ABSTRACT

Four major disease-modifying therapies are discussed within the context of relapsing and remitting multiple sclerosis. The major trials leading to approval by the US Food and Drug Administration (FDA) for these medications (interferon beta-1a; Avonex, Biogen Idec, Cambridge, Mass; interferon beta-1a; Rebif, Serono, Geneva, Switzerland; interferon beta-1b; Betaseron, Berlex, Montville, NJ; and glatiramer acetate; Copaxone, Teva Neuroscience, Kansas City, Mo) are compared, examining various endpoints, including relapse rate, disease progression, time to next exacerbation, and magnetic resonance imaging findings. There is also discussion of natalizumab (Tysabri, Biogen Idec, Cambridge, Mass, and Elan, New York, NY), which is currently being evaluated by the US FDA and may become available again soon. An analysis of comparative data and side-effect profiles are among the issues discussed in an effort to guide clinicians to work with individual patients in making the best possible treatment decisions.

(Adv Stud Med. 2006;6(7D):S694-S700)

T

here are currently 4 US Food and Drug Administration (FDA)-approved immunomodulatory drugs for the treatment of relapsing-remitting multiple sclerosis (RRMS). Three are interferons (Avonex, Biogen Idec, Cambridge, Mass [interferon beta-1a]; Rebif, Serono, Geneva, Switzerland [interferon beta-1a]; and Betaseron, Berlex, Montville, NJ [interferon beta-1b]), and the fourth is glatiramer acetate (Copaxone, Teva Neuroscience, Kansas City, Mo). Table 1 lists the major controlled clinical trials that have evaluated these medications. These trials differ in their design: early treatment trials have examined the role of various medications in the setting of a single clinical event, whereas other trials have looked at an individual drug’s activity throughout the course of multiple sclerosis (MS). A relatively few number of trials have been comparative, during which 2 different medications are evaluated in 1 patient population. A variety of endpoint measures have also been used, including the number of relapses or the annual relapse rate; magnetic resonance imaging (MRI) findings including new lesion counts/enhancing lesions; the percentage of patients who remained exacerbation-free; and disease progression as measured by the Kurtzke Expanded Disability Status Scale (EDSS). Let us consider some of these pivotal trials in detail.

INTERFERON BETA-1B (BETASERON)

The first medication to be US FDA approved for the treatment of RRMS was Betaseron in 1993, based on a multicenter, randomized, double-blind, placebo-controlled trial of interferon beta-1b in 372 patients with RRMS. Patients enrolled in the trial had to have an EDSS score of 0 to 5.5 and had to have had 2 or more exacerbations in the previous 2 years. They were randomized to 175 µg/week or 875 µg/week of
Betaseron or placebo—all by subcutaneous injection. The primary endpoint was differences in exacerbation rates. After 2 years, the annualized exacerbation rates were 1.27 for patients receiving placebo and 1.17 and 0.84 for those in the low-dose and high-dose Betaseron groups, respectively (Figure 1). Exacerbation rates were significantly lower in both treatment groups compared to the placebo group (875 µg vs placebo [P = .0001]; 175 µg vs placebo [P = .0101]; and 875 µg vs 175 µg [P = .0086]). There was a 2-fold reduction in the frequency of moderate and severe attacks in the 875-µg treatment group (n = 36) at 2 years compared to the placebo group (n = 18; P = .007). Patients treated with Betaseron were also significantly more likely to have inactive MRIs (16% vs 35%; P = .001). EDSS scores changed little from baseline in the placebo and treatment arms.1

**INTERFERON BETA-1A (AVONEX)**

The pivotal Avonex trial was designed to determine if weekly intramuscular injections of interferon beta-1a (30 µg) could affect the progression of physical disability associated with MS. This was a randomized, double-blinded, placebo-controlled, multicenter phase III trial involving 301 patients with RRMS. The primary outcome was time to sustained disability progression of at least 1.0 point on the EDSS, sustained for 6 months. The authors found that interferon beta-1a treatment produced a significant delay in time to sustained EDSS progression (P = .02). The proportion of patients progressing by the end of 104 weeks was 34.9% in the placebo group and 21.9% in the interferon beta-1a-treated group. Patients treated with interferon beta-1a also had significantly fewer exacerbations (P = .03) and a significantly lower number and volume of gadolinium-enhancing brain lesions on MRI (P values ranging between .02–.05). Over 2 years, the annual exacerbation rate was 0.90 in placebo-treated patients versus 0.61 in interferon beta-1a–treated patients.2 Interestingly, in those patients who only completed 1 year of the study, those who received Avonex actually had a higher relapse rate than patients taking placebo (Figure 2). One possible explanation for this has been that the patients who entered

<table>
<thead>
<tr>
<th>Table 1. Representative Major Therapeutic Trials in RRMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual Drugs</strong></td>
</tr>
<tr>
<td>IFN-beta MS Study Group (Betaseron)</td>
</tr>
<tr>
<td>Copolymer-1 MS Study Group (Copaxone)</td>
</tr>
<tr>
<td>MS Collaborative Research Group (Avonex)</td>
</tr>
<tr>
<td>PRISMS (Rebif)</td>
</tr>
</tbody>
</table>

IFN = interferon; BENEFIT = Betaseron in Newly Emerging MS for Initial Treatment; CHAMPS = Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study; ETOMS = Early Treatment of Multiple Sclerosis; EVIDENCE = Evidence of Interferon Dose-Response: European North American Comparative Efficacy; INCOMIN = Independent Comparison of Interferon; PRISMS = Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis; RRMS = relapsing-remitting multiple sclerosis.

Reprinted with permission from Neurology. 1993;43:655-661.1

**Figure 1. Relapse Rate for Patients Taking Betaseron**

![Graph showing annualized exacerbation rate for patients taking Betaseron with different dosages.](image-url)
the study late or who exited the study early represent-
ed a biased cohort, a different patient population than
those who remained in the trial for 2 years. The find-
ing may also be representative of the heterogeneous
nature of MS; some patients were drug responders and
others were nonresponders.

**Glatiramer Acetate (Copaxone)**

In one of the pivotal Copaxone studies, Johnson et
al conducted a multicenter, randomized, phase III trial
of patients \( (n = 251) \) with RRMS.\(^3\) Fifty percent of the
subjects received glatiramer acetate at a dosage of 20
mg subcutaneously daily for 2 years; 50% received
placebo. The primary endpoint was the difference in
relapse rate, which was \(1.19 \pm 0.13\) for patients receiv-
ing glatiramer acetate and \(1.68 \pm 0.13\) for those receiv-
ing placebo. There was a statistically significant 29% 
reduction in favor of the study medication \((P = .007; \ 
annualized rates = 0.59 \text{ for Copaxone and } 0.84 \text{ for } \ 
placebo; \ Figure 3).\) Trends in the proportion of relapse-
free patients, median time to first relapse, and indica-
tors of disability (as measured by the EDSS) all favored
Copaxone, but were not always statistically significant.
In terms of MRI results, those on Copaxone had fewer
new lesions versus placebo-treated patients, again sup-
porting the efficacy of glatiramer acetate \((P = .01)\).

**Interferon Beta-1A (Rebif)**

In the Prevention of Relapses and Disability by Interferon Subcutaneously in Multiple Sclerosis study, 560 patients with RRMS were randomized to receive placebo or subcutaneous interferon beta-1a 22 or 44 µg 3 times weekly for 2 years. Patients who had been receiving placebo were then rerandomized to 1 of the 2 doses of interferon beta-1a for an additional 2 years. Patients taking the original study medication continued at the same dose. As with prior studies, relapse rate was the primary endpoint, and investigators also wanted to determine if so-called “delayed therapy” would have any effect on overall disease progression.\(^4\)

Looking at the data from the first 2 years (patients on drug or placebo without crossover), there was a statistically significant difference \((P < .005)\) between placebo and drug in terms of the relapse rate. However, there was no significant difference between the 2 doses of Rebif; they were both better than placebo (Figure 4).\(^5\) When investigators looked at that same data at the

4-year mark, taking the placebo arm and crossing them
over to a 44-µg dose (the higher dose of Rebif), the
patients now had a benefit that mirrored the long-
term–treated patients in terms of relapse rate. These
data suggest that if therapy is delayed in a patient with
clinically definite MS, their relapse rate is still compa-
ritable to patients who have been on the drug all along.
However, these data do not determine whether long-
term disability is worse in patients with a delay in

treatment (Figure 5).\(^6\)
When investigators looked at disease progression, which in this study was defined as a 1-point change in EDSS scale over 3 months, there was a trend in favor of Rebif therapy with not a statistically significant difference between the 2 doses in terms of the 2-year data. The same trend was noted at 4 years, and it is clear that over 4 years, MS symptoms progressed despite therapy. Although disease progression did slow significantly compared to placebo, the medication did not entirely stop disability from occurring. In terms of MRI data, 100% of patients on placebo developed new T2 lesions within the first 2 years of study. In contrast, approximately 66% of patients on the lower dose of Rebif and 33% of patients on the higher dose developed new lesions; there was a statistically significant difference between the 2 doses. After 2 years, when the placebo arm was crossed over to the higher dose of medication, the rate of new T2 lesions dropped among this group—only 50% of the scans obtained in this crossover arm had new T2 lesions over years 3 and 4, a significant improvement from years 1 and 2.

### Comparing Therapies

Ideally, clinicians would be able to evaluate the evidence from these 4 major trials of immunomodulatory drugs and determine which therapy is best for any given patient. In practice, this becomes very complex. Comparing trials using reduction of relapse rate or disease progression, we find that there is no significant statistical difference between the medications. Even more importantly, these trials should not and cannot be compared; they differ in study design, primary endpoints, and patient populations (in terms of disease activity and EDSS baselines). Some of the studies had extensions and potential design biases cannot be controlled for when trying to compare data between different studies. Head-to-head trials comparing individual therapies are the only method by which we can begin to answer, with some certainty, whether there is a distinct difference between the available disease-modifying MS drugs.

Two such trials were the EVIDENCE (Evidence of Interferon Dose-Response: European North American Comparative Efficacy) trial, which compared Rebif and Avonex, and the INCOMIN (Independent Comparison of Interferon) trial, which involved Betaseron and Avonex. The EVIDENCE trial demonstrated that interferon beta-1a 44 µg administered subcutaneously 3 times weekly (Rebif) was significantly more effective than intramuscular interferon beta-1a 30 µg administered once weekly (Avonex) in reducing clinical relapses and MRI activity in patients with RRMS. This was true at 24 and 48 weeks of therapy. Follow-up studies revealed that the efficacy of Rebif depended to some extent on whether patients were neutralizing antibody positive or negative, but a difference between Rebif and Avonex persisted even over 4 years, and it is clear that
when this was taken into account. Whether this apparent difference will be retained throughout the duration of therapy remains to be proven.

When we compare another set of high- versus low-dose interferon data (Betaseron vs Avonex) from the INCOMIN trial, we see that there is still a difference, although not quite as robust in this study, in terms of the patients who are relapse-free—51% in the Betaseron-treated group (administered interferon beta-1b 250 µg on alternate days) versus 36% in the Avonex-treated group (administered once-weekly interferon beta-1a 30 µg; \( P = .03 \)). In addition, 55% of patients compared to 26% on Betaseron versus Avonex, respectively, had no new T2 lesions at MRI at 24 months (\( P < .0003 \)).

In addition, 55% of patients compared to 26% on Betaseron versus Avonex, respectively, had no new T2 lesions at MRI at 24 months (\( P < .0003 \)). When we compare another set of high- versus low-dose interferon data (Betaseron vs Avonex) from the INCOMIN trial, we see that there is still a difference, although not quite as robust in this study, in terms of the patients who are relapse-free—51% in the Betaseron-treated group (administered interferon beta-1b 250 µg on alternate days) versus 36% in the Avonex-treated group (administered once-weekly interferon beta-1a 30 µg; \( P = .03 \)). In addition, 55% of patients compared to 26% on Betaseron versus Avonex, respectively, had no new T2 lesions at MRI at 24 months (\( P < .0003 \)). In both groups, the differences between the 2 treatment groups increased during the second year of study, suggesting that, at least in short-term trials (1–2 year data), higher-dose interferon may be more effective. The question remains as to whether there will any differences between these dosing regimens over the long term.

**Natalizumab**

Although not currently available for the treatment of RRMS, natalizumab (Tysabri, Biogen Idec, Cambridge, Mass, and Elan, New York, NY) is currently under consideration by the US FDA for a return to the market after an investigation of safety concerns. Natalizumab is a monoclonal antibody that prevents leukocytes from infiltrating the brain and causing myelin disruption. In early trials by Miller et al, this drug did have a statistically significant impact in terms of decreasing the percentage of patients with relapses, and an even stronger impact on MRI data. At a dose of 3 or 6 mg per kilogram, 19% of natalizumab-treated patients experienced relapses, compared to 38% of patients receiving placebo. Treated patients had a median number of new gadolinium-enhancing MRI lesions of zero, compared to 2 new lesions in the placebo group. These results were seen after only 6 months of the study.

**To Treat or Not to Treat**

Evidence from CHAMPS (Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study) and ETOMS (Early Treatment of Multiple Sclerosis) trials demonstrate that early treatment of a clinically isolated syndrome appears to delay progression to clinically definite MS. However, whether early treatment makes a difference in the ultimate outcome is still an unanswered question. In other words, are patients less disabled over the long run if treatment is begun immediately after their first episode? Thus, although ETOMS and CHAMPS provide evidence of benefit for early treatment in demyelinating disease, there are several caveats. First, some patients who are never going to progress to MS may be started on therapy unnecessarily, with its associated costs and adverse effects. Second, there is no long-term data to show that early treatment makes a difference in disability (but there is some evidence to suggest that prevention of relapses may prevent disability). Lastly, longer exposure to interferon may increase the risk of developing neutralizing antibodies, which may limit efficacy later. These issues must be balanced against the potential to prevent disability by starting treatment early. Early therapy should be routinely offered, but these complex issues need to be discussed with every patient, thus they can make a well-informed decision.

**Clinical Trials in Multiple Sclerosis**

There are many challenges in designing and interpreting clinical trials in MS. For example, how do we define treatment failure? If the population studied at the onset has clinically isolated syndromes, treatment failure may be defined as conversion to clinically definite MS or as the development of disability. How do we determine the proper endpoint for a study, how do we decide if the treatment has been a success or a failure? Do we select disease progression as the endpoint? Do we look at the occurrence of relapses within a given length of time? MS is a disease that by its very nature has relapses and remissions with fluctuations in symptomatology. What evidence of disease progression should we utilize? Should we examine patient-defined symptoms or confirmed test results, such as MRI data? And, how do we effectively blind our study population, when adverse events from the medications under investigation are common? Finally, there is the issue of “regression to the mean” (ie, the inherent probabilities within patient populations with MS that there are going to be changes over time). When we look at a regression to the mean analysis, even among the placebo arms from previous trials, there is great variability in the relapse rates (Figure 6). Ultimately, the most useful data would be measures of disability over time.
**ADVERSE EFFECTS**

This leaves us with the challenge of making difficult decisions with our patients regarding the risks and benefits of various treatments. Often, patients will look at the side-effect profiles of medications to choose the best drug for them. With the interferons, injection site reactions are most common (although less common with Avonex because it is an intramuscular, not a subcutaneous injection), along with flu-like symptoms, depression, headaches, leukopenia, and elevated liver function tests (Table 2). Patients taking Copaxone may have site reactions and an idiosyncratic reaction within minutes after an injection, with flushing, palpitations, chest pain, and shortness of breath (Table 3). This is still not understood, but is usually a 1-time event that resolves within 20 to 30 minutes. It is not an allergy, and it is not a contraindication to continuing Copaxone therapy. However, it is important to warn patients about this reaction because it can be a cause for alarm, and for inappropriately discontinuing the medication. It is important for patients to have careful instruction in appropriate injection technique for all 4 medications, thus minimizing side effects such as site reactions.

**CONCLUSIONS**

As researchers continue to search for a cure for MS, clinicians continue to attempt to select the best therapy for their patients based on the available clinical trial evidence. There are 3 major aspects to counseling patients about MS treatment and improving their adherence to therapy. The first key is to communicate a clear understanding of goals. The goal of MS treatment is a reduction in disease activity—not a cure. Frequently, patients may discontinue therapy if they have an exacerbation. They need to understand that the goal is to reduce the number of relapses; unfortunately, we cannot yet prevent all of them. The second key is the management of side effects, with careful attention to lifestyle issues. Finally, it is critical to have a clear long-term plan, especially in patients with clinically isolated syndromes. Patient education and counseling are essential as we work with them to treat this disease with our, at best, imperfect tools to date.
REFERENCES


