Disease Modifying Drugs for OA: from research to clinical evidence

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## OA treatments and limitations

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Limitations</th>
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</table>
| Prescription NSAIDs Including COXIB | GI bleeding or other complications  
CV risks  
Renal complications |
| OTC NSAIDs | GI bleeding or other complications  
CV risks  
Renal complications |
| Acetaminophen | Hepatotoxicity |
| Patient education, physical and occupational Therapy, weight loss | Poor patient compliance |

What’s a DMOAD?

**Disease-Osteoarthritis Modifying Drugs (DMOAD)** is a category of otherwise unrelated drugs defined by their use in OA to slow-down disease progression.

**Primary outcome**
- Joint space narrowing
- MRI (volume)
- Time to surgery
- Number of prothesis

**Most popular candidate**
- Glucosamine (GlcN) S or HCL
- Chondroïtin sulfate (CS)
- Unsaponifiable of Soybean/Avocado (ASU)
- Diacerein

**Chemical structures**
- **Chondroitin sulfate**: A polysaccharide with a backbone of disaccharide units.
- **Glucosamine sulfate/HCL**: A derivative of glucosamine with a sulfate group and a hydrogen chloride salt.

*www.bcru.be*
CS/GlcN: How do they work?

Henrotin et al. Ther Adv Musc Dis, 2010

Internalization through HARE or CD44 (HA)

Inflammation

IL-6, IL-1β

MAP kinases
P38, Erk1/2

CS

Oxidative stress

Free radicals

Cytoplasm

Nucleus

Gene transcription

Inflammation Cartilage degradation

Apoptosis

iNOS → NO

COX-2 → PGE2

MMPs

ADAMTS-4 and -5

NF-κB

O-GlcNacylation

UDP-N-Acetylglucosamine

Chondrocyte

Caspase-3, -7

HARE or CD44 (HA)
GLcN/CS 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><strong>-</strong></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>Chondroitin sulfate</td>
<td>0.75 (0.50, 1.01)</td>
<td>-</td>
</tr>
</tbody>
</table>

*All Studies

GAG effect size is superior to NSAIDs with less GI adverse events

ES < 0.2 = None
ES 0.2 – 05 = Weak
ES 0.5 – 08 = Moderate
ES > 08 = Strong

versus placebo at 1-4 weeks

www.bcru.be
GLcN/CS have a weak effect on disease modification

- **Chondroitin sulfate**
  Estimated Effect Size for reduction in rate of decline of minimum joint-space width (SMD):
  Ranges from 0.26 (0.14–0.38) to 0.30 (0.00–0.59) WEAK

- **Glucosamine sulfate**
  Estimated Effect Size for reduction in rate of decline of minimum joint-space width (SMD):
  0.08 (−0.12–0.27) NONE

McAlindon et al. O&C 2014
Rationale to use GlcN or CS in OA treatment?

- Level of evidence: strong
- Quality of evidence: good
- Analgesic effect: moderate (> NSAIDS or Acetaminophen)
- Disease-modifying effect: None to weak (possible deleterious effect of NSAIDS)
- Safety: good (Severe adverse effect with NSAIDs)

BUT........
### GLcN/CS in Recent Guidelines

<table>
<thead>
<tr>
<th>Society</th>
<th>recommendation</th>
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<tr>
<td>ACR 2012</td>
<td>Conditionally recommend that the patients with knee or hip OA should not use chondroitin sulfate or glucosamine</td>
</tr>
<tr>
<td>NICE 2013</td>
<td>Nutraceuticals: do not offer glucosamine and chondroitin products for the management of OA</td>
</tr>
<tr>
<td>OARSI 2014</td>
<td>« Uncertain » for symptoms relief &lt;br&gt;« Inappropriate » for structural effects</td>
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</table>
Why this reluctance for DMOAD?

- Lack of confidence in clinical trial?
- Geographical different practice?
- Inconsistency between industry-sponsored and independent studies?
- Heterogeneity among studies?
- Gap between expert opinion and real life?
- Cost of the treatment? Economical concern?
The risk

« ….iatrogenesis due to the overuse NSAIDs, paracetamol and corticosteroids infiltration… »

Letter of the « Section arthrose »
of the french society of rheumatology to
CNEDIMTS
Conclusions

At least 2 good reasons to use DMOAD in OA:
- To control OA symptoms with a good safety
- To decrease NSAIDs consumption

But
- Evaluate DMOAD efficacy at individual level
- Stop treatment after 6 months if no clinical relevant pain effect
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)