Biochemical markers to monitor the effects of drugs in knee OA patients

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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.

Biomarkers of cartilage metabolism

NO + O₂ → ONOO⁻

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

Coll2-1
HRGYPGLDG
NH₂
Coll2-1NO₂
HRG(Y(NO2))PGLDG
NO + O₂
ONOO⁻

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

Type II collagen degradation

Coll2-1NO₂

Type II collagen synthesis

PIINP
PIICP

Oxidative stress

Aging

D-COMP

COMP

Fib3-1

Fib3-2

ARGS
NITEGE
CS-846
KS
Aggrecan degradation
Aggrecan turnover

www.bcru.be
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of disease</td>
<td>Biomarker associated with extent of severity of OA.</td>
</tr>
<tr>
<td>Investigative</td>
<td>Biomarker not yet meeting criteria for another category.</td>
</tr>
<tr>
<td>Prognostic</td>
<td>Predicts incidence of progression of disease or likelihood of response to a treatment.</td>
</tr>
<tr>
<td>Efficacy of treatment</td>
<td>Efficacy of intervention « Indicative or predictive of treatment efficacy and for which the magnitude of the change is considered pertinent to the response. »</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>Dissociate diseased from non-diseased.</td>
</tr>
<tr>
<td>Safety</td>
<td>Identify adverse effects and provide means of safety.</td>
</tr>
</tbody>
</table>
Biochemical marker concentration differed statistically significantly between patient populations with or without treatment, or before and after treatment within patient.
Levels of qualification of biomarkers for drug development use

*Kraus et al. Osteoarthritis Cart, 2011*

- **Surrogate**
  - None

- **Characterization**
  - uCTX-II, sMMP-3

- **Demonstration**
  - sC2C, sHA, NTX-1, Coll2-1, Coll2-1NO2

- **Exploratory**
  - COMP, C1,2C, CTX-1, CS846

« To qualify for the efficacy of intervention category, a marker must demonstrate a statistically significant relationship between treatment-related changes in a biomarker and the clinical or imaging outcome »
Is CTX-II an efficacy of intervention biomarker? Interpretation pitfalls!

<table>
<thead>
<tr>
<th>Intervention</th>
<th>CTX-II levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA</td>
<td>↓</td>
</tr>
<tr>
<td>CS</td>
<td>0</td>
</tr>
<tr>
<td>Naproxen, Licofelone</td>
<td>0</td>
</tr>
<tr>
<td>Tibolone</td>
<td>0</td>
</tr>
<tr>
<td>Risedronate</td>
<td>↓</td>
</tr>
<tr>
<td>Calcitonine</td>
<td>↓</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>↓</td>
</tr>
<tr>
<td>SERM</td>
<td>↓</td>
</tr>
<tr>
<td>Estradiol</td>
<td>↓</td>
</tr>
</tbody>
</table>

All antiresorptive therapies decrease CTX-II

Richette, Roux Osteoporosis Int 2012

u CTX-II reflects bone rather than cartilage metabolism

TIFLEXY Study
Bio-optimized curcuminoids (BOC)

Curcuminoids /Low availability

« Proof-of-concept study »
- 22 knee OA patients
- 2x3 caps (42 mg BOC)/days
- 3 months treatment

TIFLEXY Study
A proof-of-concept study
Henrotin et al., BMC Complem Altern Med, 2014

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>84 days of treatment</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sColl2-1 (nmol/L)</td>
<td>302.21 +/- 53</td>
<td>257.84 +/- 52.78</td>
<td>0.002*</td>
</tr>
<tr>
<td>sColl2-1NO2 (nmol/L)</td>
<td>0.71 +/- 0.78</td>
<td>0.80 +/- 0.24</td>
<td>NS</td>
</tr>
<tr>
<td>sCTX-II (ng/L)</td>
<td>11.81 +/- 7.98</td>
<td>13.17 +/- 4.96</td>
<td>NS</td>
</tr>
<tr>
<td>sFib3-1 (pmol/L)</td>
<td>707.05 +/- 178.79</td>
<td>765.20 +/- 261.90</td>
<td>NS</td>
</tr>
<tr>
<td>sFib3-2 (pmol/L)</td>
<td>580.58 +/- 103.59</td>
<td>636.74 +/- 119.73</td>
<td>NS</td>
</tr>
<tr>
<td>sCRP (mg/L)</td>
<td>10.42 +/- 30.27</td>
<td>3.10 +/- 2.40</td>
<td>NS</td>
</tr>
<tr>
<td>sMPO (ng/ml)</td>
<td>27.20 +/- 29.05</td>
<td>21.96 +/- 14.65</td>
<td>NS</td>
</tr>
</tbody>
</table>
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>
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)
MOVES study
CS + GuHCL (Droglican) vs Celecoxib
Preliminary data

- 416 knee OA (PP)
- 1200 mg CS/1500 GuHCL
- 200 mg celecoxib
- 6 months treatment

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>AGE</th>
<th>SEX</th>
<th>Weight (Kg)</th>
<th>Height (cm)</th>
<th>BMI (kg/m2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>celebrex</td>
<td>202</td>
<td>64</td>
<td>165/37 (82%)</td>
<td>78 (14)</td>
<td>162 (18)</td>
<td>30 (6)</td>
</tr>
<tr>
<td>droglican</td>
<td>214</td>
<td>62</td>
<td>187/27 (87%)</td>
<td>81 (16)</td>
<td>161 (18)</td>
<td>31 (7)</td>
</tr>
<tr>
<td>PP</td>
<td>416</td>
<td>63</td>
<td>352/64 (85%)</td>
<td>80 (15)</td>
<td>162 (18)</td>
<td>30 (6)</td>
</tr>
</tbody>
</table>

Both drugs decreased sColl2-1
Only Droglican decreased significantly Coll2-1
No significant difference between groups
MOVES study
CS + GuHCL (Droglican) vs Celecoxib

OMERACT- OARSI Responders

KL grade III

Joint Swelling

WOMAC baseline ≤369 mm

\[ p = 0.009 \]

\[ p = 0.039 \]

\[ p = 0.026 \]

\[ p = 0.028 \]

**Mean values + IC (95%)**

P value = droglican vs celebrex

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Conclusions

- Soluble biomarkers should be included early in the development of a drug: "Drug development tool"
→ Preclinical development and phase 1-4 trials

Why?
→ to assist with selection of lead compound
→ to assess safety, mechanism of action, dose finding and selection, dose response profile, enrichment of a target population, enrichment for progressors, post-marketing safety surveillance
→ Companion biomarker (personalized medicine)
Thank you for your attention!

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)