THE CLINICAL EFFECTIVENESS OF HYALURONAN PRODUCTS

We read with interest the review article "Hyaluronans: Is Clinical Effectiveness Dependent on Molecular Weight?" that was published in the September 2006 issue of *The American Journal of Orthopedics* (Vitanzo PC Jr, Sennett BJ. "Hyaluronans: is clinical effectiveness dependent on molecular weight?" *Am J Orthop*. 2006;35(9):421-428.). We were surprised that despite the authors' well-researched bibliography, with references dating back as early as 1993, the review failed to note: 1) several studies that showed differences in efficacy across intra-articular hyaluronan (HA) products and 2) one human study that demonstrated the lack of an antibody-mediated immune mechanism for adverse reactions to hylan G-F 20 (Synvisc®). We also wish to highlight one case of acute pseudoseptic arthritis after injection with sodium hyaluronate (Hyalgan®) that was presented at the 19th Congress of the French Rheumatology Society,[1] after the publication of this review.

In a large (n=348), prospective, observer-blinded, randomized-controlled study, Raman and colleagues[2] compared the clinical effectiveness between hylan G-F 20 (Synvisc®) and sodium hyaluronate (Hyalgan®) over a period of 1 year. Improvement in the WOMAC (Western Ontario and McMaster Universities Orthopedic Index) pain and physical activity subscales were significantly superior in the hylan G-F 20 group at 3 months ($P = .02$), 6 months ($P = .01$), and 12 months ($P = .02$). VAS (Visual Analog Scale) Pain scores also were significantly better for hylan G-F 20 compared with sodium hyaluronate at 6 weeks ($P = .001$), 3 months ($P > .05$), 6 months ($P = .02$), and 12 months ($P = .01$). Directionally similar results, with multiple significant differences, were also captured using the Tegner, UCLA, and Oxford knee scores.

Differences between hylan G-F 20 and other viscosupplements were also noted in a meta-analysis that examined the therapeutic effect of intra-articular injection of hyaluronic acid versus placebo across 20 blinded, randomized-controlled trials.[3] While reduction in pain with activities and improvement in function were observed for all HA therapies examined, results showed that trials involving hylan G-F 20 demonstrated much greater improvement compared with placebo, as measured by SPID% (sum of pain intensity differences), ASPID% (adjusted sum of pain intensity differences), and ASFID% (adjusted sum of function index differences), than trials involving non-cross-linked hyaluronic acid therapies.

In addition, we note the authors' oversight of the study by Marino and colleagues,[4] the only human study that examined potential immunogenic mechanisms for local adverse reactions to hylan G-F 20. In this study, serum and synovial fluid parameters were compared among hylan G-F 20–treated OA patients who experienced a local inflammation of the knee, never experienced a local reaction, or were naïve to any viscosupplement therapy. Results indicated that local inflammatory reactions to hylan G-F 20 were not due to an antibody-mediated immune response, given: 1) the absence of anti–hylan G-F 20 antibodies in the synovial fluid or serum of patients, and 2) the similar concentrations of tryptase detected in all 3 study groups. Since a study in human OA patients has been published, the animal findings described by the authors are irrelevant to clinicians.

Also of interest is one case of acute pseudoseptic arthritis that occurred after injection of sodium hyaluronate.[1] In this case, the adverse reaction resulted in fever and acute arthritis, with arthrocentesis of the knee showing purulent liquid but negative cultures. After hospitalization for 5 days and a course of antibiotics and intra-articular (IA) corticosteroids, the patient's symptoms resolved.

In contrast to the author's conclusions, current evidence suggests superiority of hylan G-F 20 compared with other viscosupplements and that local adverse reactions to hylan G-F 20 are not immunogenic in nature. Published evidence also shows that patients may develop a severe acute adverse reaction after treatment with sodium hyaluronate. We thank the editors for the opportunity to respond to this review article.

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AUTHORS' REPLY

I had the pleasure of reviewing the letter from Genzyme Biosurgery in reference to the article "Hyaluronans: Is Clinical Effectiveness Dependent on Molecular Weight?" Kraines and Roaf, of Genzyme, the producers of hylan G-F 20 (Synvisc), have presented several additional studies since the submission of our review paper. The articles are worthy of discussion and add to the body of knowledge with respect to hyaluronans.

These articles were not included in the publication from September 2006, as these articles were published after the submission of our article. However, they do not change the general conclusions of the article. They add to the body of knowledge that hyaluronans are beneficial

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options in the management of osteoarthritis and do exhibit complications, including synovial flare reactions. While the correspondents add to the literature a case report of sodium hyaluronate's resulting in a pseudoseptic flare reaction, it does not change the relative risk of this occurrence being more prevalent with use of hylan G-F 20. The fact that Marino and colleagues (*Clin Orthop*. 2006;442:187-194) were unable to demonstrate an immunologic cause for the flare reactions involving hylan G-F 20 does not change the fact that these injection flares are real and do occur in patients. It just demonstrates that we do not understand the etiology of the flare reactions observed with hylan G-F 20. These flare reactions do occur at a higher rate with use of hylan G-F 20 than with use of sodium hyaluronate despite the addition of the one case presented in the French literature. I appreciate the opportunity to respond to Genzyme's correspondence.

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