In an ideal world, clinicians would decide on the relative merits of treatments based on high-quality evidence from randomized, double-blind, controlled clinical trials. The need for such evidence is particularly acute when there are several treatments available but no trials comparing efficacy. In this issue of Neurology, two randomized clinical trials report the relative benefits of different strategies of MS treatment with parenteral interferons. Although both interferon β-1a and interferon β-1b have been shown to delay the progression of disability in relapsing-remitting MS, there remains uncertainty about the relative benefits of the products available, as well as the optimal dosage, route, and frequency of administration of those products.

The study by Clanet et al. was a randomized, double-blind, parallel group trial of two dosages of interferon β-1a. The participants were followed for a minimum of 3 years and the primary outcome variable was the time from randomization until a sustained increase of 1 or more points on the Expanded Disability Status Scale, a commonly used outcome variable in MS trials. The investigators compared 30 g with 60 g, each given IM once weekly. The clinical efficacy, tolerability, incidence of neutralizing antibodies, and MRI outcomes were essentially the same between the two groups. This study provides clear, high-quality evidence that the higher dosage of this preparation given on a once-weekly basis confers no therapeutic advantage. This type of “negative” study is of great utility to clinicians and patients in avoiding the unnecessary use of higher dosages, which may be associated with higher long-term toxicity and higher costs.

In the study by Panitch et al. (the EVIDENCE trial), the investigators chose to study two different preparations of interferon β-1a with the objective of determining the relative efficacy of the two products. There are major methodologic shortcomings of this study, and the end result is more questions rather than clear evidence that can guide therapeutic decisions. Key methodologic features differentiate this trial from the trial by Clanet et al. First, this is a trial of 6 months’ duration, with relapse freedom (not a disability measure) as the outcome variable. Second, the subjects themselves were not blinded to the treatment regimen, which could bias the reporting of relapses. Third, two different commercial products were compared. Last, and perhaps most important, is the fact that the investigators, in addition to comparing two different products, also compared two different routes of administration, two different dosages, and a different frequency of administration. The relapse-free rate was lower in those receiving 30 μg IM weekly compared with those receiving 44 μg subcutaneously (SC) three times weekly (tiw) (63% vs 75%). MRI outcomes were also better in the tiw group. However, neutralizing antibodies (25% vs 2%) and adverse events (particularly injection site disorders and abnormalities of white blood counts and serum liver transaminase levels) were more common in the tiw group.

The interpretation of the findings of the EVIDENCE trial is seriously limited by the methodologic shortcomings. Although we know that one treatment strategy is associated with a higher short-term relapse-free rate, we have no information on the long-term progression of disability. Although some studies have suggested that there is an association between early relapse rate and subsequent development of disability, the investigators have yet to demonstrate that a lower relapse-free rate, particularly of the magnitude found in the EVIDENCE trial, will translate into a faster progression of disability. Given that the relative impact of the two treatment strategies on disability is unknown, does the benefit on relapses and MRI outcomes associated with the 44 μg three times weekly regimen outweigh the risks in terms of the higher rates of neutralizing antibodies and clinical adverse events? The EVIDENCE trial was not designed to provide a definite answer to this question. Furthermore, which aspect of the diff-
different treatment strategies led to the decrease in relapses, the different preparation (Avonex vs Rebif), the frequency of administration, the route of administration (IM vs SC), or the higher weekly dosage?

What conclusions can be drawn from these studies? It is clear from the trial of Clanet et al.\(^1\) that for individuals receiving interferon β-1a by weekly IM injection, 30 μg should be favored over 60 μg. The EVIDENCE trial, however, which compared two currently available interferon β-1a treatment regimens, appears to have been designed to satisfy primarily regulatory and marketing concerns rather than scientific ones. It is unfortunate that the large investment made in this trial was not directed toward comparing the impact of different preparations or routes or frequencies of administration (while holding the other factors constant) on disability. Only through well-designed trials will we determine the optimal preparation, dosage, and route of administration of interferon β-1a for slowing the progression of MS disability.

**References**
