HA VISCOSUPPLEMENTATION IN OA TREATMENT
PR YVES HENROTIN
**Synovial membrane**

- **IL-1β**
- **IL-6**
- **IL-8**
- **PGE₂**
- **MMP**
- **ROS**

**Complement deposition**

**Fibroblast**

**Toll-like receptor**

**Hyaluronisase**

**↓Hyaluronic acid**

**↓Molecular weigh**

**Loss of SF viscosity**

**Degradation Products Microcrystals**

**Cartilage**

**Chondrocytes**

**MMP**

**ROS**

**Synovial fluid**

**Lymphocyte nodes**

**macrophages**

**Vessels**
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>
<tr>
<td></td>
<td>5 Pa.s à 37 °C</td>
<td></td>
</tr>
</tbody>
</table>

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

HYALURONIC ACID

- Synthesized by synoviocytes (B)
- Released into the synovial space
- HA belongs to the family of glycosaminoglycans
- HA is composed of 1000s of repeating disaccharide units (N-acetylglucosamine and glucuronic acid)
- A long polysaccharide chain of different length with a high molecular weight
- Accumulates on cartilage and ligament surfaces (boundary-layer lubrication)
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

Mechanical effects

- Rheologic properties of the synovial fluid (visco-elastic)
- Shock absorbing (cushion)
- Lubrication

Viscoinduction

• The clinical benefits of intra-articular HA (e.g. restoration synovial cell metabolism, normalization HA biosynthesis) that go well beyond the physical lubricant/cushioning effect are defined as **VISCOINDUCTION**.

• Viscoinduction ensures that the effect is maintained for several months despite the short half-life of intra-articular HA

Biological activities

Clustering of CD44

Homeostasis

ROS IL-1

↑MMP-3
↑Aggrecanases
↑HAS2
↑Collagen II

High MW HA

Small oligosaccharides

CD44

Small oligosaccharide

NF-kB
# Biological activity of HA

## Cartilage

<table>
<thead>
<tr>
<th>HA Type</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>High MW HA</td>
<td>↑ Proteoglycan production</td>
</tr>
<tr>
<td></td>
<td>↓ NO induced chondrocyte apoptosis</td>
</tr>
<tr>
<td>Small HA oligosaccharides</td>
<td>↑ Aggrecanases</td>
</tr>
<tr>
<td></td>
<td>↑ MMP-3</td>
</tr>
<tr>
<td></td>
<td>↑ HAS-2</td>
</tr>
<tr>
<td></td>
<td>↑ Type II collagen</td>
</tr>
</tbody>
</table>

## Bone

![Toll-like receptors diagram]

- CD44
- RHAMM

## Synovial membrane

<table>
<thead>
<tr>
<th>HA Type</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>High MW HA (&gt;500kDa)</td>
<td>↑ HA synthesis</td>
</tr>
<tr>
<td></td>
<td>↓ Leukocytes migration and proliferation</td>
</tr>
<tr>
<td></td>
<td>↓ Production of inflammatory and catabolic mediators</td>
</tr>
<tr>
<td>Small HA oligosaccharides</td>
<td>↑ Angiogenesis</td>
</tr>
</tbody>
</table>
HA: different forms?

- Molecular weight: 0.7 to 92 Mda
- Concentration: 0.8 to 2%
- Prize: 0.83 to 4.13 € per mg.
- Chemical form: linear or cross-linked
- Origin: bacterial or animal
- Injection protocol: multiple or mono
<table>
<thead>
<tr>
<th>Trade name</th>
<th>Company</th>
<th>Vol/Conc. MI/%</th>
<th>MW MDa</th>
<th>Nb of Injection</th>
<th>Price/injection</th>
<th>Price/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adant</td>
<td>Sankyo</td>
<td>2.5 (1)</td>
<td>0.9 – 1.2</td>
<td>5</td>
<td>100</td>
<td>1.33</td>
</tr>
<tr>
<td>Arthrum</td>
<td>LCA</td>
<td>2 (2)</td>
<td>2.4</td>
<td>3</td>
<td>100</td>
<td>0.83</td>
</tr>
<tr>
<td>Durolane</td>
<td>Genévrier</td>
<td>3 (2)</td>
<td>92</td>
<td>1</td>
<td>230</td>
<td>3.83</td>
</tr>
<tr>
<td>Euflexxa</td>
<td>Grunenthal</td>
<td>2 (1)</td>
<td>3</td>
<td>3</td>
<td>120</td>
<td>2</td>
</tr>
<tr>
<td>Go-On</td>
<td>Rottapharm</td>
<td>2.5 (1)</td>
<td>1.4</td>
<td>3</td>
<td>100</td>
<td>1.33</td>
</tr>
<tr>
<td>HappyCross</td>
<td>LABRHA</td>
<td>2 (1.6)</td>
<td>1.5</td>
<td>1</td>
<td>159</td>
<td>1.71</td>
</tr>
<tr>
<td>Hyalgan</td>
<td>Expanscience</td>
<td>2 (1)</td>
<td>0.5-0.7</td>
<td>3-5</td>
<td>88.32</td>
<td>1.47</td>
</tr>
<tr>
<td>Ostenil</td>
<td>TRB Chemica</td>
<td>2 (1)</td>
<td>1.2</td>
<td>3-5</td>
<td>100</td>
<td>1.66</td>
</tr>
<tr>
<td>Sinovial</td>
<td>Genévrier</td>
<td>2 (0.8)</td>
<td>0.8-1.2</td>
<td>3</td>
<td>100</td>
<td>2.08</td>
</tr>
<tr>
<td>Structovial</td>
<td>Pierre Fabre</td>
<td>2 (1)</td>
<td>1.6</td>
<td>3</td>
<td>100</td>
<td>1.66</td>
</tr>
<tr>
<td>Synocrom</td>
<td>Pierre Fabre</td>
<td>2 (1)</td>
<td>1.6</td>
<td>3</td>
<td>100</td>
<td>1.66</td>
</tr>
<tr>
<td>Synvisc One</td>
<td>Sanofi</td>
<td>6 (0.8)</td>
<td>6</td>
<td>1</td>
<td>198.5</td>
<td>4.13</td>
</tr>
</tbody>
</table>
# Mono-injection

<table>
<thead>
<tr>
<th>Trade name</th>
<th>concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synvisc One®</td>
<td>6 ml/48 mg</td>
</tr>
<tr>
<td>Durolane</td>
<td>3 ml/20 mg</td>
</tr>
<tr>
<td>Arthrum 2.5%®</td>
<td>3 ml/25 mg</td>
</tr>
<tr>
<td>Coxarthrum 2.5%®</td>
<td>3 ml/50 mg</td>
</tr>
<tr>
<td>Ostenil Plus®</td>
<td>2 ml/mannitol</td>
</tr>
<tr>
<td>Synocrom Forte One</td>
<td>4 ml/ 2%</td>
</tr>
<tr>
<td>Happy Cross®</td>
<td>2.2 ml/cross linked/mannitol</td>
</tr>
</tbody>
</table>

- Cross-linked
- Increased concentration
- Anti-oxidant (sorbitol or mannitol)
### Antioxidant to protect HA

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Company</th>
<th>Form</th>
<th>Injection protocol</th>
<th>Indication</th>
<th>[HA&amp;AO]</th>
<th>AO molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Happy Cross®</td>
<td>LABRHA</td>
<td>Cross-L</td>
<td>1/ 2.2 ml</td>
<td>Hip, ankle, shoulder</td>
<td>1.6 %   3.5 %</td>
<td>Mannitol</td>
</tr>
<tr>
<td>HappyMini®</td>
<td>LABRHA</td>
<td>Cross-L</td>
<td>1/ 1 ml</td>
<td>Thumb, TM, big toe</td>
<td>1.6 %   3.5 %</td>
<td>Mannitol</td>
</tr>
<tr>
<td>HappyVisc®</td>
<td>LABRHA</td>
<td>Linear</td>
<td>3/ 2 ml</td>
<td>Knee</td>
<td>1.55 %  3.5 %</td>
<td>Mannitol</td>
</tr>
<tr>
<td>Ostenil Plus®</td>
<td>TRB Chemedica</td>
<td>Linear</td>
<td>1-3/ 2ml</td>
<td>Knee, Hip, Ankle, shoulder</td>
<td>2 %     0.5 %</td>
<td>Mannitol</td>
</tr>
<tr>
<td>Synolis VA Go-On matrix®</td>
<td>APTISSEN</td>
<td>Linear</td>
<td>1-3/ 2ml</td>
<td>knee</td>
<td>2 %     4 %</td>
<td>Sorbitol</td>
</tr>
</tbody>
</table>
IAHA has a moderate effect on knee OA symptoms OARSI meta-analysis

(Zhang et al, 2010)

<table>
<thead>
<tr>
<th>Treatment</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>NSAIDs</td>
<td>0.29 (0.22,0.35)</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>IAHA</td>
<td>0.60 (0.37, 0.83)</td>
<td>0.61 (0.35,0.87)</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
### Knee OARSI GUIDELINES

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Treatment</th>
<th>ES Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>In favour of IA Corticosteroids</td>
<td>0.39 (0.12-0.65)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>=</td>
<td>0.01 (-0.21,0.23)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>In favour of IAHA</td>
<td>0.22 (-0.5 ,0.49)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>In favour of IAHA</td>
<td>0.35 (0.03, 0.66)</td>
</tr>
</tbody>
</table>

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

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 corticostéroids infiltration... » Letter of the « Section arthrose » of the French Society of Rheumatology to CNEDIMTS
OA treatments and limitations

**Benefits**
- Intraarticular steroids, viscosupplements
- Topical NSAIDs, SASYDOA
- Prescription NSAIDs
  - Including COXIB
- OTC NSAIDs
- Acetaminophen
- Patient education, physical and occupational Therapy, weight

**Risks**
- Surgery

**Limitations**
- Costly, invasive procedure
- Primarily indicated for «end stage » OA
- GI bleeding or other complications
- CV risks
- Renal complications
- GI bleeding or other complications
- CV risks
- Renal complications
- Hepatotoxicity
- Poor patient compliance

OA treatments and limitations

Benefits

- Intraarticular steroids, viscosupplements
- Topical NSAIDs, S charged as OA

Risks

- GI bleeding or other complications
- CV risks
- Renal complications

Limitations

- Costly, invasive procedure
- Primarily indicated for «end stage» OA
- GI bleeding or other complications
- CV risks
- Renal complications
- Hepatotoxicity
- Poor patient compliance

Viscosupplementation

• INDICATIONS
  → Treatment of symptoms associated with OA

• CONTRAINDICATIONS
  → On-going joint inflammation (active synovitis)
  → Crystals-induced arthropathy (gout, pseudogout)
  → Infection
  → Anticoagulant treatments
  → Allergy to poultry
Predictors of good outcome

- Mild to moderate joint deformities
- Absence of large synovial effusion
- Well-preserved periarticular muscle mass
- Minimal joint instability

BMI > 30

K & L 4 No joint space
Conclusions

• IAHA is efficient and well tolerated
• The efficacy is moderate on pain and function
• Prolonged effect compared to corticosteroids
• The injection protocol should be assessed and respected
• Should be favor US guidance
• Indication and efficacy should be evaluated at individual levels (biomarkers – theranostic)
Viscosupplementation: new directions

**Present**

**HYALURONIC ACID**
- Animal origin
- Bacterial fermentation
- Chemically Cross-linked

**HA PROTECTION**
- Manitol
- Sorbitol
- Tocopherol

**Future**

**DRUGS/ANTIBODY DELIVERY**
- NSAIDS/Coxibs
- Chlonidine
- Triamcinolone
- Doxycycline
- ⊕ Chondroitin sulfate
- ADAMTS inhibitors

**NEW MOLECULES**
- ⊕ Chitosan (Arthrovisc)
- Lubricine
- Polynucleotides (Chondrotide)
Perspectives

So...What’s about the future?

Viscosupplementation
Tribosupplementation
Drug delivery system
Biologic therapy

« Breakthough » product
Indication

Perhaps not only a dream!
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)