

Intraarticular hylan was no better than hyaluronic acids for osteoarthritis of the knee

Jüni P, Reichenbach S, Trelle S, et al. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial. *Arthritis Rheum.* 2007;56:3610-9.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Phys Med & Rehab ★★★★★★ Rheumatology ★★★★★☆

QUESTION

What is the relative efficacy and safety of intraarticular hylan and 2 hyaluronic acids (HAs) for osteoarthritis (OA) of the knee?

METHODS

Design: Randomized controlled trial (First Swiss Viscosupplementation Trial [SVIS-COT-1]).

Allocation: Concealed.*

Blinding: Blinded (patients, outcome assessors, and data analyst).*

Follow-up period: 6 months.

Setting: 165 centers in Switzerland.

Patients: 660 patients (mean age 63 y, 66% women) who had radiologically confirmed knee OA (Kellgren–Lawrence grade ≥ 2), with symptoms for ≥ 6 months and pain on most days in the past 3 months; an American College of Rheumatology functional class rating of II to IV; and insufficient response or intolerance to acetaminophen or nonsteroidal antiinflammatory drugs. Exclusion criteria were pregnancy, inflammatory joint disease, chondrocalcinosis, infection in or around the study knee, skin disease around the injection site, allergy or intolerance to experimental preparations, previous knee replacement, and current anticoagulant therapy or viscosupplementation in the past 6 months.

Intervention: 1 cycle of 3 intraarticular injections (2 mL per treated knee) of crosslinked, high-molecular-weight hylan (Synvisc; Genzyme, Cambridge, MA, USA) ($n = 222$), a noncrosslinked medium-molecular-weight

avian HA (Orthovisc; Anika Therapeutics, Woburn, MA, USA) ($n = 219$), or a non-crosslinked, low-molecular-weight bacterial HA (Ostenil; TRB Chemedica, Geneva, Switzerland) ($n = 219$). Injections were given at weekly intervals.

Outcomes: Change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score. Secondary outcomes included WOMAC global score and stiffness and disability subscores, European Quality of Life (EuroQol) score, local adverse events (effusion or flare), need for corticosteroid injections due to local adverse events, and serious adverse events. The study had $> 96\%$ power to detect a difference between groups of 0.8 units in standardized 10-point WOMAC pain scores for comparisons of hylan with each of the 2 HAs ($\alpha = 0.025$).

Patient follow-up: 99% were assessed at 6 months (intention-to-treat analysis; for continuous outcomes, last outcome carried forward for 6 patients).

MAIN RESULTS

Because no differences in efficacy were found for hylan compared with each of the HAs,

results are reported for hylan compared with the 2 HAs combined. At 6 months, the hylan and combined HA groups did not differ for WOMAC pain scores (mean 0.1, 95% CI -0.3 to 0.2 , adjusted for concomitant therapy), global scores (mean 0.1, CI -0.2 to 0.4), stiffness scores (mean 0.1, CI -0.3 to 0.4), or disability scores (mean 0.1, CI -0.2 to 0.4); EuroQol scores (mean 0.1, CI -0.2 to 0.4); or health state index (mean 0.2, CI -0.1 to 0.4). The groups did not differ for receipt of corticosteroid injections or serious or local adverse events (Table).

CONCLUSION

Intraarticular hylan was not more effective or safe than hyaluronic acids for osteoarthritis of the knee.

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For correspondence: Dr. P. Jüni, University of Berne Institute of Social and Preventive Medicine and CTU Berne, Berne, Switzerland. E-mail juni@ispm.unibe.ch.

*See Glossary.

Intraarticular hylan vs avian or bacterial hyaluronic acids (HAs) for osteoarthritis of the knee†

| Outcomes at 6 mo | Hylan | HAs | RRI (95% CI) | NNH |
|--|-------|------|------------------------|-----|
| Serious adverse events | 6.8% | 5.7% | 18% (-36 to 117) | NS |
| Local adverse events | 9.5% | 7.3% | 29% (-23 to 117) | NS |
| Steroid injections due to local adverse events | 2.3% | 1.1% | 97% (-38 to 530) | NS |

†NS = not significant; other abbreviations defined in Glossary. RRI, NNH, and CI calculated from data in article.

COMMENTARY

Several different formulations of viscosupplementation are currently available, and these formulations reportedly differ in efficacy and adverse events, with high-molecular-weight preparations having longer intraarticular presence, improved efficacy, and greater potential for adverse events (1). However, until the study by Jüni and colleagues, there was little evidence from direct comparisons of different formulations.

The large, well-designed study by Jüni and colleagues recruited patients similar to those found in clinical practice settings, in which viscosupplementation may be an option in patients with symptoms despite other pharmacologic therapy. This well-powered trial directly compared intraarticular hylan with 2 HAs and found no evidence of differences in efficacy. The more expensive hylan formulation was associated with a higher rate of local adverse effects and 1 case of anaphylactic shock, providing even less justification for its use. Further support of the lack of superiority and increased rate of adverse effects with hylan over other HAs is provided by a recent meta-analysis (2) by the same investigators.

In clinical practice, a second cycle of viscosupplementation is often offered, assuming some response to the first injection cycle. Jüni and colleagues found a much higher rate of local adverse events (9% of patients; NNH 16, CI 1.7 to 8.2) after the second administration of hylan to 50% of their patients, which suggests that caution be used with repeated administration of this agent. The study provides strong data against the continued use of hylan in clinical practice.

David Hunter, MD
New England Baptist Hospital
Boston, Massachusetts, USA

References

- Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA.* 2003; 290:3115-21.
- Reichenbach S, Blank S, Rutjes AW, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: A systematic review and meta-analysis. *Arthritis Rheum.* 2007;57:1410-8.