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

In their paper on the comparative pharmacokinetics and pharmacodynamics of two recombinant human IFN beta-1a products, Alam et al. (1) have drawn the conclusion that "The results reported here demonstrate that AVONEX™ and Rebif® are not equivalent when administered intramuscularly". We are unable to agree with this conclusion for the following reasons.

Firstly, a similar mass of each product was not administered. To compare the pharmacokinetics and pharmacodynamics of the two products it is essential to administer similar doses. It is important to base the comparison on mass because the different antiviral assays that are used in various laboratories to measure interferon activity give different potency estimates (2). When they are compared in the *same* bioassay, Avonex™ and Rebif® have identical specific activities. Different potency estimates are obtained using different assays because the international standard, which is not a highly purified preparation and which contains other cytokines, does not behave like the purified interferons in different antiviral assays (2). On a mass basis, the doses of Avonex™ and Rebif® administered by Alam et al. were approximately 30 μg and 20 μg, respectively, as indicated by the authors.

Secondly, we find that Avonex™ and Rebif® are bioequivalent according to FDA guidelines following IM administration (3). A comparative study in 30 healthy volunteers was performed in which identical doses (60 μg) of the two IFN beta-1a preparations were administered, based on protein mass. Avonex™ and Rebif® were injected intramuscularly and Rebif® was also administered subcutaneously. Following IM administration, the two preparations led to superimposable serum concentrations of IFN beta as measured by a specific immunoassay (rather than by an antiviral assay as used by Alam et al.). Bioequivalence was also confirmed by pharmacodynamic markers, intracellular 2′, 5′-oligoadenylate synthetase activity and the concentrations of $beta_2$-microglobulin and neopterin in serum.

The currently available IFN beta-1a preparations are highly purified, physico-chemically characterized proteins. Accurate protein determinations can be performed which are independent of bioassays and the problems associated with their use. When compared on a mass basis, we find that Avonex™ and Rebif® do not differ in their pharmacological parameters.

Silvano Fumero
Senior Executive Vice President
Head of R & D, Ares-Serono

REFERENCES

1. J. Alam, S. Goelz, P. Rioux, J. Scaramucci, W. Jones, A. McAllister, M. Campion, and M. Rogge, *Pharm. Res.* **14**:546–549 (1997).
2. A. Eshkol, M. Mascia, M. Terlizzese, K. Hardy, and F. Antonetti, IBC 5th Annual Conference on Multiple Sclerosis. Cambridge MA. 16–17 June 1997.
3. A. Munafo, I. Trinchard-Lugan, T. X. Q. Nguyen, and M. Buraglio, IBC 5th Annual Conference on Multiple Sclerosis. Cambridge MA. 16–17 June 1997.

The authors reply:

Dr. Fumero's comment that there are 20 μg of interferon beta-1a in "6 MU" of Rebif® versus 30 μg in "6 MU" of AVONEX™ only strengthens our conclusion that the products may not be substituted on the basis of potency units. Moreover, the 33% difference in mass amounts does not fully account for the 50% difference in area-under-curve for interferon activity that we found in our study.

In our study, identical doses of drug were administered with respect to units of activity. Yet, significant differences in serum activity and biological effect by treatment were observed. The conclusion of the study was, ". . . simple substitution of IM Rebif® for AVONEX™ at similar labeled doses is not likely to reproduce the therapeutic effects observed with AVONEX™." Since commercially available vials of Rebif® are labeled in units of interferon activity, the conclusion regarding the practical use of Rebif® and AVONEX™ remains sound.

Finally, we are limited in our ability to respond to Dr. Fumero's comments regarding their own comparison study. Their results have only been reported in abstract form and have yet to be peer-reviewed. However, we will note that in their study the C_{max} after a 60 μg dose of AVONEX™ was approximately 5 IU/mL versus the C_{max} of 33.8 IU/mL after a 30 μg dose in our study. This discrepancy suggests that the immunoassay used by their investigator may not detect the majority of systemically absorbed interferon beta-1a. Furthermore, the conclusion of bioequivalence suggested by Dr. Fumero is most likely an aberration since the assay used by their investigator has a minimum quantifiable level of 2.5 IU/mL and an assay variability of 22%. With regard to pharmacodynamic equivalence, their investigators did not present baseline-corrected parameters; thus drug-related increases in these biological activity markers cannot be compared by treatment. As a result, no conclusions regarding bioequivalence may be drawn from their findings.

By either the logic in our paper or by Dr. Fumero's points, it's evident that 6 MU of Rebif® may not be substituted for 6 MU of AVONEX™.

John J. Alam
Director, Medical Research
and
Mark C. Rogge
Manager of Development
BIOGEN
14 Cambridge Center,
Cambridge, Massachusetts 02142

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