

Are intra-articular injections of hylan more effective than injections of hyaluronic acid for knee osteoarthritis?

Original article Jüni P *et al.* (2007) Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial. *Arthritis Rheum* 56: 3610–3619

SYNOPSIS

KEYWORDS hyaluronic acid, hylan, intra-articular injection, osteoarthritis, viscosupplementation

BACKGROUND

Hylans have a higher molecular weight (MW) and a longer intra-articular half-life than hyaluronic acids (HAs), and might, therefore, produce more-effective, long-term pain relief when injected into the joints of patients with osteoarthritis (OA).

OBJECTIVE

To compare the safety and efficacy of hylan and two HA preparations in patients with OA of the knee.

DESIGN AND INTERVENTION

From June 2003 to April 2004, this multicenter, patient-blind Swiss trial enrolled patients with radiographically confirmed OA in one or both knees who had been symptomatic for at least 6 months and who had reported pain almost daily for the previous 3 months. Patients were randomly allocated to receive high-MW cross-linked avian hylan (Synvisc®; Genzyme, Cambridge, MA; $n=211$), medium-MW non-cross-linked avian HA (Orthovisc®; Anika Therapeutics, Woburn, MA; $n=207$), or low-MW non-cross-linked HA derived from bacterial fermentation (Ostenil®; TRB Chemedica, Geneva, Switzerland; $n=205$). One cycle of three intra-articular injections of 2 ml per affected knee was administered at a rate of one a week. All patients were assessed at 6 months, and 50% of patients randomly selected from each group underwent interim follow-up at 3 months. A random sample of

50% of patients from each treatment group was administered a second cycle of injections during months 7–9.

OUTCOME MEASURES

The primary outcome measure was change from baseline in the 10-point Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score at 6 months.

RESULTS

The changes in WOMAC pain score from baseline were not significantly different between the hylan group and both HA groups combined at either 3 months (0.1, 95% CI –0.3 to 0.5) or 6 months (0.1, 95% CI –0.2 to 0.3). The difference between the groups remained low after accounting for changes in quality of life measures. There was no significant difference in the number of local adverse events reported during the first cycle of treatment (21 [9.5%] with hylan vs 32 [7.3%] with either HA preparation); however, among the 330 patients who received a second cycle of treatment, considerably more patients who were administered hylan experienced a local adverse event than those receiving HAs (10 [9.1%] vs 6 [2.7%]). There was little difference between the three treatment groups in the number of reported serious adverse events (15 [6.8%], 12 [5.5%] and 13 [5.9%] for hylan, medium-MW HA, and low-MW HA, respectively). The median direct healthcare costs were significantly greater for the hylan group than for the medium-MW or the low-MW HA groups (\$1,495, \$1,238 and \$1,017, respectively; $P<0.001$).

CONCLUSION

Hylan is no more effective than HA preparations for the palliative treatment of knee OA, but is associated with more local adverse events and greater cost.

COMMENTARY

Frances MK Williams* and Tim D Spector

Preparations of HA have been developed for the treatment of OA on the basis of the observation that naturally occurring, synovial HA is altered and cleared more rapidly in the OA knee than in normal joints.¹ A variety of mechanisms have been postulated to account for the effect of exogenous HA preparations on the OA joint—summarized nicely by Jüni *et al.* in the introduction to their paper—and include local stimulation of HA synthesis and alteration of cartilage metabolism at various points. Regardless of putative actions, this paper concerns only the relative efficacy of the preparations studied, and their adverse effects. Numerous trials have compared HA with placebo as well as with various HA preparations, but the results have been inconsistent. Many trials that have reported positive findings were industry-funded;² there is evidence of publication bias in favor of strongly positive findings, which casts some doubt on their validity.³ Against this backdrop, the Swiss government funded an independent comparison of three viscosupplementation preparations of differing MW (MW influences viscosity and rate of clearance from the joint): high-MW cross-linked hylan derived from rooster combs (Synvisc®), similarly derived medium-MW non-cross-linked HA (Orthovisc®), and low-MW non-cross-linked HA derived from bacterial fermentation (Ostenil®). Efficacy in this study was assessed with the WOMAC scale 6 months after the three injections, which were administered on consecutive weeks. Local adverse events and life-threatening effects were also analyzed as secondary outcomes.

In keeping with a previous meta-analysis,³ no significant difference in outcome was found between the three preparations. There was a trend towards an increased frequency of local adverse events with hylan compared with HAs. Of note, however, two life-threatening events took place (anaphylaxis and septic arthritis with

hylan and avian HA respectively), which, as the authors say, “may be considered too high for a treatment with unclear efficacy.” Given the small effect size and the knowledge of publication bias, it is possible that these products do not work any better than placebo.

This study has a number of strengths: it has the largest sample size to date of viscosupplementation trials ($n=660$), a very low drop-out rate (at 6 months, <1% of patients were lost to follow-up), and it was certainly single-blind, if not double-blind (blinding index 0.96). The authors claim to have 95% power to detect differences as small as 0.4 SD units or 0.8 units on the WOMAC scale.¹ Thus, it seems that these products are very similar in their efficacy. The products do differ in price quite considerably, however, with the price of hylan injection almost twice that of bacterial HA. It is a shame there was no placebo group, as this would have allowed better determination of efficacy. Regrettably, the use of a placebo control group was not considered ethical at the time of the study as a meta-analysis of previous trials had shown a significant, if small, benefit of HA over placebo.³ Some would argue that a trial of viscosupplementation against intra-articular steroid treatment would still be an ethical and very useful approach: a properly conducted trial, with independent funding, would help define precisely the effect size of these products.

References

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Competing interests

The authors declared no competing interests.

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PRACTICE POINT

There is no difference in efficacy or rate of adverse effects between preparations of hyaluronic acid and hylan; therefore, there is no evidence to support the use of the more-expensive, high-molecular-weight cross-linked hylan (Synvisc®)