Recent advances and innovation in viscosupplementation

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Synovial membrane

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

Complement deposition

- Toll-like receptor

Fibroblasts

- ROS

Hyaluronidase

- ↓ Hyaluronic acid

- ↓ Molecular weight
  - Loss of SF viscosity

Degradation Products

Microcrystals

Chondrocytes

Cartilage

MMP

ROS

Lymphocyte nodes

macrophages
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: limitations and needs

- Low residency time
- Low to moderate clinical efficacy
- Not recommended in recent guidelines

Need of new products

- with a longer residency time
- a better clinical efficacy
- a disease modifying effect
Viscosupplementation: new directions

**Present**

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

**Future**

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

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

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

www.bcru.be
HA+CS (Structovial CS)
A pilot open uncontrolled study

- 30 patients with femoro-tibial OA
- 2 ml containing 24 mg HA and 60 mg CS
- 3 injections on a weekly basis

Henrotin et al. BMC research Notes, 2012
HA+CS
Pain intensity

80 % reach a clinical response according OARSI/OMERACT criteria
HA + CS
Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>(\Delta T0 - T12)</th>
<th>Trends</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coll2-1 (nM)</td>
<td>-11 ± 78</td>
<td>↓</td>
<td>Degradation</td>
</tr>
<tr>
<td>Coll2-1NO2 (nM)</td>
<td>-0.06 ±0.41</td>
<td>↓</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>CS-846 (ng/ml)</td>
<td>+1± 17</td>
<td>↑</td>
<td>Synthesis</td>
</tr>
<tr>
<td>CPII ng/ml)</td>
<td>-41± 867</td>
<td>↓</td>
<td>Synthesis</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>-5667± 21769</td>
<td>↓↓↓</td>
<td>Inflammation</td>
</tr>
</tbody>
</table>

Biomarkers changes suggest that HA/CS tends to promote return to cartilage homeostasis
Chitosan smartbeads® + chitosan hydrogel = Arthrovisc®

- Diameter: 600-900 µm
- Mushroom Chitosan: 0.5% - 42Kda
- Alginate (Pronova UP): 1.4%

Chitosan (C) smartbeads + Chitosan-derived hydrogel

**Biphasic biomaterial**

**Ratio 1/1 w/w**
A thermogelling hydrogel mimicking synovial fluid

Arthrovisc®

Synovial fluid

= HYDROGEL alone

RHEOLOGY

Energy adsorption ($G'$)
Energy loss ($G''$)
Energy adsorption ($G'$)
Energy loss ($G''$)

Time (s)

$G'/G''$ (Pa)

0 500 1000 1500 2000 2500 3000

30 min @ 37°C
Fluid @ room T°
Gel formation @ 37°C

30 min @ 37°C
Fluid @ room T°
Gel formation @ 37°C

Prototype ±4°C
Prototype ±37°C

www.bcru.be
Study design

Day 7
Single injection:
- 900 µl Arthrovisc® (n=7)
- 900 µl Hydrogel alone (n=7)
- 900 µl saline (n=7)

Day 0
Anterior cruciate ligament transection

Induction of OA
One week

6 weeks

Analysis

Histological evaluation of cartilage and synovial membrane OARSI score

Sacrifice

HYLA albinos

X-rays

X-rays

K&L score

www.bcru.be
Arthrovisc® decreases OA progression

**Radiography**

- Group I: Saline
- Group II: H
- Group III: AC+H

**Histology**

- Group I: Saline
- Group II: H
- Group III: AC+H

* P<0.012
# P=0.001
* P<0.001
Conclusions

So... What's about the future?

Perhaps not only a dream!
Thank you for your attention!

International collaborations:
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V Kraus (Duke University, USA)
L Punzi (University of Padova, Italy)
A Mobasherri (University of Notttingham, UK)
J Monfort (Hospital del mare (Spain)
P Richette (Lariboisiere, France)