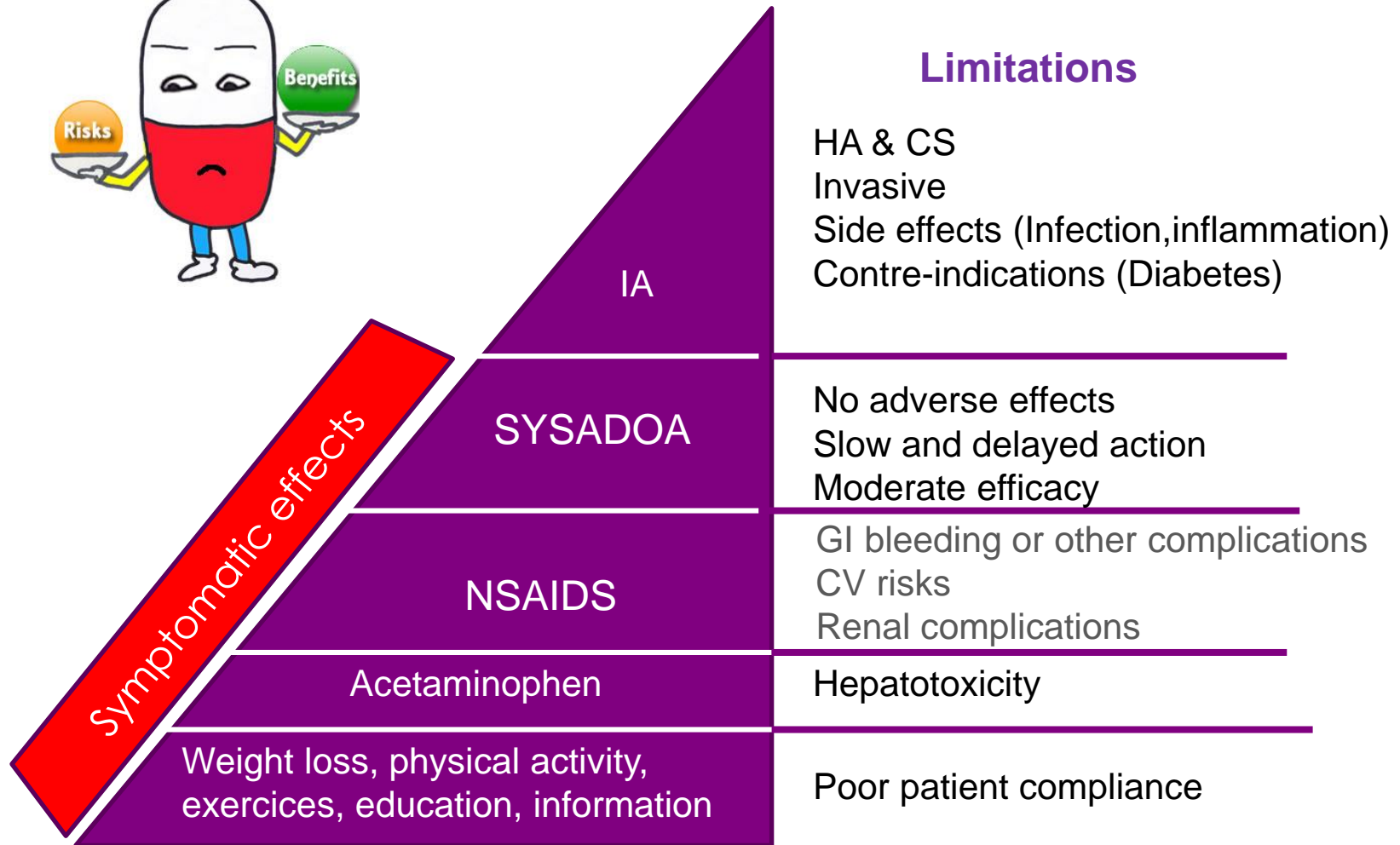


A global representation

Non-surgical treatments

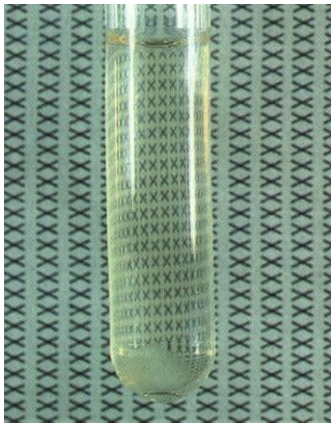
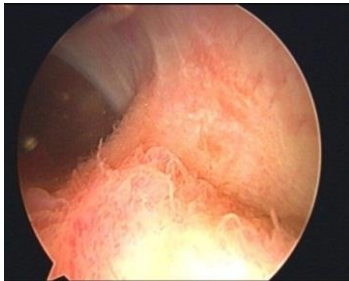


Limitations



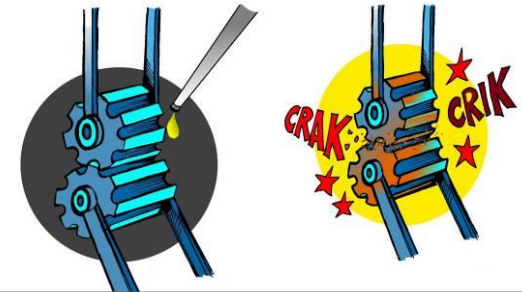
Modified Clegg et al. Eur J Orthop Surg Traumatol, 2013

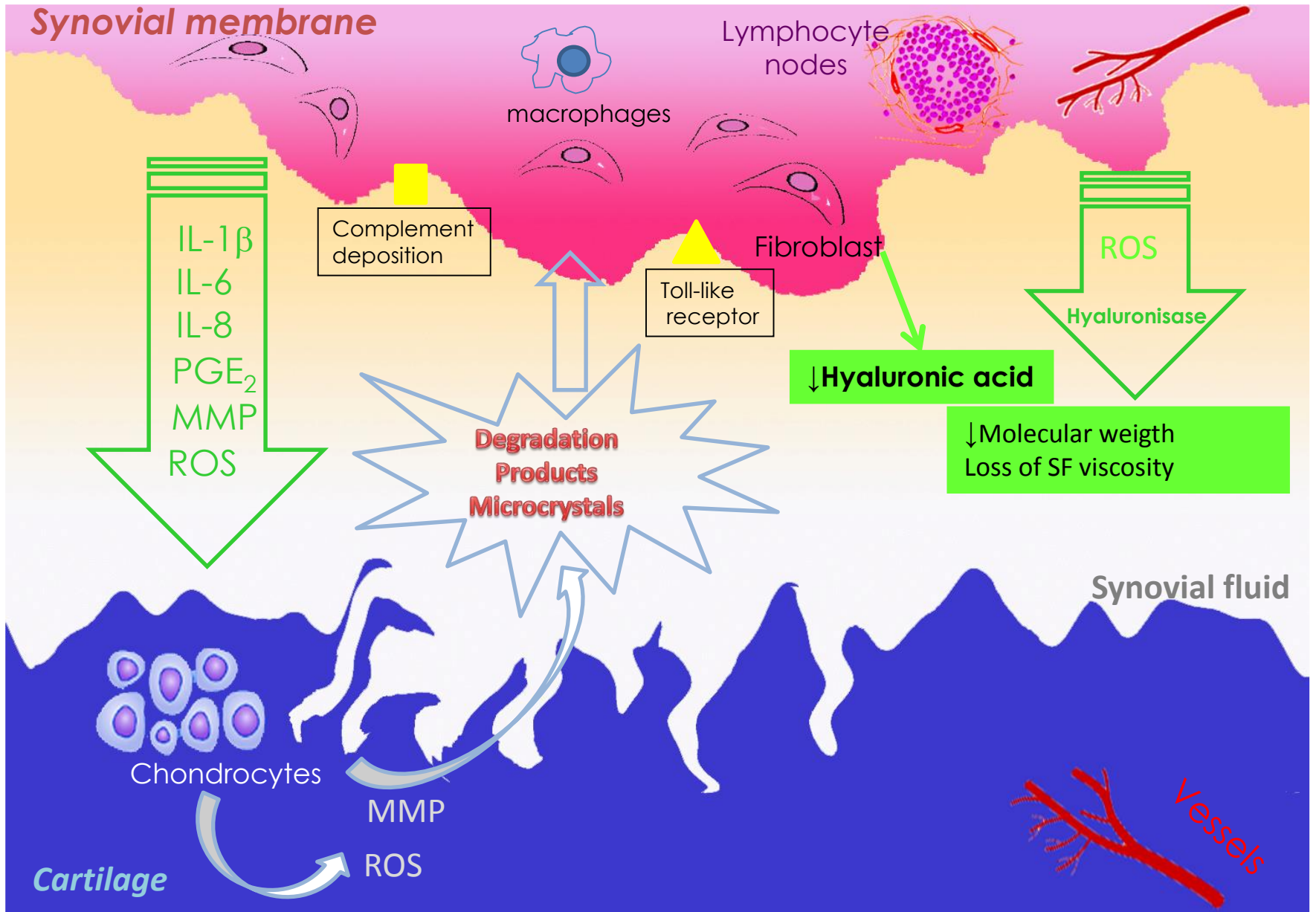
Loss of Synovial fluid lubrication properties



Synovial fluid: composition and properties	Healthy patient	Patient with osteoarthritis
Mw (MDa)	4 – 6	< 4
HA (mg/ml)	2,5 – 4	< 2
Elastic modulus (Pa à 2.5 Hz)	Close to 100	Close to 8
Viscous modulus (Pa à 2.5 Hz)	Close to 45	Close to 5
Viscosity at rest (Pa.s)	2 – 40 5 Pa.s à 37 °C	0.1 à 1

Pa: Pascal
Hz: Hertz
Pa.s: Pascal sec





Viscosupplementation

“Viscosupplementation is the process that restores the normal rheological environment in the synovial fluid, synovial tissue...and reestablishes the protection, lubrication, shock absorption and barrier effects.”

4 KEYS PROPERTIES

Visco-elasticity
Shock absorbing
Lubrication
Barrier effect

Hyaluronic acid



Viscoinduction

- **Viscoinduction** ensures that the effect is maintained for several months despite the short half-life of intra-articular HA
 - stimulate endogenous HA synthesis
 - Other biological effects (block IL-1 β activity)

IAHA has a moderate effect on knee OA symptoms OARSI meta-analysis

(Zhang et al, 2010)

	ES Pain	ES Function
Acetaminophen	0.14 (0.05,0.23)	0.09 (-0.03,0.22)
Diacerein	0.24 (0.08, 0.39)	0.14 (0.03, 0.26)
NSAIDs	0.29 (0.22,0.35)	-
Aerobic	0.52 (0.34; 0.70)	0.46 (0.25, 0.67)
Glucosamine Sulfate	0.58 (0.30, 0.87)	0.07 (-0.08,0.021)
IAHA	0.60 (0.37, 0.83)	0.61 (0.35,0.87)
Chondroitin sulfate	0.75 (0.50, 1.01)	-

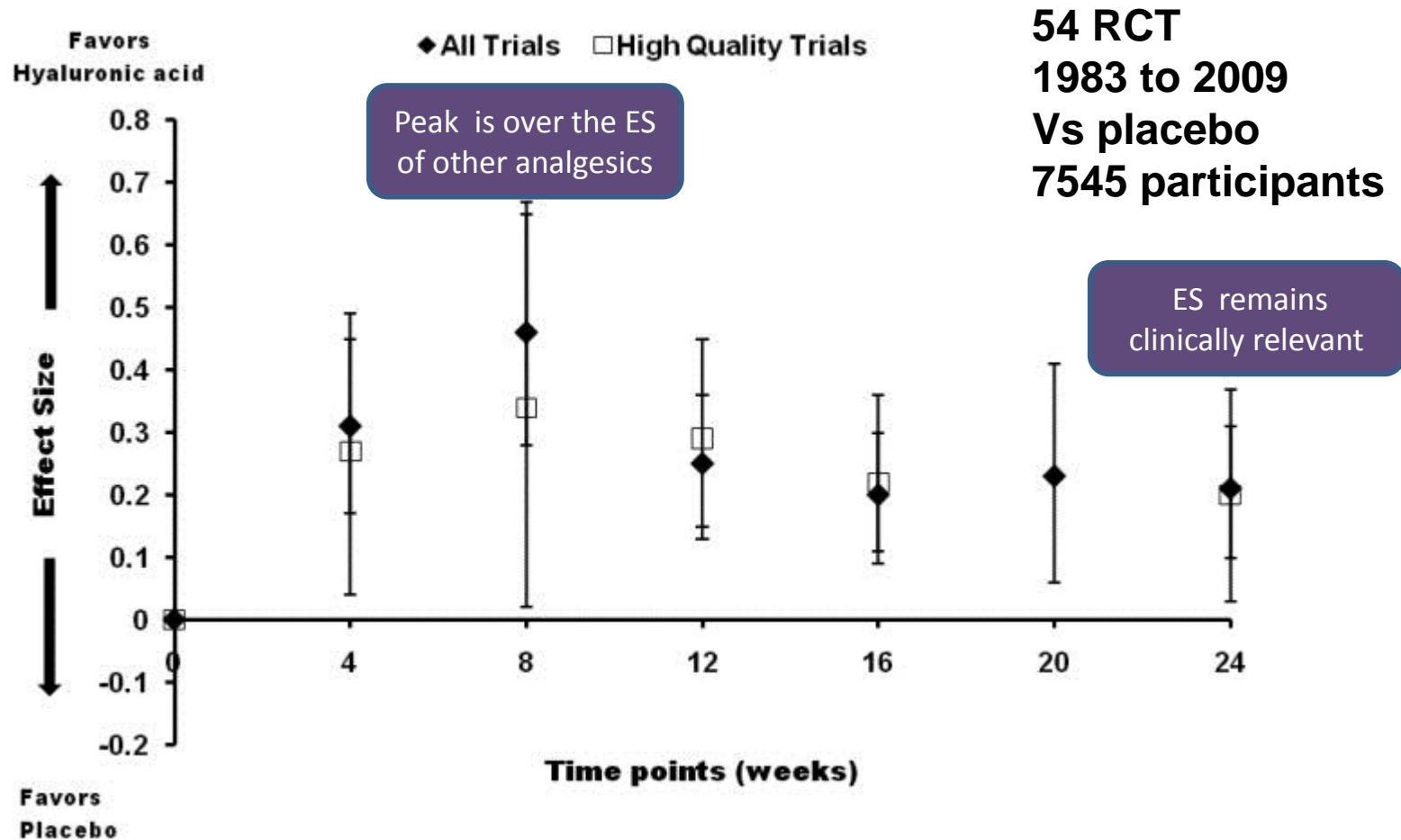
ES < 0.2 = None
 ES 0.2 – 05 = Weak
 ES 0.5 – 08 = Moderate
 ES > 08 = Strong

**versus placebo
 at 1-4 weeks**

*All Studies

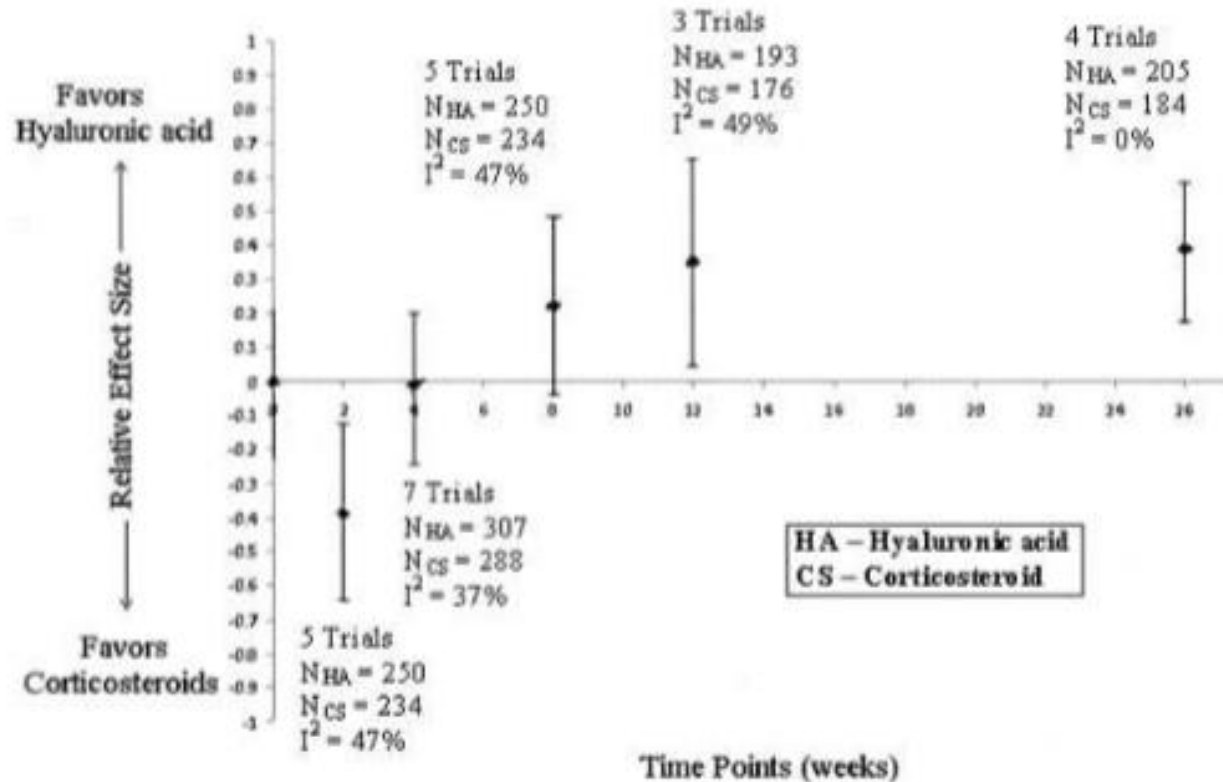
**IAHA effect size is superior to NSAIDs with less GI adverse events
 HA improves pain and function in knee OA**

Bannuru meta-analysis knee OA



AH vs corticostéroïdes

Zhang W. et al. Osteoarthritis & Cartilage 2010; 18: 473-475.



Comparing with intra-articular corticosteroids, benefits last generally longer!

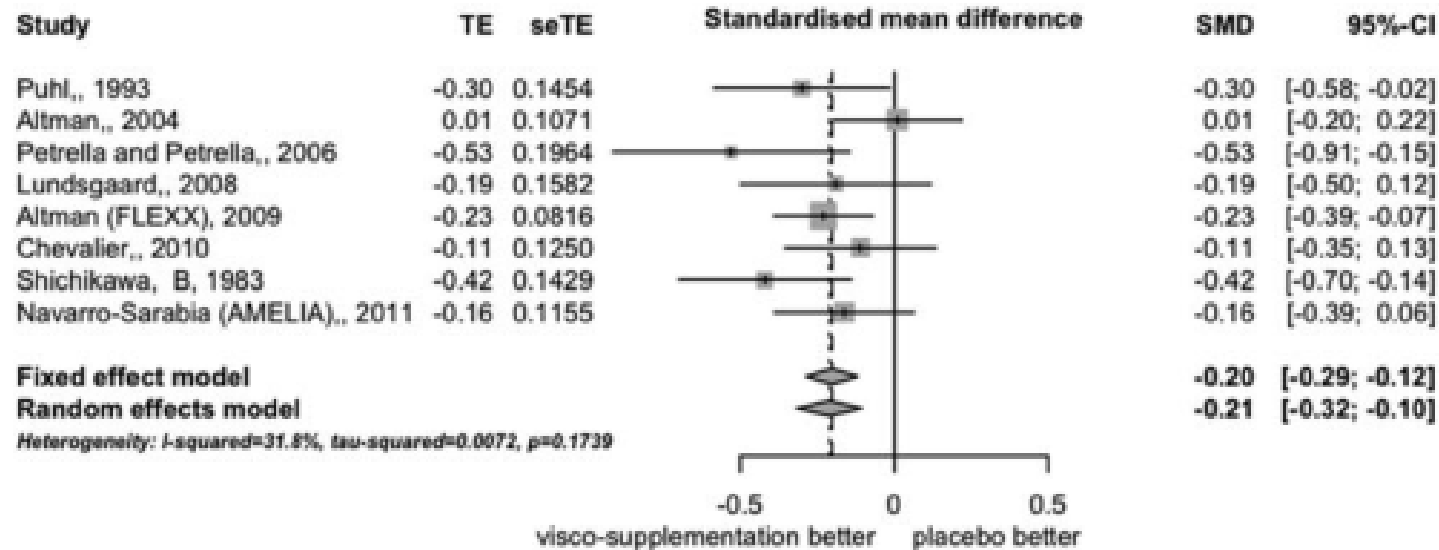
**RMD
Open**

Rheumatic &
Musculoskeletal
Diseases

EXTENDED REPORT

Hyaluronan for knee osteoarthritis: an updated meta-analysis of trials with low risk of bias

Pascal Richette,^{1,2} Xavier Chevalier,³ Hang Korng Ea,^{1,2} Florent Eymard,³
Yves Henrotin,⁴ Paul Ornetti,⁵ Jérémie Sellam,⁶ Michel Cucherat,⁷ Marc Marty,³
On behalf of the French OsteoArthritis study group



8 RCT : ES = 0,21 vs Placebo à 3 mois

Knee: HA in recent guidelines

Society		Guidelines
ACR (2012)	American College of Rheumatology	« Conditionnally recommended to not use »
AAOS (2013)	American Association of Orthropaedic Surgeons	« Not recommended »
NICE (2014)	National Institute for Health and Clinical Excellence	« Do not offer intra-articular injection of hyaluronan for the management of OA »
OARSI (2014)	Osteoarthritis Research Society International	« Uncertain » let to the appreciation of the physician
« ...iatrogenesis due to the overuse of NSAIDS, paracetamol and corticosteroids infiltration... » Letter of the « Section arthrose » of the French Society of Rheumatology to CNEDIMTS		



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journal homepage: www.elsevier.com/locate/semarthrit



Consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis

Yves Henrotin, MD^{a,b}, Raghu Raman, MD^c, Pascal Richette, MD^{d,e}, Hervé Bard, MD^f, Jörg Jerosch, MD^g, Thierry Conrozier, MD^{h,*}, Xavier Chevalier, MDⁱ, Alberto Migliore, MD^j

Viscosupplementation, when administered at early stages of OA, may have a chondroprotective effect

Viscosupplementation is a “positive” indication. It is not a “lack of anything better” indication

Excluding knee (i.e., hip, shoulder, ankle, and trapezio-metacarpal joint), viscosupplementation should always be achieved under fluoroscopy or ultrasound guidance

When viscosupplementation is performed under fluoroscopy, the amount of radio-opaque contrast agent must be as low as possible

Viscosupplementation is a cost-effective treatment for knee osteoarthritis



Cost-effectiveness analysis of intra-articular injections of a high molecular weight bioengineered hyaluronic acid for the treatment of osteoarthritis knee pain

Hind T. Hatoum, Anke L. Fierlinger, Swu-Jane Lin & Roy D. Altman



Conclusions

Results from this cost-effectiveness analysis demonstrate that BioHA injection in patients with OA of the knee with inadequate response to conventional therapies is a viable option in terms of both efficacy and cost. When compared with conventional care with NSAIDs and analgesics, BioHA was a dominant treatment strategy. When compared with conventional care with NSAIDs, analgesics, corticosteroids, and surgical options, BioHA was still the cost-effective strategy.

Early Decrease of Serum Biomarkers of Type II Collagen Degradation (Coll2-1) and Joint Inflammation (Coll2-1 NO₂) by Hyaluronic Acid Intra-Articular Injections in Patients With Knee Osteoarthritis: A Research Study Part of the Biovisco Study

Y. Henrotin,¹ X. Chevalier,² M. Deberg,³ J.C. Balblanc,⁴ P. Richette,⁵ D. Mulleman,⁶ B. Maillet,⁷ F. Rannou,⁸ C. Piroth,⁹ P. Mathieu,¹⁰ T. Conrozier¹¹ and On behalf of the Osteoarthritis Group of the French Society of Rheumatology

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EPIKART

Annals of the Rheumatic Diseases

Early Effect of Hyaluronic Acid Intra-Articular Injections on Serum and Urine Biomarkers in Patients with Knee Osteoarthritis: An Open-Label Observational Prospective Study

Thierry Conrozier,¹ Jean-Charles Balblanc,² Pascal Richette,³ Denis Mulleman,⁴ Bernard Maillet,⁵ Yves Henrotin,⁶ Francois Rannou,⁷ Catherine Piroth,⁸ Pascal Hilliquin,⁹ Pierre Mathieu,¹ Anne Walliser-Lohse,² Isabelle Rousselot,¹⁰ Valerie Plattner,¹¹ Jean-François Maillefer,^{9,12} Eric Vignon,¹ Xavier Chevalier¹³ and on behalf of the Osteoarthritis Group of the French Society of Rheumatology

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ed 19 May 2011; accepted 5 October 2011

Extended report: Reduction of the Serum Levels of a Specific Biomarker of Cartilage Degradation (Coll2-1) by Hyaluronic Acid (KARTILAGE® CROSS) Compared to Placebo in Painful Knee Osteoarthritis Patients: the EPIKART Study

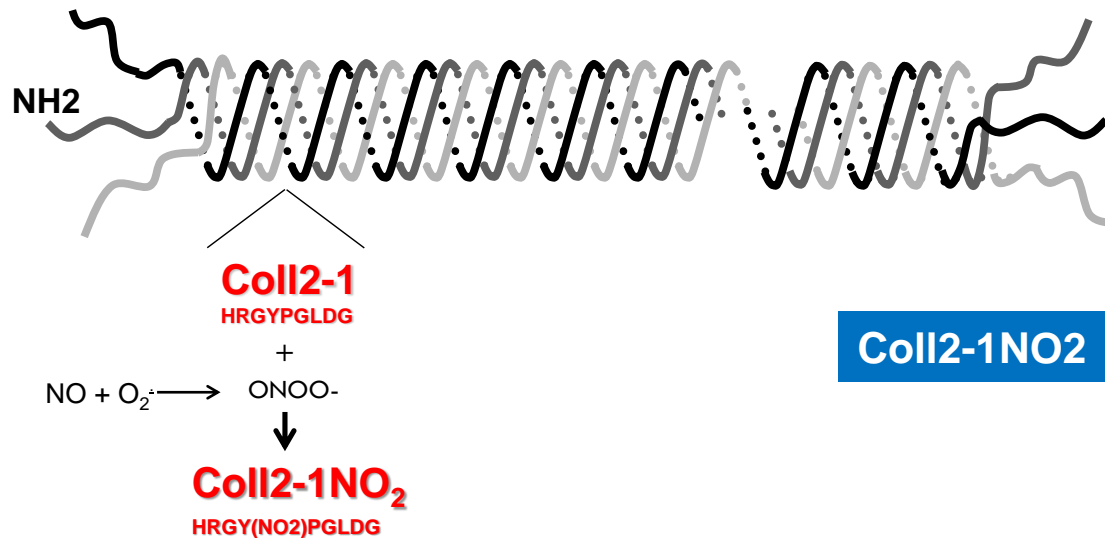
Yves Henrotin¹, Francis Berenbaum², Xavier Chevalier³, Marc Marty³, Pascal Richette⁴, François Rannou⁵

1. Bone and Cartilage Research Unit, Arthropole Liège, CHU Sart-Tilman, Liège, Belgium ;
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5. University Paris Descartes, PRES Sorbonne Paris Cité, Service de rééducation et réadaptation de l'appareil locomoteur et des pathologies du rachis, Hôpital Cochin, AP - HP, INSERM UMR-S-1124, UFR Biomédicale des Saints Pères, Paris, France

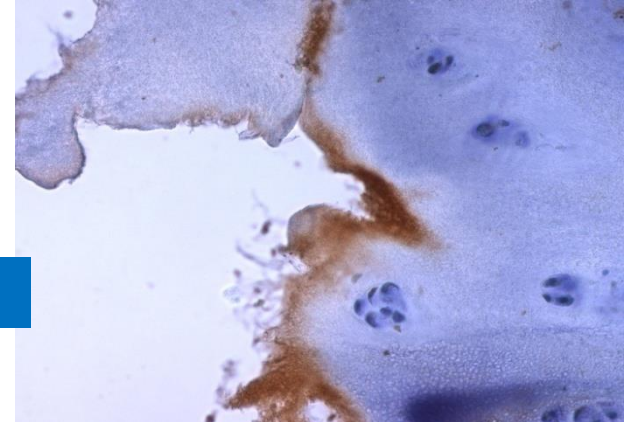
BIOVICO

HA on
Biomarkers

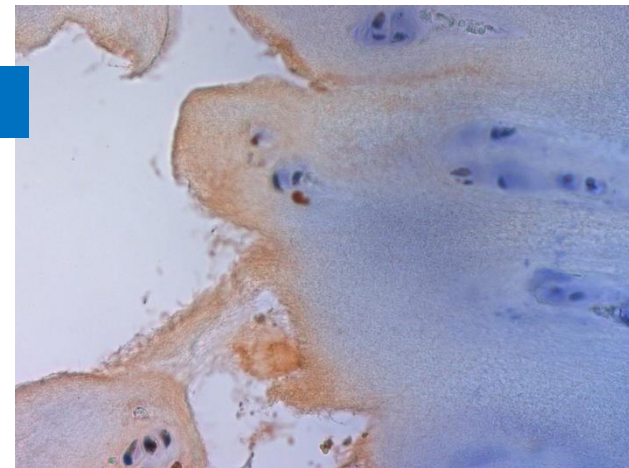
Coll2-1 and Coll2-1NO₂: two cartilage specific biomarkers



Coll2-1NO₂



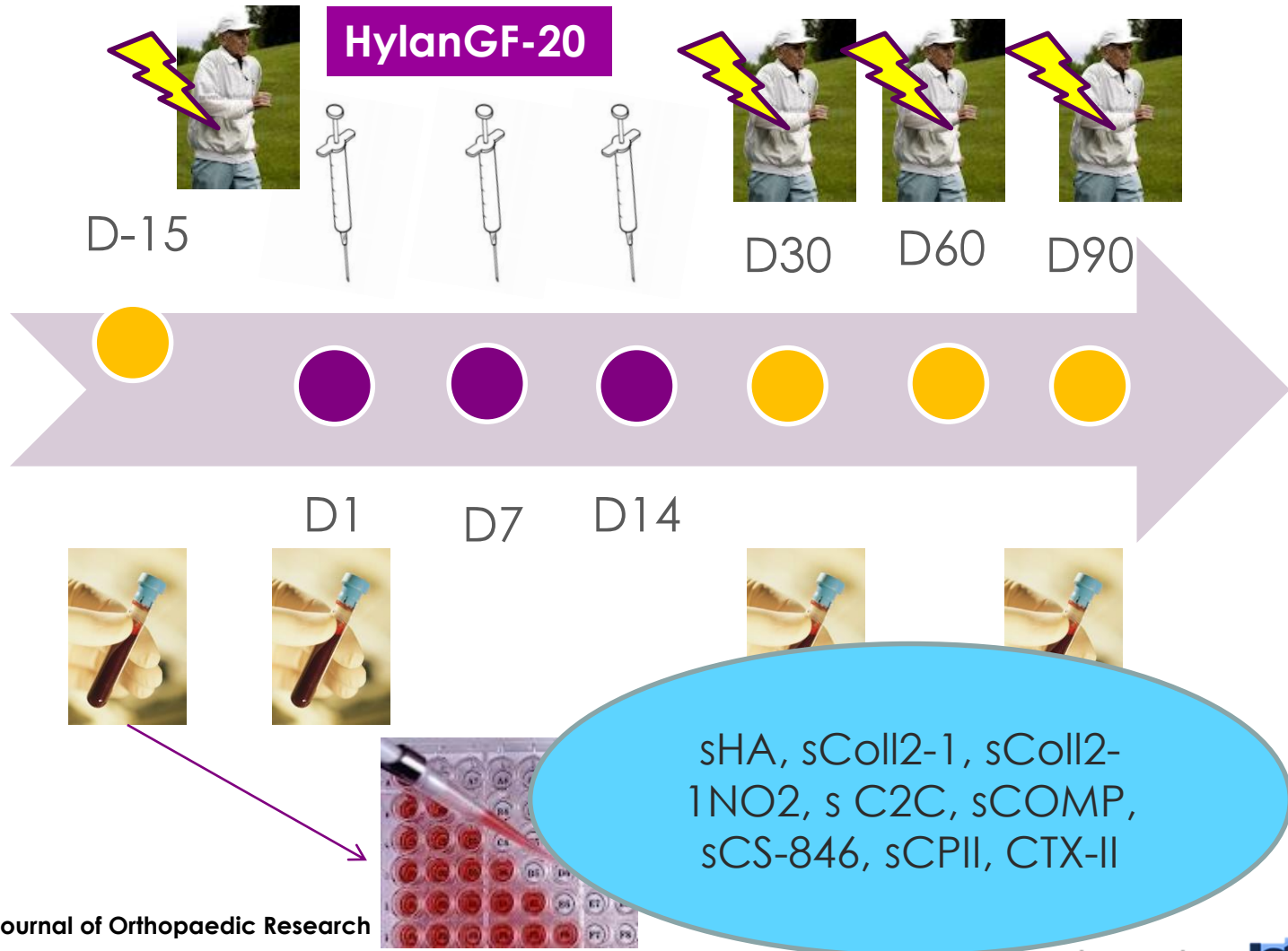
Coll2-1



- Specific of degraded cartilage
- Measure cartilage catabolism

BIOVISCO study: Study design

Open-label, observational prospective study





BIOVISCO study

An open label observational prospective study

Conrozier et al, J Orthp Res, 2012; Henrotin et al, J Orthp Res, 2013.

- ✓ 45 patients with unilateral symptomatic tibiofemoral and/or patellofemoral OA
- ✓ 3-weekly intraarticular injection of hyalan G20 (Synvisc®)
- ✓ Follow-up D1, D30 and D90 after the last injection

	D1 (after the last injection)	90 days (after the last injection)	p-Value D1 vs D90
sColl2-1 (nM)	140.34(882.44-285.32)	128.41 (85.6-241.34)	0.05*
sColl2-1NO2 (nM)	0.400 (0.050-1.010)	0.370 (0.14-0.870)	0.025*
uCTX-II (ng/nmolcreat)	392.7 (90.0-816.4)	306.0 (90-1123.9)	0.02*
sPIICP (ng/ml)	817.9 (131.4-1848.6)	874.8.3 (326.4-1435.0)	0.41
sC2C (ng/ml)	223.6 (99.4-329)	209.5 (135.9-291.7)	0.11
sCOMP (U/L)	10.9 (6.0-20.2)	10.5 (6.0-20.0)	0.82
sCS846 (ng/ml)	99.8 (45.9-172.3)	102.2 (53.0-190)	0.38
sHA (ng/ml)	34.1 (15.4-211)	33.3 (9.5-230.1)	0.38



The EPIKART study

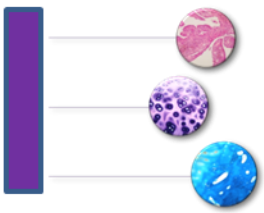
- A 6-month prospective, randomized, double blind, controlled study
- A single injection of KARTILAGE®Cross or saline solution

KARTILAGE®Cross

- 2.2 ml (16 mg HA/ml)
Reticulated
- Biofermentation
- Mannitol (35 mg/g of gel)

- PRIMARY OUTCOME

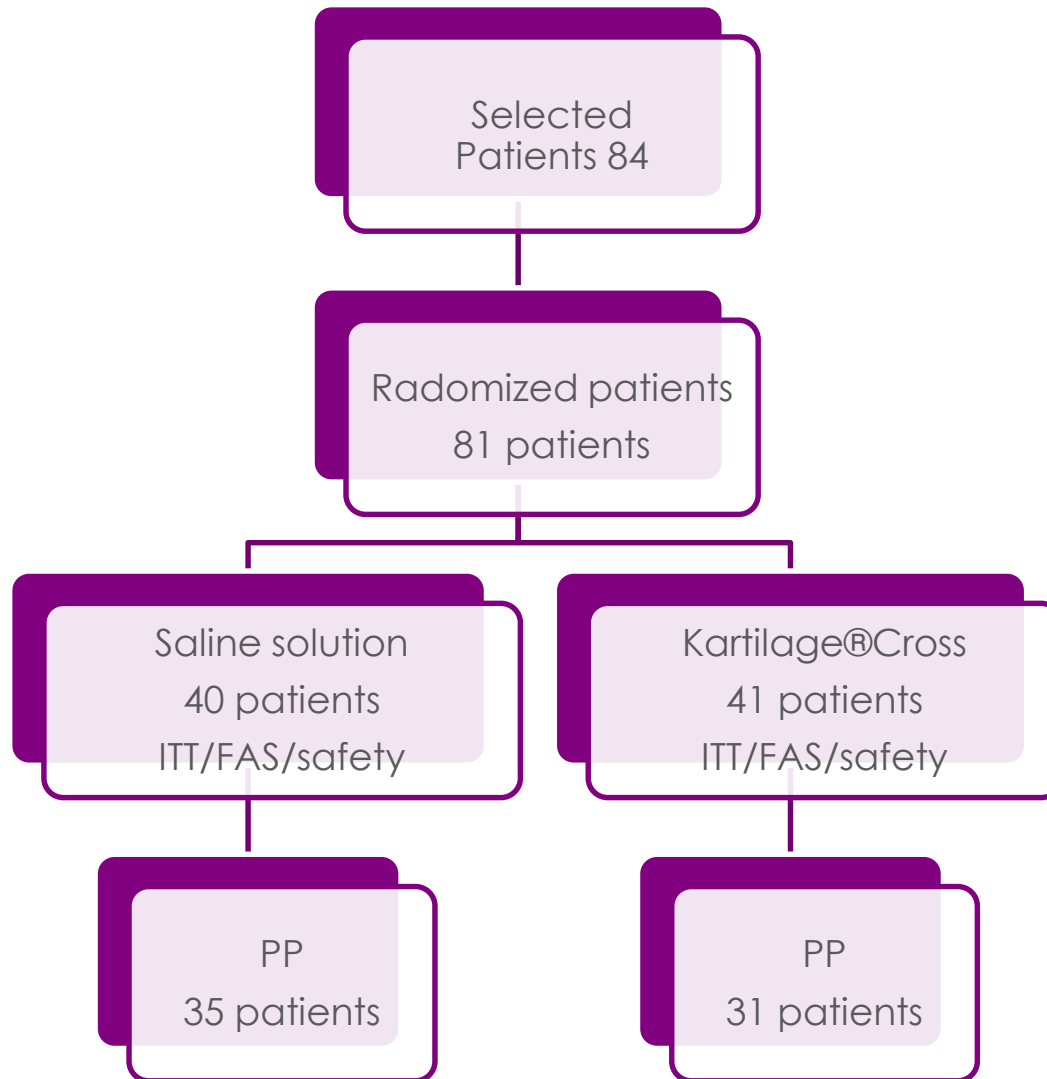
- *the variation of Coll2-1 in serum between inclusion visit (D-10) and D90 (3 months after injection)*



Inclusion criteria

- Men or women aged between 45 and 80 years old
- With symptomatic femoro-tibial OA
- VAS > 40 mm
- K&L II or III

Flow Chart



EPIKART : Study design

Lequesne Index
Global patient assessment



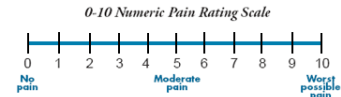
D-10

**Kartilage®
Cross**



Safety

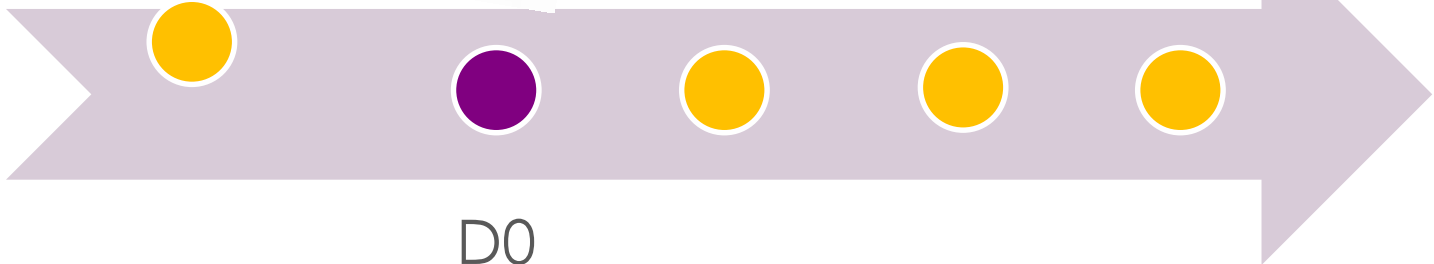
Lequesne Index
Global patient assessment
Safety



D30

D90

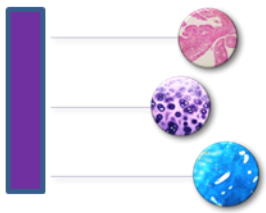
D180



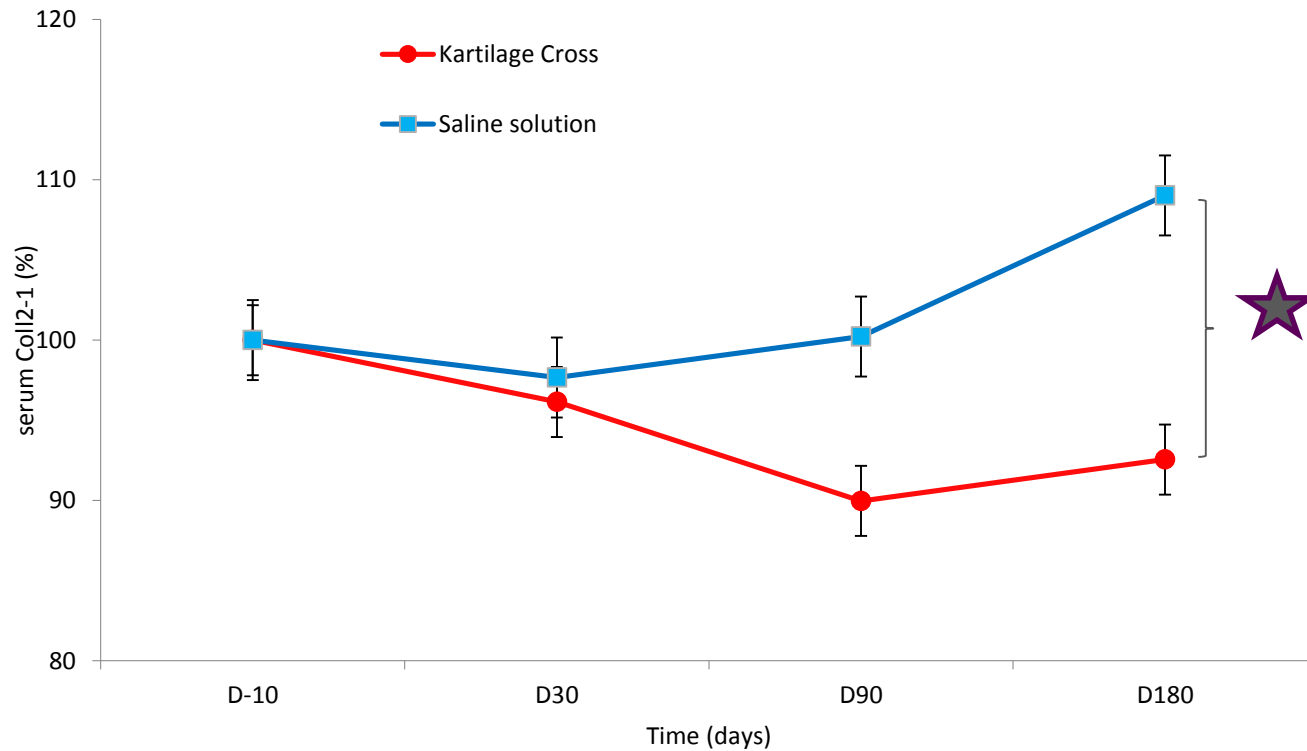
D0



sColl2-1, sColl2-1NO2, MPO, usCRP



Coll2-1 variation with time



Conclusions

- IAHA is efficient and well tolerated
- IAHA is a cost-effectiveness treatment
- The efficacy is moderate on pain and function
- The efficacy is superior to NSAIDS at 1-month
- Prolonged effect compared to corticosteroids
- Indication and efficacy should be evaluated at individual levels (biomarkers – theranostic)



Bone and Cartilage Research Unit



MERCI!

International collaborations:

- F Blanco (La coruna, Spain)
- T Conrozier (CHU Lyon, France)
- V Kraus (Duke University, USA)
- L Punzi (University of Padova, Italy)
- A Mobasher (University of Nottingham, UK)
- J Monfort (Hospital del mare (Spain)
- P Richette (Lariboisiere, France)
- J Runhaar (Erasmus MC, Rotterdam)

