The Use of Viscosupplementation in FDA-Approved & Non–FDA-Approved Joints

Ramon Cuevas-Trisan, MD

Disclosure

- Consultant/Speakers Bureau: Allergan
- Speakers Bureau: Ipsen, Merz
Learning Objectives

- Describe the indications for joint viscosupplementation
- List the various products available, their shared and unique features, contraindications and possible side-effects
- Review the medical evidence for the use of viscosupplements in FDA-approved and non-FDA-approved joints

Nature and Relevance of the Problem

- Nearly 46 million people in the US (10%-12% of adult population) have symptomatic OA
- OA: fastest increasing major health condition
- Majority (64%) of people with OA are of working age (15-64 y/o)
Nature and Relevance of the Problem (cont’d)

Contributors to the development of OA:

- Genetic factors
- Age
- Ethnicity
- Nutritional factors (vitamin K and D deficiencies)
- Gender (female >> male)
- Obesity?

Hyaluronic Acid: More than just skin deep....

- Has reached prominence in cosmetic practice
  (injectable dermal filler of choice)
- Naturally occurring biopolymer
- First described in 1934, used across a wide variety of medical fields as diverse as neurosurgery and cutaneous wound healing
Synovial Fluid: Pathophysiology

- Hyaluronic acid (HA): polysaccharide biopolymer composed of continuously repeating molecular sequences of glucuronic acid and acetylglucosamine

- Normal molecular mass: 6,500-10,900 kDa

- In OA it depolymerizes (MM 2,700-4,500 kDa) and cleared at higher rates
  - These changes reduce the viscoelasticity of the synovial fluid in OA

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Synovial Fluid: Pathophysiology (cont’d)

- HA gives synovial fluid the viscous quality that helps to lubricate and/or absorb shock
- Native HA
  - Analgesic and anti-inflammatory properties
  - Inhibits macrophage phagocytosis and neutrophil adherence
  - Reduces the release of arachidonic acid from synovial fibroblasts
  - Possible binding of sP
Exogenous HA

- Thought to improve viscosity of synovial fluid:
  allows smoother movement and reduced pain

- Also claimed to exert analgesic, anti-inflammatory and
  possibly chondroprotective effects on articular cartilage
  and joint synovium

Exogenous HA (cont’d)

Mechanism of action: (not clear but suggested)

- Replenish joint fluid
- Improve cushioning properties, lubricate and protect
  articular cartilage
- Increase cell integrity
- Reduce rate of cell death
- Reduce synovitis
- Increase native HA production
- Enzymatic changes
Exogenous HA (cont’d)

- Clinical effects usually last much longer than the residence time of exogenous HA in synovial fluid
- May re-establish joint homeostasis by increasing the endogenous production of HA that persists long after the exogenous material has left the joint

US FDA-Approved Indication

- Only approved in the US for knee OA
- “Pain in OA of the knee in patients who have failed to respond adequately to conservative nonpharmacological therapy and simple analgesics (eg, acetaminophen)”
  - Mild to moderate in degree
  - Not severe
## Products Available (US)

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Protocol</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synvisc®</td>
<td>Genzyme</td>
<td>3/1 (2-6 mL)</td>
<td>6000 kDa</td>
</tr>
<tr>
<td>Synvisc-One</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyalgan®</td>
<td>Sanofi-Aventis</td>
<td>3-5 (2 mL)</td>
<td>500-730 kDa</td>
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<tr>
<td>Orthovisc®</td>
<td>Depuy-Synthes</td>
<td>3-4/1 (2 mL)</td>
<td>1000-2900 kDa</td>
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<tr>
<td>Monovisc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euflexxa®</td>
<td>Ferring</td>
<td>3 (2 mL)</td>
<td>2400-3600 kDa</td>
</tr>
<tr>
<td>Suparz FX®</td>
<td>Bioventus</td>
<td>3-5 (2.5 mL)</td>
<td>620-1170 kDa</td>
</tr>
<tr>
<td>Gel-One®</td>
<td>Zimmer</td>
<td>1 (3 mL)</td>
<td></td>
</tr>
</tbody>
</table>

## Practical Indications

Medical treatment for knee OA patients who:

- Have pain that affects daily activities, such as extended standing and walking
- Are sensitive to NSAIDs / don’t get adequate relief
- Don’t get adequate pain relief from PT, including modalities, weight loss, etc
- Don’t get adequate pain relief from aspirations, CSIs, or want to avoid these
- Want to avoid or postpone surgery
EU Approved Indications

- **Synvisc®**: knee, hip (2002), shoulder, ankle (10/2006); same in Canada
- **Suparz® (Durolane®)**: knee and hip (2004)

### The Big Picture

<table>
<thead>
<tr>
<th>Joint</th>
<th>Approved</th>
<th>Proven Effective</th>
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</thead>
<tbody>
<tr>
<td>Knee</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Hip</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Shoulder</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Ankle</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>TMJ</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Facets</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CMC</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

62 HA products marketed in Italy!

Contraindications/Warnings

- **Absolute**
  - Infection
  - Skin breakdown at injection site
  - Allergy to any of the components

- **Relative**
  - Internal derangement
  - Large effusion w/o aspiration
  - Systemic bleeding disorders

Side Effects

- **Pseudoseptic joint**
  - Usually 24-72 hrs post

- **Infection**

- **Hemarthrosis**
Products Available

Some unique features
- One injection: Synvisc-One®, Gel One®, Monovisc®
- Genetically engineered: Euflexxa®
- Nonavian: Euflexxa®, Orthovisc®
- Highest viscosity: Synvisc®

Products Available (cont’d)

Others
- GenVisc® – analogous to Suparz®
- Durolane® – in EU for hip and knee
  (1 injection analogous to Suparz®)
- Cyngal® – HA (analogous to Ortho/Monovisc®) + triamcinolone
- Hymovis® – in EU (2 injections analogous to Hyalgan®)
Application Technique

- Importance of guidance methods mainly for nonknee injections
- Strict sterile technique
- Local anesthetic; large bore needle
- Aspirate effusion
- Relative rest for 48-72 hrs
- Warn about delayed onset

Application Technique (cont’d)
Application Technique

The Evidence: Knee

- Despite approval by the FDA and longstanding use, the efficacy has been questioned
  - AAOS: strong recommendation against use\(^1\)
  - Ann Int Med: small and clinically irrelevant benefit and an increased risk for serious AEs\(^2\)
  - OARSI 2014 – “uncertain”\(^3\)

The Evidence: Knee (cont’d)

- Challenged by TEP at the International Symposium on Intra-Articular Treatments 2013
  - Need to merge data from both RCTs and registers
  - Use only studies with strong level of evidence
  - Need a common threshold of efficacy to compare txs
  - Evaluation of hard outcomes is essential
  - Effect size of placebo is a concern
  - Concerns for different phenotypes of OA
  - Compliance and long-term SEs should be evaluated
  - Pharmacoeconomics


The Evidence: Knee (cont’d)

- Reviewed published clinical trials conducted in the US, Europe, and Canada
- Conclusions:
  - Viscosupplementation effectively reduces knee pain and improved function caused by OA, particularly 5 to 13 weeks after injection
  - Several viscosupplement products have greater efficacy than CSIs

The Evidence: Knee (cont’d)

- Other publications that recommend use:
  
  — Ray TR. Physician Sportsmed 2013: 41(4); 16-24

The Evidence: Hip

- VA/DoD Clinical Practice Guideline for Non-Surgical Management of Knee & Hip OA 2014

- Recommend against the use of HA intra-articular hip injections at this time due to:
  
  • Lack of high-quality studies that have demonstrated that these delay the need for THA
  • Because not currently FDA-approved for hip
The Evidence: Hip (cont’d)

- Pooled data from 186 patients in fair quality studies
- Intra-articular HA injections were not associated with statistically significant improvement in pain compared to placebo (mainly delay in THA)
- No high quality studies have examined the use of fluoroscopy-guided intra-articular corticosteroid injections in the hip as a treatment to delay THA


The Evidence: Hip (cont’d)

- Concern: glucocorticoid-induced osteonecrosis leading to rapid collapse of the femoral head¹
- No evidence to indicate which patients will benefit from intra-articular CSI for hip (or knee) OA²
- These injections continue to be commonplace with many patients reporting pain relief despite inconclusive evidence to support their use for hip OA

The Evidence: Shoulder

- Systematic review (8 studies) – HA, NSS, CSI
- HA effect sizes of 2.07, 2.02, and 2.11 at 6, 12, and 26 weeks, respectively
- NSS effect sizes of 1.60, 1.82, and 1.68 at the same time points
- Efficacy of corticosteroids (CS) decreased rapidly at follow-up
  (1.08, 0.43, and 0.19)


The Evidence: Shoulder (cont’d)

- Multicenter RCT: n=150 each arm
  - 3 weekly injections of HA vs NSS
  - Evaluated over 26 weeks
- Numeric advantage for HA w/o statistical significance
- Subset of HA patients without concomitant pathologies reached statistical significance

The Evidence: Hip/Shoulder

- Retrospective short case series fluoroscopically-guided Hylan G-F 20
- Shoulder n = 21 / hip n = 31 over 4 years

The Evidence: Hip/Shoulder (cont’d)

- Effective pain relief (up to 4 months in approximately half of the patients with a few patients experiencing pain relief during the whole observation period (24-30 months)
- Age, race, # of comorbidities, opiate use, and severity of joint disease
  - No significant effects on clinical outcomes
- No SEs
- Better efficacy in lean individuals regardless of severity (metabolic OA phenotype?)


Results

Other Joints

- Short series described for:
  - SIJ
  - Ankle
  - Lumbar facet joints
  - TMJ
  - Wrist/hand joints
Summary of the Evidence

- Variability of findings: heterogeneous populations, outcome measures (pain at rest/certain movements, ROM, function, delay replacement surgery), COIs, publication bias

- Use in less than ideal populations: obese, severe disease previously failed Tx (harder-to-treat cohorts)

Evidence-Based Medicine

“the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients...It means integrating individual clinical expertise with the best available external clinical evidence from systematic research.”*

- Our own observations and practice with our patients is part of it, not just RCTs...

*Dr. D. Sackett
Conclusions

Pragmatic recommendations:

- Use in younger patients with milder disease
- Use when CSIs do not provide sufficiently long effect
- Use guiding methods when applying
- May try with select recalcitrant patients

Conclusions (cont’d)

- Most physicians consider it a useful treatment option, to be used when other methods of nonsurgical pain relief have failed to provide sufficient pain relief
- There is evidence for clinical efficacy but may not be better than CSI or even placebo in RCTs
- Relatively low-risk but present
- May work better early (many exceptions)
- Longer-lasting effects than CSI
Thanks!