New Agents for Multiple Sclerosis and the Difficulties that Lie Ahead

Douglas R Jeffery, MD, PhD

Associate Professor, Department of Neurology, Wake Forest University Health Science Center

Abstract

A host of new oral agents are being developed for use in relapsing forms of multiple sclerosis (MS). Although many of these agents may be both safe and effective, they could fail in clinical trials because the population of patients enrolled in such trials may behave in a fashion not taken into account by the statistical assumptions used in trial planning. In recent trials on study relapse, rates have been far lower than those observed in earlier clinical trials. This could decrease the power of a trial and result in failure to meet statistical significance even if the agent in question is effective. The same problem could also result in the failure of trials to meet disability outcomes. If too few patients progress on trial it may be difficult to demonstrate an effect on disability progression. The outcome of current MS clinical trials may stimulate the development of new designs and surrogate markers.

Keywords

Multiple sclerosis, clinical trials, relapse rate, oral agents, disability progression

Disclosure: Douglas R Jeffery, MD, PhD, has been a speaker for Teva, Novartis, Bayer, and Biogen and a consultant for Teva, Biogen, Bayer, Novartis, Serono, and GSK, and has received research support from Bayer, Biogen, Teva, and Serono.

Received: November 3, 2008 **Accepted:** July 27, 2009 *DOI: 10.17925/USN.2009.05.01.54*

Correspondence: Douglas R Jeffery, MD, PhD, Department of Neurology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157
E: djeffery@wfubmc.edu

The future of therapeutic alternatives in multiple sclerosis (MS) at first glance appears brighter now than at any time in the history of modern MS therapeutics. A host of new agents, both oral and intravenous, are in various stages of development. Patients and physicians alike have been clamoring for oral agents and drugs with greater efficacy and safety and better side-effect profiles than those currently available. Of the oral agents in phase II or III clinical trials, there are cladribine, laquinimod, fingolimod, BG-12, teriflunamide, and oral VLA-4 antagonists. There are also new parenteral agents that promise better efficacy but are not as far along in development as the oral agents. These include dacluzimab, ofatumumab, ocreluzumab, alemtuzumab, and atacicept. While there is considerable excitement about the newer agents on the part of patients and physicians, problems with clinical trial design could prevent these agents from coming to market even though they may be safe and effective.

Several issues with clinical trial design could pose serious problems for both ongoing and future clinical trials in MS. One major problem is that clinical trial populations in recently completed or ongoing studies have been much less active than the clinical trial populations studied in the pivotal trials of the mid-1990s.[1] This was evident in the AFFIRM trial and may have played a role in the failure of the REGARD, BEYOND, and FORTE trials.[2–4] In each of these trials, the overall on-study relapse rate was very low: in REGARD it was 0.29, in BEYOND 0.35, and in FORTE 0.27. Phase II studies of glatiramer acetate suggested the 40mg dose was superior to the 20mg dose, but the FORTE trial—which compared the 20 and 40mg doses in patients with relapsing–remitting MS—failed. This could have occurred because the actual on-trial relapse rate was far lower than that predicted in the power calculations, so statistical significance could not be achieved. The same held true for the BEYOND study. A safety trial comparing 250–500µg of interferon (IFN)-β-1b suggested that the 500µg dose was superior.[5] In the large phase III trial no difference between the two doses was evident. Relapse rates were quite low at 0.35 overall, suggesting that the population in this trial had very little activity or very mild disease. In patients with mild disease it may be difficult to distinguish between two effective agents, or between two doses of a single effective agent. One would not be able to distinguish placebo from an effective agent in a trial population of patients with benign MS.

There are several reasons why the populations of patients entering clinical trials differ from those in past trials and why patients enrolled in current trials may have very low levels of disease activity. One reason is that there are now many treatment alternatives and investigators are reluctant to risk putting active patients into a clinical trial where they might be exposed to a placebo or to an agent with a perceived efficacy that is less than what might be desired. Another reason is that patients may now satisfy diagnostic criteria for MS using McDonald criteria and may not experience a second relapse.[6] The most important reason probably lies in the inclusion

© TOUCH BRIEFINGS 2009

standards. The majority of recent clinical trials have employed inclusion criteria that require one relapse in the 12 months prior to study entry, or two relapses in 24 months, or one enhancing lesion in month 0–12 and one relapse in the 24 months prior to study entry. As a result, the easiest way for a patient to satisfy entry criteria is to have a single relapse in the 12 months prior to study entry and the majority of patients entering the trial will likely be enrolled according to that criterion. This relapse may be mild or severe, as long as there is sufficient documentation of relapse. This criterion poses a problem: simply, one relapse in the 12 months prior to study entry does not predict a sufficiently high rate of on-study relapse to satisfy the power calculations employed in most trials. Patients enrolled on the basis of a single attack in the year prior to study entry are likely to show a placebo relapse rate of between 0.4 and 0.5. While the BENEFIT trial was carried out on patients with clinically isolated syndromes with two more magnetic resonance imaging lesions, 85% satisfied McDonald criteria after two years, so that patients enrolled in that trial already had MS.[7] The placebo relapse rate was 0.4. If one back-calculates relapse rates in BEYOND and REGARD, assuming a 35% decrease as reported in pivotal trials, the result would be will in the range of 0.5.

Most power calculations predict a placebo relapse of around 0.7 to 0.8, based on the results of AFFIRM. If the actual placebo relapse rate that occurs in a given trial is only half that predicted, the number of on-trial events will be far too few to reach statistical significance unless the magnitude of the effect on relapses far exceeds that predicted in the power calculations. That is an unlikely scenario. One solution to this problem is to prolong the trial until an adequate number of on-trial events have occurred. This is expensive and could significantly prolong the clinical trial, but there is another problem with this approach. Relapse rates are basically a surrogate for inflammatory disease activity. Counting relapses in theory is quite simple, but the reality is more complicated. There are confirmed relapses accompanied by a change in expanded disability status scale (EDSS) and unconfirmed relapses that are not accompanied by a change in EDSS. There are also pseudo-relapses, which may mistakenly be counted as real relapses. In practice, new or recurrent symptoms may be due to environmental factors or to mild inflammatory disease activity. Whether or not these are counted as relapse may depend on a variety of different factors. Even experienced investigators may have difficulty deciding whether or not the event should be counted as a relapse. The result is that, in patients with very low levels of disease activity, the signal-to-noise ratio may drop and even prolonging the trial to obtain the necessary number of events will not solve the problem.

Another problem lies in the main secondary end-point: progression of disability as measured by a one-point increase in EDSS confirmed at three or six months. A review of past clinical trials reveals that the number of patients who progress is in proportion to the placebo relapse rate. The greater the placebo relapse rate, the greater the proportion of patients who progress according to the above criterion. In the PRISMS trial the placebo relapse rate was 1.5, and 36% progressed.[8] In AFFIRM the placebo relapse rate was 0.75, and 29% of the placebo group progressed.[4] In BENEFIT the placebo relapse rate was 0.4, and only 20% progressed.[7] Most of the phase III clinical trials currently in progress have employed the progression of disability as their main secondary end-point and predict that 30% of the patients on placebo will progress over a two-year period. This end-point is used so that the registration with regulatory authorities will include an indication for decreasing the progression of disability. Since the placebo relapse is tied to the proportion of patients with disability progression, the inclusion of patients with low levels of disease activity will jeopardize this end-point. Also, a lower proportion of placebo-treated patients will have progression of disability.

Given the nature of the trial populations, it is entirely conceivable that agents that are safe and effective could fail in clinical trials because of faulty power calculations and inactive patient populations. The oral cladribine trial (CLARITY) will soon be complete. The results of this trial could serve as an indicator for future trials since it enrolled patients with relapsing–remitting MS with one relapse in the year prior to study entry and a predicted placebo relapse rate of approximately 0.75. Despite its potent anti-inflammatory effects, it could still fail in clinical trials.

It seems that an easy solution to the problem would be to restrict inclusion criteria to those that predict a higher on-study relapse rate, such as including only patients with two relapses in the two years prior to study entry, or to those with one relapse and one enhancing lesion.[9] However, there is huge competition for clinical trial patients and only so many are available. At present there are at least eight large-scale phase II and III trials competing for the same patients. Pharmaceutical companies are reluctant to limit entry and make it more difficult to enroll patients. Limiting entry prolongs the duration of time required to fully enroll and is far more expensive. Further, access to the agent in some markets may require that patients satisfy the inclusion criteria used in the trial. This could severely limit access to the drug once it has been approved.

The alternative is to risk having drugs that are both safe and effective fail in clinical trials. Given that clinical trials cost hundreds of millions of dollars, it would appear more prudent to restrict entry to those patients with more active disease. The next few years will see a number of trials that used the entry criteria cited come to completion. It will be a very interesting future full of uncertainty that will eventually lead to the use of surrogate markers or vast modifications in clinical trial design. ■

Douglas R Jeffery, MD, PhD, is an Associate Professor of Neurology at the Wake Forest University School of Medicine, where he established the multiple sclerosis (MS) clinic. His area of clinical and research interest is MS, and he remains active in MS research and has served on the steering committee for numerous clinical trials in MS. He is also involved in neuroimaging studies in MS using diffusion tensor, spectroscopy, and magnetization transfer imaging.

1. Uitdehaag B, et al., *Neurology*, 2008;70(Suppl. 1):P02.155,A89.
2. Mikol D, et al., *Mult Scler*, 2007;13(Suppl. 2)119.
3. O'Connor P Filippi M, Arnason BGW, et al., Magnetic resonance Imaging findings of a phase III trial comparing Betaferon with Copaxone treatments in relapsing-remitting multiple sclerosis, Late breaking news, Academy of Neurology, April 2008.
4. Polman CH, et al., *N Engl J Med*, 2006;354:899–910.
5. Hurwitz BJ, et al., *Clin Ther*, 2008;30(6):1102–12.
6. Polman CH, et al., *Ann Neurol*, 2006:59(4):727–8.
7. Kappos L, et al.; for the BENEFIT Study Group, *Lancet*, 2007;370:389–97.
8. *Lancet*, 1998;352(9139):1498–1504.
9. Sormani MP, et al., *Neurology*, 2007;69(12):1230–35.