HA INTRAARTICULAR INJECTION:
THERAPEUTIC AND ECONOMIC CONSIDERATIONS
Osteoarthritis
A complexe and severe disease

- Sarcopenia
- Ligament hyper laxity
- Pain
- Tendinopathy
- Kinesiophobia
- Metabolic syndrome
- Obesity
- Cardio-vascular disease
- Sedentarity
- Physical deconditioning
- Inflamminating
  - Meta-inflammaging
  - Cartilage degradation
  - Subchondral bone sclerosis
  - Synovial inflammation

A global representation

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Non-surgical treatments

IA

Limitations

HA & CS
Invasive
Side effects (Infection, inflammation)
Contre-indications (Diabetes)

SYSADOA
No adverse effects
Slow and delayed action
Moderate efficacy

NSAIDS
GI bleeding or other complications
CV risks
Renal complications

Acetaminophen
Hepatotoxicity

Weight loss, physical activity, exercises, education, information
Poor patient compliance

Symptomatic effects

Loss of Synovial fluid lubrication properties

<table>
<thead>
<tr>
<th>Synovial fluid: composition and properties</th>
<th>Healthy patient</th>
<th>Patient with osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mw (MDa)</td>
<td>4 – 6</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>HA (mg/ml)</td>
<td>2.5 – 4</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Elastic modulus (Pa à 2.5 Hz)</td>
<td>Close to 100</td>
<td>Close to 8</td>
</tr>
<tr>
<td>Viscous modulus (Pa à 2.5 Hz)</td>
<td>Close to 45</td>
<td>Close to 5</td>
</tr>
<tr>
<td>Viscosity at rest (Pa.s)</td>
<td>2 – 40</td>
<td>0.1 à 1</td>
</tr>
</tbody>
</table>

Pa: Pascal
Hz: Hertz
Pa.s: Pascal seconds

Synovial membrane

**IL-1β, IL-6, IL-8, PGE₂, MMP, ROS**

- Complement deposition
- Toll-like receptor

**Fibroblast**

**Macrophiages**

**Lymphocyte nodes**

**Chondrocytes**

**Cartilage**

**Synovial fluid**

**Degradation Products Microcrystals**

↓**Hyaluronic acid**

↓Molecular weight Loss of SF viscosity

↓**Molecular weight Loss of SF viscosity**

**Hyaluronidase**

↓**Molecular weight Loss of SF viscosity**

**Syovial fluid**

**Vessels**
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

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-1β activity)

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

(Zhang et al, 2010)

<table>
<thead>
<tr>
<th></th>
<th>ES Pain</th>
<th>ES Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>0.14 (0.05,0.23)</td>
<td>0.09 (-0.03,0.22)</td>
</tr>
<tr>
<td>Diacerein</td>
<td>0.24 (0.08, 0.39)</td>
<td>0.14 (0.03, 0.26)</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td><strong>0.29 (0.22,0.35)</strong></td>
<td>-</td>
</tr>
<tr>
<td>Aerobic</td>
<td>0.52 (0.34; 0.70)</td>
<td>0.46 (0.25, 0.67)</td>
</tr>
<tr>
<td>Glucosamine Sulfate</td>
<td>0.58 (0.30, 0.87)</td>
<td>0.07 (-0.08,0,021)</td>
</tr>
<tr>
<td><strong>IAHA</strong></td>
<td><strong>0.60 (0.37, 0.83)</strong></td>
<td><strong>0.61 (0.35,0.87)</strong></td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>0.75 (0.50, 1.01)</td>
<td>-</td>
</tr>
</tbody>
</table>

*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

54 RCT
1983 to 2009
Vs placebo
7545 participants

Peak is over the ES of other analgesics

ES remains clinically relevant
Comparing with intra-articular corticosteroids, benefits last generally longer!
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

<table>
<thead>
<tr>
<th>Society</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR (2012)</td>
<td>« Conditionnally recommended to not use »</td>
</tr>
<tr>
<td>AAOS (2013)</td>
<td>« Not recommended »</td>
</tr>
<tr>
<td>NICE (2014)</td>
<td>« Do not offer intra-articular injection of hyaluronan for the management of OA »</td>
</tr>
<tr>
<td>OARSI (2014)</td>
<td>« Uncertain » let to the appreciation of the physician</td>
</tr>
</tbody>
</table>

« ...iatrogenesis due to the overuse of NSAIDS, paracetamol and corticosteroids infiltration... » Letter of the « Section arthrose » of the French Society of Rheumatology to CNEDIMTS
Consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis

Yves Henrotin, MD\textsuperscript{a,b}, Raghu Raman, MD\textsuperscript{c}, Pascal Richette, MD\textsuperscript{d,e}, Hervé Bard, MD\textsuperscript{f}, Jörg Jerosch, MD\textsuperscript{g}, Thierry Conrozier, MD\textsuperscript{h,*}, Xavier Chevalier, MD\textsuperscript{i}, Alberto Migliore, MD\textsuperscript{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. Mullenan, 6 B. Maillet, 7 F. Rannou, 8 C. Piroth, 9 P. Mathieu, 10 T. Conrozier 11 and On behalf of the Osteoarthritis Group of the French Society of Rheumatology

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Received 19 December 2011; accepted 27 November 2012
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/acr.22297

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 Mullenan, 6 Bernard Maillet, 5 Yves Henrotin, 6 François Rannou, 5 Catherine Piroth, 8 Pascal Hilliquin, 5 Pierre Mathieu, 6 Anne Walliser-Löhse, 2 Isabelle Rousselot, 10 Valerie Plattner, 11 Jean-François Maillefer, 2, 12 Eric Vignon, 1 Xavier Chevalier 13 and on behalf of the Osteoarthritis Group of the French Society of Rheumatology

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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 Henrotin 1, Francis Berenbaum, 2 Xavier Chevalier, 3 Marc Marty, 3 Pascal Richette 2, François Rannou 1

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

- Specific of degraded cartilage
- Measure cartilage catabolism

Coll2-1

HRGYPGLDG

NH2

Coll2-1NO2

HRGY(NO2)PGLDG

NO + O2 → ONOO-

Coll2-1NO2
BIOVISCO study: Study design
Open-label, observational prospective study

D-15  D1  D7  D14  D30  D60  D90

HylanGF-20

sHA, sColl2-1, sColl2-1NO2, s C2C, sCOMP, sCS-846, sCPII, CTX-II

Henrotin Y et al. Journal of Orthopaedic Research
19 FEB 2013
**BIOVISCO study**

An open label observational prospective study


- 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

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

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The EPIKART study

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

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

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

Selected Patients 84

Randomized patients 81 patients

Saline solution
40 patients
ITT/FAS/safety

Kartilage®Cross
41 patients
ITT/FAS/safety

PP
35 patients

PP
31 patients
EPIKART: Study design

Lequesne Index
Global patient assessment

Kartilage® Cross

Safety

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

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Coll2-1 variation with time

- **Kartilage Cross**
- **Saline solution**

**Time (days)**: D-10, D30, D90, D180

**serum Coll2-1 (%)**
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)
International collaborations:
F Blanco (La coruna, Spain)
T Conrozier (CHU Lyon, France)
V Kraus (Duke University, USA)
L Punzi (University of Padova, Italy)
A Mobasheri (University of Nottingham, UK)
J Monfort (Hospital del mare (Spain)
P Richette (Lariboisiere, France)
J Runhaar (Erasmus MC, Rotterdam)