Soluble biomarkers in OA: can they be used as indicator of HA re-injection?

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Osteoarthritis: A global disease affecting all joint tissues

- Synovial membrane inflammation
- Subchondral bone sclerosis/resorption
- Cartilage degradation
  - Fibrillation/fissuration
  - Mineralisation/vascularization

...to identify metabolic changes in joint tissues

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Joint is an organ

- Pro-inflammatory mediators
- Peptides
- Glycated products
- Adipokines

Local inflammatory reaction «Synovitis»
Low grade systemic inflammation «Inflammaging»

To decrease «degradative peptides» release is a therapeutic target «Metabolic responders»
OA diagnosis: symptoms and standard radiography

**X-ray**

- Osteophytes
- Joint space narrowing
- Bone sclerosis
- Attrition
- Geodes

**Symptoms**

- Pain
- Stiffness
- Swelling
- Cracks
- Deformity
- Malalignment

These signs and symptoms occur in the late stage of the disease.
Radiographic and clinical signs are preceded by a silent molecular phase (D Patra & L Sandell, J Knee Surg, 2011)

<table>
<thead>
<tr>
<th>Pre-OA initiation</th>
<th>Silent molecular phase</th>
<th>Pre-radiographic phase</th>
<th>Radiographic phase</th>
<th>Joint replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic biomarkers</td>
<td>Biochemical biomarkers</td>
<td>MRI Imaging</td>
<td>X-ray imaging</td>
<td>Joint death</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>Cartilage and joint tissue metabolic changes</td>
<td>Structural changes in bone, cartilage, and other soft tissues</td>
<td>Structural changes in bone, JSN and pain</td>
<td>End-stage disease</td>
</tr>
</tbody>
</table>

...To diagnose the disease at the silent molecular phase
Drug discovery is protracted, risky and costly

Nothing new to offer at the patients and the OA research community
Clinical trials end-point

- **Symptoms modification** (3 to 6 months)
  - Pain
  - Physical function
  - Patient global assessment

- **Structure modification** (1 to 3 years)
  - Imaging outcomes
  - Joint Space Narrowing

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The main limitations of JSN

- Indirect measure of the alteration in articular cartilage.
- Fails to measure a dynamic process.
- Confounded by the presence of meniscal lesions and extrusion.
- Changes overtime are small, and occur in only a subset (progressors) of patients.
- Poorly reproducible (full extension).
- Poorly correlated with joint function and pain.
Why do we need biological markers in treatment development?

- To predict who will respond to a treatment
- To surrogate clinical end-point
- To monitor the effect on tissue metabolism
FDA and EMA recommendations

- “a higher level of integration of biomarkers in the development and testing of new drugs to advance decision-making on dosing, time and treatment effect, trial design, and risk/benefit analysis. Biomarkers can be used not only in the process of drug development, but also in assessment of individual patient’s response to treatment.”

Kraus et al. O&C 2015
A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

OA Biomarkers

Cartilage
- sColl2-1
- sFibulin3
- sCOMP
- sYKL40
- sC2C
- uCTX-II
- PIIANP
- CPII
- Agrec-1

Synovium & inflammation
- sColl2-1NO2
- sPIIINP
- sHA
- sCRP ultrasensible
- Cytokines, MPO

Metalloproteases
- sMMP1 (collagenase)
- sMMP3 (stromelysin)

Bone
- sPINP
- uCTX-I

Blood ~5 liters

lymphatics

cartilage

Synovium

Bone

kidney

urines

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Biomarkers of cartilage metabolism

Type II collagen degradation
- PIINP
- PIICP
- C2C
- CTX-II
- Coll2-1
- CIIM
- Coll2-1NO2

Oxidative stress
- Coll2-1NO2

Aging
- D-COMP
- COMP

Type II collagen synthesis

C2C, CIIM
Cleavage site of MMP-1,-8,-13

NO + O2 → ONOO-

Coll2-1NO2

Oxidative stress

Aging

Type II collagen synthesis

PIINP
PIICP

Arg5, NITEGE

Aggrecan turnover

ADAMTS-5

AGS

Aggrecan degradation

CS-846
KS

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Type II collagen biomarkers

- Cleavage neoepitopes
- Telopeptide epitopes
- Denaturation neoepitope
- Propeptide epitopes

Diagram showing the cleavage sites and epitopes for Type II collagen.
BIPEDS classification
Bauer et al. Osteoarthritis Cart 2006

- **Burden of disease**
  - Biomarker associated with extent of severity of OA

- **Investigative**
  - Biomarker not yet meeting criteria for another category
  - Predicts incidence of progression of disease or likelihood of response to a treatment
  - Investigative

- **Prognostic**
  - Predicts incidence of progression of disease or likelihood of response to a treatment
  - Prognostic

- **Efficacy of treatment**
  - Indicative or predictive of treatment efficacy and for which the magnitude of the change is considered pertinent to the response.

- **Diagnostic**
  - Dissociate diseased from non-diseased.

- **Safety**
  - Identify adverse effects and provide means of safety.
Biochemical marker concentration differed statistically significantly between patient populations with or without treatment, or before and after treatment within patient.

<table>
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<tr>
<th>BIPEDS</th>
<th>Biomarkers</th>
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<tr>
<td>Efficacy of intervention</td>
<td>uCTX-II, sColl2-1, sColl2-1NO2, sC2C, sCOMP, sKS, sYLK40, sPIIANP, uNTX-I, sOC, sHA, sMMP-3, sCRP</td>
</tr>
</tbody>
</table>
Is CTX-II an efficacy of intervention biomarker? Interpretation pitfalls!

**Intervention** | **CTX-II levels**
--- | ---
HA | ↓
CS | 0
Naproxen,Licofelone | 0
Tibolone | 0
Risedronate | ↓
Calcitonine | ↓
Strontium ranelate | ↓
SERM | ↓
Estradiol | ↓

All antiresorptive therapies decrease CTX-II

*Richette, Roux Osteoporosis Int 2012*

u CTX-II reflects bone rather than cartilage metabolism

*van Spil W E et al. Ann Rheum Dis 2013*
BIOVISCO study: Study design
Open-label, observational prospective study

HylanGF-20

D-15 D1 D7 D14 D30 D60 D90

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

- Specific of degraded cartilage
- Multiple pathological processes (inflammation + degradation)
- Not confounded
BIOVISCO study
Other observations

✓ Only sColl2-1 was significantly decreased 30 days after final injection
✓ Only uCTX-II variation correlated with clinical response (walking pain decrease)
✓ uCTX, sColl2-1 and sHA were independently predictive of clinical response
  (WP decrease > 30 mm over 90 days)
The concept of « metabolic » responders

- According to clinical trial results, some patients did respond to the treatment in term of catabolism reduction but others did not.
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

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4. Service de Rhumatologie - Centre Viggo Petersen, Hôpital Lariboisière, Paris, France.
5. Service de Rééducation, Hôpital Cochin, Paris, France.

ARD 2016, under submission
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)
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
### Demographic data of the FAS population (N=81)

<table>
<thead>
<tr>
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<th>Treatment N=40</th>
<th>Placebo N=41</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>66.9 ± 10.4</td>
<td>63.0 ± 8.9</td>
<td>0.0752</td>
</tr>
<tr>
<td><strong>Sexe</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Women</td>
<td>62.5 %</td>
<td>75.6 %</td>
<td>0.2016</td>
</tr>
<tr>
<td>- Men</td>
<td>37.5 %</td>
<td>24.4 %</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>29.0 ± 7.4</td>
<td>30.8 ± 7.2</td>
<td>0.2465</td>
</tr>
</tbody>
</table>
IAHA decreased of Coll2-1 in the FAS population

<table>
<thead>
<tr>
<th></th>
<th>IAHA</th>
<th>Saline solution</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=40 at D-10</td>
<td>N=41 at D-10</td>
<td></td>
</tr>
<tr>
<td>Serum Coll2-1 at D-10</td>
<td>840.3 ± 375.8 (N=40)</td>
<td>766.1 ± 359.2 (N=41)</td>
<td>0.3663</td>
</tr>
<tr>
<td>Serum Coll2-1 at D90</td>
<td>745.4 ± 343.5 (N=37)</td>
<td>782.3 ± 233.7 (N=35)</td>
<td>0.5975</td>
</tr>
<tr>
<td>Adjustment on basal value</td>
<td>-80.2 ± 44.1</td>
<td>-14.6 ± 45.3</td>
<td>0.0030</td>
</tr>
<tr>
<td>Reduction of at least 10 nmol/l</td>
<td>56.8 %</td>
<td>28.6 %</td>
<td>0.0158</td>
</tr>
</tbody>
</table>
Conclusions

- A single injection of KARTILAGE®Cross induced a reduction of Coll2-1 30 days after treatment
  →sensibility of the biomarker to a single joint metabolic change
  →IAHA modulate cartilage catabolism « chondromodulator »
  →Confirmatory study
Conclusions

- No clinical effect
  Concept of « metabolic responders » ≠ « symptomatic responders »

- No effect on other biomarkers (specificity)
To use a specific biomarker of cartilage degradation to identify the metabolic responders.
L’avenir!
New concepts

- Notion of « metabolic responders »
- Therapeutic algorithm to identify the IAHA responders
- Coll2-1 alone or in « aggregate score » as indicator of reinjection
- Personalized approach of the viscosupplementation
Statements

- The effect of viscosupplementation on cartilage metabolism is a valuable outcome in the follow-up of OA patients.
- Soluble biomarkers are good tools/useful for monitoring the effects of viscosupplementation on cartilage metabolism.
- Soluble biomarkers are predictive of the response to viscosupplementation.
- Soluble biomarkers variation can be used as indicator of HA re-injection.
Thank you for your attention!

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J Runhaar (Erasmus MC, Rotterdam)