

Hyaluronic acid and knee osteoarthritis

To the editor:

I read with interest the meta-analysis of hyaluronic acid's effects on pain, stiffness and disability in knee osteoarthritis (Medina JM, Thomas A, Denegar CR, "Knee osteoarthritis: should your patient opt for hyaluronic acid injection?" *J Fam Pract* 2006; 55[8]:669–675). It is of note that of the previous systematic reviews of the hyaluronic acid class of products using meta-analytic techniques, the publication recognizes only two (Wang et al 2004¹ and Modawal et al 2005²) and not all five (Lo et al 2003,³ Arrich et al 2005,⁴ and Bellamy et al 2006⁵). In particular, the extensive Cochrane review of viscosupplementation in knee osteoarthritis, first published in 2005 and revised in 2006,⁵ is not considered.

We have observed that class-based analyses of hyaluronic acid products are method dependent,⁶ bringing into question the value of class-level meta-analyses. Furthermore, the results of class-level analyses may not adequately reflect the clinical benefits of individual contributing products, because product-level observations may be obscured in class-level analyses. Clinicians and their patients are probably most interested in the strength of evidence supporting the use of individual products rather than class-level evidence. Furthermore, there is a high level of heterogeneity in the hyaluronic acid literature and few head-to-head comparisons of hyaluronic acid products, such that there is a paucity of evidence rather than evidence of absence of clinically important difference between products. The aforemen-

tioned factors should lead to caution in conducting class-level analyses of hyaluronic acid products, particularly in an area in which method-dependent results have been observed.⁶ In our own Cochrane review⁵ we observed several important differences between class-level vs product level analyses.

Medina et al have rightly recognized many of the nuances of conducting meta-analyses, but a number of factors limit the general applicability of the results of the Medina meta-analysis, as follows:

1) The majority (80%) of potentially eligible studies were excluded, such that only the study by Huskisson and Donnelly (1999)⁷ remains common across all 6 published class-level meta-analyses of hyaluronic acid products.

2) While the WOMAC and Lequesne indexes are recognized as valid, reliable, and responsive measures of outcome in knee osteoarthritis, they were infrequently used in the early hyaluronic acid literature, and the index-specific inclusion criterion effectively excludes many of the previously conducted hyaluronic acid studies, some of which are positive.⁵

3) Although the authors note that all groups across all included studies were similar at baseline, the spectrum of joint severity is broad, such that in the Karlsson et al study,⁸ all participating patients had either Ahlbäck Grade 1 (~60%) or 2 (~40%) radiographs, and, therefore, had little or no joint space as measured by plain radiography. This group of patients is very different from those with Kellgren and Lawrence Grade 2, and probably different from some patients with Kellgren and Lawrence Grade 3 radiographs entered in other studies included in the same meta-analysis. This issue notwithstanding, it is

noteworthy that the Karlsson study,⁸ when meta-analyzed with other Hylan G-F20 studies yielded a positive result in the Cochrane product-level analysis at 5 to 13 weeks for pain on weight-bearing (0 to 100 mm visual analogue scale): weighted mean difference (random-effects model) was -22.46 (95% confidence interval [CI], -35.24 to -9.68), $P=.0006$ based on 5 randomized controlled trials.⁵

4) The time-dynamic of the response to hyaluronic acid products is such that taking a 6-month period obscures the trajectory of a response that is often quite different at 1 to 4 weeks vs 5 to 13 weeks vs 14 to 26 weeks postinjection.⁵

5) While the severity of radiographic osteoarthritis appears to influence the probability of response, the comment by Medina et al suggesting lesser effects in older patients is at variance, at least with the observations made by Lohmander et al,⁹ who reported that patients older than 60 years with significant symptoms (Lequesne Index ≥ 10) were most likely to benefit from hyaluronic acid treatment and confirmed by Puhl¹⁰ in a reanalysis of data from a previously reported hyaluronan trial showing that patients over the age of 60 years benefited most from hyaluronic acid treatment.

6) Finally, the costs of treatment need to be weighed against the clinical benefit. A previous pharmacoeconomic evaluation of Hylan G-F20 plus appropriate care vs appropriate care alone¹¹ provided support for the incorporation of treatment with Hylan G-F20 into routine clinical practice paradigms for the treatment of knee osteoarthritis.

The meta-analysis published by Medina et al emphasizes the influence that methodology has on the observed clinical benefit of hyaluronic acid intervention when conducting meta-analyses, particularly at a class level.^{6,12} In performing hyaluronic acid meta-analyses, researchers should be encouraged to focus more on product-level analyses rather than class-level analyses, in order to generate information directly relevant to practitioners

and their patients in supporting individual treatment decisions, and to policy makers and third-party payers in considering clinical guideline and reimbursement issues.

Nicholas Bellamy, MD, MSc, MBA, DSc, FRCP(C), FRCP (Glas, Edin), FACP, FRACP

Professor and Director, CONROD, University of Queensland, Mayne Medical School, Brisbane, Queensland, Australia

REFERENCES

1. Wang C-T, Lin J, Chang C-J, Lin Y-T, Hou S-M. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2004; 86-A:538-545.
2. Modawal A, Ferrer M, Choi HK, Castle JA. Hyaluronic acid injections relieve knee pain. *J Fam Pract* 2005; 54:758-767.
3. Lo GH, La Valley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis. A meta-analysis. *JAMA* 2003; 290:3115-3121.
4. Arrich J, Piribauer F, Mad P, Schmid D, Klaushofer K, Müllner M. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. *CMAJ* 2005; 172:1039-1043.
5. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006; (2):CD005321.
6. Bellamy N, Campbell J, Gee T. Influence of methodology on conflicting results of meta-analyses in systematic reviews: implications for decision-making in osteoarthritis. *Ann Rheum Dis* 2006; 65(Suppl II):224.
7. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology (Oxford)* 1999; 38:602-607.
8. Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology (Oxford)* 2002; 41:1240-1248.
9. Lohmander LS, Dalen N, Englund G, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double-blind, placebo controlled multicentre trial. *Ann Rheum Dis* 1996; 55:424-431.
10. Puhl W. Intra-articular hyaluronan treatment for osteoarthritis. *Ann Rheum Dis* 1997; 56:441.
11. Torrance GW, Raynauld JP, Walker V, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results. *Osteoarthritis Cartilage* 2002; 10:518-527.
12. Hunter DJ, Felson DT. *Osteoarthritis*. *BMJ* 2006; 332:639-642.

FAST TRACK

Clinicians and their patients are probably more interested in the evidence supporting individual products than whole classes