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Editorial

When marketing and science intersect

Do patients with MS benefit?

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MS entered the treatment era a scant 9 years ago with US Food and Drug Administration (FDA) approval of interferon β-1b. Since then, two interferon β-1a preparations, an amino acid polymer, glatiramer acetate; and a chemotherapeutic agent, mitoxantrone, have received regulatory approval in the United States and many other countries for various forms of relapsing MS. Approval is based on modest but clear-cut efficacy and acceptable toxicity. The details of the studies leading to these approvals are well described in a review article in the January 22, 2002 issue of *Neurology*.[1] Although we now have a fuller treatment armamentarium, our understanding of the mechanisms of action of these agents is speculative, with much of what we think we know "reverse engineered" from the outcomes of the clinical trials. Equally important, information as to optimal dose, route of administration, and dosing frequency is quite limited for any of the agents, to say nothing about their comparative efficacy and safety. Thus, there is little in the way of science to inform the use of these agents in a clinical setting, as compared to therapeutics in most other areas of neurology, e.g., anticonvulsants, antiparkinsonian agents, migraine.

In this issue of *Neurology*, Panitch et al.[2] report a randomized, single-blind (assessors) comparison of two different doses and dosing schedules of interferon β-1a. The results favor a higher dose administered more frequently. This is an important article, and worthy of publication in *Neurology*. As the assessors of the primary clinical and MRI outcome measures were blinded, this is class I evidence. However, this is far from a perfect study.

The design was single blind: patients were aware of their treatment assignment and presumably knew that a new, and hopefully better, form of an available therapy was being tested. The study also had limited objectives, lasting only 48 weeks, with a 24-week primary outcome. Because the comparative agents were delivered by different routes and in different doses and frequencies, the study does not clarify whether the reported superiority of one agent is related to dose, route, or frequency of use—an issue that is key to understanding how to use interferon β-1a optimally. As with any trial, additional criticism can, and likely will, be levied.

Perhaps the main criticism of this trial is that it was apparently designed primarily to provide evidence to the FDA that one brand of interferon had sufficient therapeutic superiority to justify overturning the Orphan Drug Act protection of another. Although there is precedent for overturning such protection, even for MS medications, it has usually been based on a more favorable safety profile rather than clinical superiority. Nonetheless, provisions of the Orphan Drug Act allow for such action should clinical superiority be demonstrated to the satisfaction of the FDA. The trial of Panitch et al. has led to an overturning of orphan drug protection.

A similar concern—that comparative market issues have a role in trial design—might be raised by a second study by Clanet et al.[3] also published in this issue of *Neurology*. However, in this well-conducted trial, the investigators are able to provide convincing evidence of an absence of dose effect of interferon β-1a when it is administered IM once weekly, while avoiding confounding issues of different routes and frequencies of delivery.

Marketing-influenced studies are usually less interesting by their very nature, as the scientific questions tend to be secondary. Had these studies been done without concern for marketing issues, they could have been designed differently and thus could have been more informative to the physician and patient community. Moreover, in a primarily market-driven study, there is justifiable concern that the trial design can be manipulated to favor a predetermined outcome. Although there is no indication of this in the current trials or in prior MS disease–modifying agent (DMA) studies, this is not a trivial issue in a DMA marketplace that exceeds $2.5 billion worldwide. Should we be more concerned about the

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potential "Enronization" of the data analyses provided by corporate entities?

So, why are these important trials worthy of publication in *Neurology*? Despite some design limitations, the Panitch et al.[2] study provides the best available head-to-head comparative data to date of any of the DMA studies. Given the minimal extant dosing/frequency/route information available, the new data provided are useful. These studies then can help guide physician and patient treatment decisions in a way not previously possible. Consequently, we have a true intersection of a marketing interest and a scientific need. Additionally, because the Panitch et al.[2] study data were submitted for FDA review, there was a separate analysis by that agency. The FDA analysis, which is available on the FDA Web page (*http://www.fda.gov/cber/review/ifnbser030702r3.pdf*), provides an independent, detailed, well-analyzed affirmation of the report of Panitch et al.[2] and mitigates much of the concern raised in the preceding paragraph. Finally, Panitch et al.[2] and Clanet et al.[3] serve to increase our ability to choose more rationally among the therapeutic options for treating MS. They also highlight the obvious remaining gaps in our knowledge and understanding in treating this enigmatic illness.

References

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