OsteoArthritis and Cartilage (2005) **13,** 1037–1038

doi:10.1016/j.joca.2005.07.006

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Letter to the Editor: Reply to the letter by Max I. Hamburger

To the Editor

We thank Dr Hamburger for the opportunity to revisit the issue of the safety of Hylan G-F 20 (Synvisc).

As a group of investigators our primary papers published in 2002[1,2] as well as the subsequent *a posteriori* analyses[3–5] were driven by statistical plans and protocols that carefully defined the variables we would look at as well as the hypotheses that would drive our analyses and discussion. Since we were doing many subsequent analyses than were originally planned in the primary protocol, we felt that we had to be very stringent in describing how we use the alpha values that would declare a *P* value statistically significant. In our case[3], we chose to be explicit with how we used the Bonferroni adjustment to prevent these secondary analyses from dominating the primary purpose of the study. Dr Hamburger has chosen to interpret the findings with the conventional level of significance, namely the 5% level. As a reader of our work he is free to choose his own level of significance for his interpretation. We simply disagree with his choice of the level criterion. To our knowledge, our study is the only published report in which hypotheses were generated and tested systematically to establish the efficacy and safety of repeat exposure to a viscosupplement (Hylan G-F 20), using data from a large multicentered, randomized clinical trial.

Dr Hamburger claims we failed to consider the work that he and others have published long after we designed and analyzed our data. We conducted a pragmatic study so did not require the clinicians to do all the measurements on reasons for arthrocentesis as well as any other side effects claimed by Dr Hamburger. Indeed, we did not even have the clinicians agree as to what they would call an arthrocentesis, and so we are not certain as to their reliability of scoring and meaning. Moreover, acute pain and swelling of the knee may in fact be an aggravation of the underlying disease itself, including effusion that warrants aspiration and not necessarily related to a local reaction to intra-articular injections of the viscosupplement.

We did not ask for additional measures that would have permitted a differential diagnosis. Since this was not part of our protocol, we cannot be accused of "failing to do" so when the papers being cited were two in 2002, and one each in 2004 and 2005. Finally, our protocol did not specify that any adverse reactions would be combined in a meta-analysis with the other reports in the literature. Most of Dr Hamburger's information on local adverse events are drawn from case reports, reviews of case reports, excerpts from trials, and similar observational data. Indeed, we are not sure how one would properly combine case reports, case series, database cohorts and randomized trials to provide anything except clues as to possible mechanisms; and certainly not the precise numerical estimates.

Dr Hamburger seems to have confused how we chose to report our data. We chose to report rates of events that he claims are incidence rates. This is incorrect since an incidence rate is the conversion of a patient from non-disease to disease over a specific time frame, so his use of the word "incidence" should always be a rate, because the time frame has not been stated at any point in his letter.

Finally, taking rates for rabbits and other primates without doing similar measures in humans can give clues as to possible causes, but certainly does not provide evidence of a human mechanism unless it has been similarly measured in humans. Many of Dr Hamburger's suggestions that he leveled as criticisms of our work could be the focus of head to head studies of the various hyaluronic products to see if the claims that Hylan G-F 20 is different from the rest is indeed born out in humans. Such studies do not appear to have been done to make the claims that Dr Hamburger is making in his letter. While we agree such studies would be clinically valuable, drawing the conclusion that Hylan G-F 20 is worse in multiple course therapy and different from other hyaluronic products seems to be a premature conclusion.

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