To the Editor

In their *a posteriori* analysis of data from a previous randomized, controlled trial, “Effectiveness and safety of repeat courses of hylan G-F 20 in patients with knee osteoarthritis” (2005;13:111–119) by Raynauld et al.1, the authors concluded that the data indicate no difference in the safety profile of hylan G-F 20 in patients receiving a single-vs repeat-course of 3 weekly injections. While I agree that the use of the hyaluronan class for the chronic pain management of osteoarthritis (OA) has a favorable safety profile2, there is a significant safety concern related specifically to the repeat use of hylan G-F 20. Raynauld et al. have failed to consider their safety findings in the context of the now extensive data regarding the risks of repeat treatment with hylan G-F 20.

These safety issues have been recently reviewed by Goldberg and Coutts3 who clinically defined the pseudo-septic reactions (also termed Severe Acute Inflammatory Reactions, SAIRs) that were encountered with repeat treatment with hylan G-F 20, outlined appropriate treatments, and reviewed 16 published reports (case reports, retrospective analyses and clinical studies) documenting this adverse reaction4. The authors also did not mention the presumably related and more serious clinical adverse reaction of severe granulomatous reaction5, which has now been associated with hylan G-F 20 use in four separate published reports. While Raynauld et al. did not provide sufficient details of their adverse event assessments to allow differential diagnosis, they provided data on the frequency of arthrocentesis, a primary intervention for SAIRs. They noted that the rate of arthrocentesis was 0% in the single-course group and 8.3% in the second-course group (Fisher’s Exact, P = 0.007). This result is at odds with their overall conclusion of no difference in the frequency of adverse events with repeat- vs single-treatment course.

A statistical comparison was also made between groups receiving a single course of hylan G-F 20, one repeat course of hylan G-F 20, and more than one repeat course, with regard to the incidence of local adverse events and of the numbers of patients requiring arthrocentesis. This analysis was conducted using Fisher’s Exact Test where applicable, with a Bonferroni adjustment. It is my understanding that this adjustment may be used when multiple pairwise comparisons are made and that this makes it more difficult for any one comparison to be statistically significant. I question the appropriateness of this method when evaluating a safety issue, when the more conservative approach is desirable, and when only three pairwise comparisons are involved. The rates of arthrocentesis in the first course of treatment in the repeat-course subgroup (1 of 48 patients) and the second course of treatment in the repeat-course subgroup (4 of 48 patients) (P = 0.0194, Fisher’s Exact) were indeed significantly different without this adjustment. Irrespective of the statistical analyses, the incidence of patients requiring arthrocentesis following treatment increased 4-fold upon repeat treatment, 2.1% vs 8.3%; in my view, this finding raises concern worthy of discussion in the context of previous reports in the literature.

The authors’ comparisons to the results of Leopold et al.6 and Lussier et al.7 are difficult to interpret and reconcile, as it appears that the former reported on the incidence of SAIRs, while the latter reported on the incidence of all local adverse reactions of varying degrees of intensities. Neither of these was a randomized study; they were both retrospective and appeared to rely on spontaneous reports from non-standardized methods of safety data capture used by the individual practices. Accordingly, the true incidence of SAIRs may have been underrepresented in these reports. With that said, the 8.3% incidence of arthrocentesis in the present study (if representative of the SAIRs’ frequency) is in line with a number of published reports.

At this point, the evidence associating hylan G-F 20 but not sodium hyaluronates with SAIRs appears to be quite solid: numerous published case reports and small clinical studies have indicated that SAIRs are associated with hylan G-F 20 injections (reviewed in Refs.2,3 with four primary reports8–11 published since). None of these 16 published reports to date are associated with the naturally extracted avian products approved in the US that have been in global use for 18 years, although a single report of a SAIRs-like reaction to a fermented hyaluronic product (not approved for use in the US) was recently published12. The preclinical data are equally compelling for a hylan G-F 20-specific reaction, and indicate that the mechanism for SAIRs is immunologically based. We were the first to report that rabbits developed antibodies to chicken proteins when injected with hylan G-F 20 but not with sodium hyaluronate. Several reports in rabbits, guinea pigs and mice have all confirmed this original observation that hylan G-F 20 can elicit antibody responses, passive cutaneous anaphylaxis, inflammatory infiltrates after repeat exposure and granulomatous reactions, while two comparator naturally derived sodium hyaluronate elicited no discernible reaction13–15. Primates have also been shown to make antibody responses to chicken proteins and/or hylan G-F 20 following repeated intra-articular injections16. Most recently, we identified a 6–8 kDa protein band that may be the immunogenic target during SAIRs.17 In clinical studies, antibodies to hylan or chicken proteins have also been noted in the sera of a patient undergoing a severe pseudoseptic reaction18.

Although I applaud an investigation of product safety, it is prudent to consider all available clinical and preclinical data regarding hylan G-F 20 in conjunction with the safety...
conclusions to allow readers to make informed decisions on the appropriate therapeutic options for their OA patients.

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References