Letter to the Editor

Comparative Pharmacokinetics and Pharmacodynamics of Two Recombinant Human Interferon Beta 1a (IFNβ-1a) Products Administered Intramuscularly in Healthy Male and Female Volunteers

Alam and coworkers[1] recently described the results of a study comparing the pharmacokinetics and pharmacodynamics of two recombinant human interferon beta 1a molecules. To compare the pharmacokinetics and pharmacodynamics of any two human recombinant cytokines, equal doses should be administered.[2] The authors state that 6 million units of Avonex™ is 30 μg and 6 million units of Rebif is approximately 20 μg. This either reflects differences in specific activity or that the label doses and units were not calibrated by the same assay. Conclusions based on biological units depends on the assay methodology employed; the standard is the antiviral assay. Although an international standard has been developed, its use, rather than direct intra-assay comparison of activity may confound interpretation of a study such as that of Alam et al. Neopterin, a function of macrophage activation, may or may not reflect antiviral activity.

Interferon beta 1a has a variety of immunomodulatory effects, its mechanisms of action in diseases such as multiple sclerosis are not fully understood. The observed serum neopterin profile differences may well be due to differences in dose by mass of the two products. As the result of intersubject variability, single pharmacodynamic assays cannot be reliably used alone to compare pharmacokinetics.[3–4] Pharmacodynamic studies have generally relied upon a variety of biological markers in addition to neopterin, such as beta 2 microglobulin and 2-5A synthetase, to more fully characterize the biological response. The authors do not comment on other markers of biological response.

In conclusion, the lack of equivalent dose and selection of a single pharmacodynamic parameter in assessing biological effects of interferon beta 1a are flaws in a study which is addressing an important question. The difference in dose by mass may well explain differences in the profile of the two interferons. However, resolution of such questions would best occur if manufacturers work together to define similarities or differences in biological potency or pharmacodynamic responses.

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The authors reply:

We acknowledge in our paper that a difference in dose by mass may account for a portion of the difference in the pharmacokinetic profiles of the two products, AVONEX® and Rebif®. However, the difference in dose by mass is 33% while the area-under-curve for serum interferon levels was 50% lower for Rebif® compared to AVONEX®. Thus, as we note in our paper, even after accounting for the difference in dose by mass, serum interferon exposure is lower for Rebif®.

Perhaps more importantly, the relevant comparison is by dose as labeled on the vial. Although published phase III trial data in multiple sclerosis are available only for AVONEX®, both drugs are available to clinicians in Europe. We are aware that on occasion neurologists will substitute AVONEX® with Rebif®. Since Rebif® is only labeled in units of activity, it is this labeled activity that clinicians have to rely upon to guide dosing when making such substitutions. It is the effects of this type of substitution based upon labeled dose that we were testing in our study. While we could have tested vials side-by-side in the same assay and adjusted the dose of Rebif® accordingly, such an adjusted dose would have no clinical relevance.

With regard to Dr. Borden's second criticism, we believe that the use of a single protocol specified primary pharmacodynamic endpoint is justified when evaluating products for differences in biologic response. The use of multiple markers is important when the objective is to either "fully characterize" the response to a novel interferon compound, or when the objective is to demonstrate that two products are similar; neither was the objective of our study. The specific example Dr. Borden references as one in which multiple pharmacodynamic markers were used was a case where the objective was to establish bioequivalence. We agree that under such circumstances similarity of response across multiple markers provides reassurance of the bioequivalence of the tested materials. In our case, we could have assessed other markers, but results with other markers would not change the fact that with at least one marker there is unequivocally a difference between the two products. Finally, Dr. Borden's specific issue regarding inter-subject variability does not apply because the statistical comparison we performed was based upon within-subject comparisons of the pharmacodynamic responses to the two products.

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