Disease-Modifying Drugs for Relapsing-Remitting Multiple Sclerosis and Future Directions for Multiple Sclerosis Therapeutics

Richard A. Rudick, MD

With the development of effective therapies for multiple sclerosis (MS), therapeutic nihilism, which was so prevalent just 10 years ago, has given way to exuberance and optimism. The current mood is understandable because MS is such a devastating disease. Within 10 years of symptom onset, 50% of patients with MS are unable to carry out household and employment responsibilities; within 15 to 20 years, 50% are unable to walk unassisted; and within 25 years, 50% are unable to walk at all. The average annual cost of MS in the United States has been estimated at greater than $6.8 billion, or $34,103 per person.1 This review summarizes evidence that disease-modifying drugs can significantly improve the course of patients with relapsing-remitting MS (RRMS) and frames key issues relating to the use of current drugs. Major issues confronting experimental MS therapeutics are discussed.

DRUGS FOR RRMS

Recombinant interferon beta-1b (IFN-β-1b) (Betaseron; Berlex Laboratories Inc, Wayne, NJ), recombinant interferon beta-1a (IFN-β-1a) (Avonex; Biogen Inc, Cambridge, Mass), and glatiramer acetate (Copaxone; Teva Pharmaceutical Industries Ltd, Petah Tikva, Israel) have been approved by the US Food and Drug Administration for patients with RRMS (Table 1). These 3 drug therapies were tested in separate multicenter, placebo-controlled, double-masked clinical trials. Key elements of the studies leading to their regulatory approval are summarized in Table 2.

Interferon beta-1b therapy was tested in 372 patients at a dosage of 8 million IU (MIU) (250 µg) or 1.6 MIU (50 µg) by subcutaneous injection every other day for up to 5 years, compared with placebo. The primary outcome measure was the drug therapy effect on the relapse rate. Treatment with the higher dosage reduced the relapse rate by 33%, increased the proportion of relapse-free patients from 16% to 31%, and reduced by 2-fold the number of patients having moderate or severe relapses.14 Beneficial effects were maintained for patients who elected to remain in the blinded trial for up to 5 years.15 There was a statistically nonsignificant trend (P = .16) suggesting that patients in the 8-MIU dosage arm were less likely to experience a worsening by at least 1.0 point from the baseline score on the Expanded Disability Status Scale (EDSS)16 sustained for at least 3 months.

Interferon beta-1a therapy was tested in 301 patients who were given weekly intramuscular injections (6 MIU [30 µg]) or placebo for up to 2 years.4,5 The primary outcome measure was the time to the onset of sustained disability progression, which was defined as deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months. Treatment with IFN-β-1a resulted in a significantly lower probability of sustained disability progression,4 and significantly fewer patients treated with IFN-β-1a therapy became severely disabled, defined as at least 6 months of sustained worsening to an EDSS score of 4.0 or 6.0.17 Patients with an EDSS score of 6.0 require assistance to walk, and their disease course has usually evolved into secondary progressive MS (SPMS). This finding suggests that IFN-β therapy can prevent or delay transition...
from RRMS to SPMS in some patients. Treatment with IFN-β-1a significantly reduced the relapse rate by 32% in the cohort of patients treated for 2 years and by 18% in all patients regardless of the time of participation in the study.\(^7\)

Both forms of IFN-β therapy had beneficial effects on the disease process as measured by cranial magnetic resonance imaging (MRI) scans. Interferon beta-1b therapy resulted in significantly fewer new or enlarging T2-weighted lesions in 52 patients who underwent MRI scan at 1 of the clinical sites every 6 weeks, and IFN-β-1b therapy resulted in significantly less annual accumulation of T2-weighted lesions in the entire study group.\(^6\) In a separate study, IFN-β-1b therapy reduced the frequency of brain lesions that were enhanced on MRI with gadolinium.\(^10\) In the phase 3 trial, IFN-β-1a therapy sig-

### Table 1. Drugs for Relapsing-Remitting Multiple Sclerosis (MS) Approved by the US Food and Drug Administration*

<table>
<thead>
<tr>
<th>Drug</th>
<th>IFN-β-1a (Avonex, Rebif)</th>
<th>IFN-β-1b (Betaseron)</th>
<th>Glatiramer Acetate (Copaxone)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Recombinant IFN-β; glycosylated, amino acid identical to native protein</td>
<td>Recombinant IFN-β; nonglycosylated, serine for cysteine substitution</td>
<td>Random polymer of basic amino acids</td>
</tr>
<tr>
<td><strong>Possible mechanisms</strong></td>
<td>Immunomodulatory; inhibits cell migration and cell-mediated inflammation; antiviral effects</td>
<td>Immunomodulatory; inhibits cell migration and cell-mediated inflammation; antiviral effects</td>
<td>Inhibits T-cell recognition of myelin antigens; induces myelin-reactive regulatory cells</td>
</tr>
</tbody>
</table>

*At the time of this review, IFN-β-1a (Rebif) was approved for use in Canada and Europe, and applications were pending in the United States and Australia (G. Francis, MD, oral communication, August 1998). Relapsing-remitting MS refers to the patient with discrete episodes of neurologic deterioration separated by periods of recovery and clinical stability;\(^7\) MS begins in this fashion in approximately 85% of patients. More than 50% of patients enter a stage of continuous neurologic deterioration, termed secondary progressive MS, commonly 10 to 20 years after the initial MS symptoms. Therapeutic options have advanced more rapidly for relapsing-remitting MS than for secondary progressive MS (reviewed by Rudick et al\(^12\)). IFN-β indicates interferon beta.

### Table 2. Phase 3 Controlled Clinical Trials in Patients With Relapsing-Remitting Multiple Sclerosis*

<table>
<thead>
<tr>
<th>Trials</th>
<th>IFN-β-1a (Avonex)</th>
<th>IFN-β-1b (Betaseron)</th>
<th>Glatiramer Acetate (Copaxone)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>143</td>
<td>123</td>
<td>126</td>
</tr>
<tr>
<td>Active treatment</td>
<td>158</td>
<td>125 (1.6 MIU)</td>
<td>125</td>
</tr>
<tr>
<td><strong>EDSS score range (No. of patients)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0-3.5</td>
<td>0.67 (2 in 3 y)</td>
<td>1.0 (2 in 2 y)</td>
<td>1.0 (2 in 2 y)</td>
</tr>
<tr>
<td><strong>Doseage</strong></td>
<td>6 MIU (30 µg) IM weekly</td>
<td>8 MIU (250 µg) or 1.6 MIU (50 µg) SC QOD</td>
<td>20 mg SC QD</td>
</tr>
<tr>
<td>Primary outcome measure</td>
<td>Sustained disability</td>
<td>Relapse rate</td>
<td>Relapse rate</td>
</tr>
<tr>
<td>Primary result</td>
<td>37% Reduction in disability progression</td>
<td>33% Reduction in relapse rate</td>
<td>29% Reduction in relapse rate</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Flulike symptoms (first 2-3 mo)</td>
<td>Flulike symptoms (first 2-3 mo); skin reactions (occasionally severe)</td>
<td>Mild skin reactions; rare systemic reaction with flushing, sweating, and palpitations</td>
</tr>
<tr>
<td>NAB</td>
<td>Phase 3 study: 14% NAB after 12 mo, 22% after 24 mo (Jacobs et al(^9))</td>
<td>Phase 3 study: 38% NAB after 24 mo; decreased clinical efficacy (IFNB Multiple Sclerosis Study Group and University of British Columbia MS/MRI Analysis Group(^11))</td>
<td>100% Binding antibodies; no known method to determine significance of binding antibodies</td>
</tr>
<tr>
<td>Open-label study</td>
<td>7% NAB after 12-18 mo; decreased in vivo response to injections (Rudick et al(^12))</td>
<td>Open-label study: 35% NAB after 12-18 mo (Rudick et al(^12))</td>
<td></td>
</tr>
</tbody>
</table>

* A multicenter phase 3 placebo-controlled trial of IFN-β-1a (Rebif) was recently completed.\(^13\) The study randomized 560 patients to placebo, 6-MIU (22-µg) dosage of IFN-β-1a, or 12-MIU (44-µg) dosage of IFN-β-1a administered 3 times weekly subcutaneously (SC). There was a 37% reduction in the relapse number after 1 year and a 33% reduction after 2 years at the higher dosage compared with placebo. There were significant beneficial effects on magnetic resonance imaging (MRI) parameters in both dosage arms compared with placebo, and the MRI benefits were greater in the high-dosage compared with the low-dosage group. IFN-β indicates interferon beta; MS, multiple sclerosis; IM, intramuscularly; QOD, every other day; QD, every day; EDSS, Expanded Disability Status Scale; and NAB, neutralizing antibodies.

\(^\dagger\) Scale, 0-10.
ificantly reduced the number of gadolinium-enhanced MRI brain lesions after 1 and 2 years of treatment and decreased the number of new and enlarging T₂-weighted lesions after 1 and 2 years. These studies indicate that IFN-β therapy inhibits new brain lesion formation. The prominent effect on gadolinium-enhanced MRI lesions suggests that IFN-β therapy reduces brain inflammation. This conclusion was supported by the finding that IFN-β-1a therapy lessened cerebrospinal fluid pleocytosis.

Both IFN-β preparations cause transient flulike symptoms. Headache, myalgia, fever, malaise, and occasionally increased MS symptoms commonly last 24 to 48 hours after each injection; the severity of these symptoms typically lessens after 6 to 12 weeks of therapy. Interferon beta-1b therapy causes redness and swelling at the injection site and skin necrosis in 5% of patients. In the phase 3 clinical trials, neutralizing antibodies to IFN-β-1b were observed in 38% of patients[11] and antibodies to IFN-β-1a in 22% of patients after 2 years of treatment. The presence of neutralizing activity in the IFN-β-1b study was associated with reduced clinical and MRI efficacy. In an open-label study, a single biological assay was used to determine titers of neutralizing antibodies in patients treated clinically with IFN-β-1b or IFN-β-1a. After 12 to 18 months of treatment, neutralizing antibodies were observed in 35% of the patients treated with IFN-β-1b and 7% of patients treated with IFN-β-1a, suggesting that IFN-β-1b therapy is more immunogenic. This may be because of known molecular differences between the preparations. Additionally, the dosage, route, or timing of administration may affect immunogenicity. The presence of neutralizing antibodies in the open-label study was associated with significantly blunted in vivo induction of β₂-microglobulin and neopterin following IFN-β-1a injections. This indicates that patients receiving IFN-β preparations who develop neutralizing antibodies have significantly blunted in vivo biological responses to IFN-β injections at the time they are antibody-positive.

Interferon β induces the expression of many genes, so the mechanisms of action in MS are probably complex. Putative mechanisms include (1) inhibition of autoreactive T cells; (2) inhibition of major histocompatibility complex class II expression, with reduced antigen presentation within the central nervous system; (3) inhibition of metalloproteinases or altered expression of cell-associated adhesion molecules, leading to reduced cellular migration into the central nervous system; and (4) induction of immunosuppressive cytokines and inhibition of proinflammatory cytokines, leading to resolution of the inflammatory process.

Glatiramer acetate (Copaxone) is a polypeptide consisting of a random arrangement of 4 basic amino acids. The drug is thought to mimic myelin basic protein and is postulated to induce myelin-specific suppressor T cells and to inhibit myelin-specific effector T cells. Glatiramer acetate therapy was tested in 251 patients who were given daily subcutaneous injections (20 mg or placebo) for 2 years. The primary outcome measure was the effect of the drug on the relapse rate. In the original 2-year study, glatiramer therapy reduced the relapse rate by 29%. At the end of 2 years of therapy, patients were offered entry to an extension study that was continued in a double-masked manner for about 1 year. A large majority of patients continued in the extension study, and the beneficial effect on the relapse rate was maintained. No significant effect was observed on sustained changes in EDSS scores, either in the original study or the extension study. Glatiramer therapy was well tolerated by the patients. Mild swelling and redness occurred at each injection site and 15% of the patients experienced brief episodes of flushing, chest tightness, palpitations, dyspnea, and anxiety.

Magnetic resonance imaging scans were not included as part of the glatiramer phase 3 study, but 27 cases had serial MRI scans at 1 of the sites. There was a trend toward reduced gadolinium-enhanced MRI lesions for patients receiving glatiramer therapy, but no statistically significant benefits were noted on any MRI parameter (J. A. Cohen, MD, oral communication, October 1998). A similar trend toward reduced gadolinium-enhanced MRI lesions was found in a small study of 10 patients receiving glatiramer therapy. A placebo-controlled study was recently completed and demonstrated a significant 30% reduction in new MRI lesions with glatiramer (Copaxone) therapy (G. Comi, MD, oral communication, April 1999).

CONTEMPORARY ISSUES ABOUT APPROVED MS DRUGS

Which of the Available Drugs Is Most Efficacious?

The phase 3 studies convincingly demonstrated that each drug is partially effective, but precise comparisons are problematic. The studies were done by different investigator groups using separate primary outcome measures in separate patient populations. Traditional clinical outcome measures, such as relapse rate and EDSS scores, are imprecise and not adequately standardized to allow direct comparisons among studies. Therefore, efficacy comparisons are based on expert opinions rather than definitive comparison studies. Neurologists who recommend IFN-β therapy as the first-line drug therapy argue that the overall weight of evidence favors IFN-β over glatiramer therapy. Three separate study groups independently demonstrated the efficacy of IFN-β therapy in large, well-controlled, double-blind clinical trials, while a single phase 3 study evaluated glatiramer therapy. Furthermore, IFN-β therapy has been shown to favorably affect disease parameters visualized by MRI and has been shown to decrease cerebrospinal fluid cellularity. Data on the effects of glatiramer therapy on biological correlates of the MS disease process are currently limited. Proponents of IFN-β-1b therapy argue that (1) demonstrated beneficial effect on T₂-weighted lesion accrual after 2 years was greater with IFN-β-1b therapy than with IFN-β-1a therapy; (2) IFN-β-1b therapy is given at a higher weekly dosage, which may be better; and (3) IFN-β-1b therapy was associated with a larger reduction in the relapse rate than was IFN-β-1a therapy. Proponents of IFN-β-1a therapy argue that (1) results showed reduced disability progression that was not evident in the IFN-β-1b
therapy study; (2) injection site reactions that are commonly caused by IFN-β-1b therapy are not observed with IFN-β-1a therapy; (3) IFN-β-1a therapy is less immunogenic than IFN-β-1b therapy, resulting in greater biological response over time; and (4) patients prefer the weekly dosage schedule and favorable side-effect profile of IFN-β-1a therapy. Proponents of glatiramer therapy argue that (1) the drug is better tolerated than IFN-β preparations and (2) glatiramer therapy circumvents the problem of IFN-β–neutralizing antibodies observed in a proportion of IFN-β therapy recipients who take either preparation. Since there are no studies comparing the efficacy of the available drugs within a single study, the question of relative efficacy is considered unresolved.

When Should Therapy Be Initiated, and What Is the Optimal Duration of Therapy?

There is a growing consensus that disease-modifying therapy should be initiated early in the course of MS before irreversible disability has occurred. The rationale for early therapy includes (1) concerns that the immunologic process leading to tissue injury becomes more complex as time passes and may be more difficult to control with immuno suppressive therapy,31,32 (2) increasing awareness that the inflammatory process is active in many patients with RRMS during periods of clinical remission,13-15 and (3) concern that the inflammatory process results in irreversible axonal injury36 that accumulates over time during the relapsing-remitting stage of MS. These considerations imply that disease-modifying therapy should be started when MS is definitively diagnosed because the patient is at risk for subsequent disability progression. Trials of IFN-β-1a therapy beginning with the first MS symptom are under way and may help to clarify this issue.

Identifying patients at higher risk for progressive MS for early therapy is an alternative to treating all patients at the time of diagnosis. Unfortunately, clinical features are only weak predictors of subsequent disease severity, and their value for assigning prognosis to individual patients is limited. Disease severity as measured by cranial MRI scans at the time of onset of first symptoms has been shown to predict MRI and clinical disease progression.37 This implies that patients with minimal disease detected by MRI scans could be evaluated with follow-up MRI scans to determine the need for disease-modifying therapy. Identifying prognostic factors early in the course of MS is an important goal of future MS research.

The optimal duration of therapy for MS has not been determined. For patients doing well, therapy should be continued, since a study of IFN-alfa-2a therapy showed increased disease activity when therapy was discontinued after 6 months.38 Studies are needed in which patients are randomly assigned to continue or stop therapy and then are carefully evaluated under double-masked conditions.

Different disease-modifying therapies should be considered for patients whose condition is deteriorating,39 particularly patients receiving IFN-β therapy with neutralizing antibodies that persist. Standardized methods for evaluating patients receiving disease therapy are needed, including definitions for those patients who do not respond to treatment.

Should a Patient Receiving One of the Current Drug Therapies Be Evaluated With Periodic MRI Scans?

The poor relationship between clinical relapses and the severity of brain inflammation implies that more accurate and sensitive markers of the pathologic process in RRMS will be required. Periodic cranial MRI scans may be useful in estimating MS disease activity and progression in some patients, to determine the need for disease-modifying therapy in patients with clinically benign disease, and to evaluate the response to disease-modifying therapy. Studies are needed to precisely define the methods and frequency for using MRI to monitor patients receiving disease-monitoring therapy.

Should Patients Receiving IFN-β Therapy Routinely Have Tests for Neutralizing Antibodies?

Patients who continue to have clinical disease activity despite IFN-β therapy should have their serum levels tested for neutralizing antibodies.39 If the assay is negative, IFN-β therapy could be continued and the addition of other medications, such as azathioprine or methylprednisolone, could be considered. There is controversy about whether patients receiving IFN-β therapy who are doing well should be routinely tested for neutralizing antibodies. Advocates argue that high levels of neutralizing antibodies block in vivo IFN-β biological responses and that it is not possible to rule out ongoing brain inflammation based only on the clinical symptoms. Further studies on the use of neutralizing antibody tests in clinical practice are needed.

Should Patients With SPMS Be Treated With Available Drugs?

A multicenter, placebo-controlled study of IFN-β-1b was completed in Europe recently. The study found a significantly longer time to sustained worsening in EDSS scores, reduced relapse frequency, and beneficial effects observed by serial MRI scans in patients who received IFN-β-1b therapy.41 Separate studies of IFN-β-1b and IFN-β-1a therapy are ongoing in populations of patients with SPMS. In the near future, there will be a great deal of data on which to judge the magnitude of clinical benefit of IFN-β treatment in patients with SPMS.

What Are the Long-term Benefits and Risks of Current MS Drug Therapies, and Do the Long-term Benefits Justify the Cost of the Drugs?

Long-term benefits of the current drug therapies can only be surmised from existing studies because clinical trials run 3 to 5 years, while the disease course of MS unfolds over decades. Clinical trials provide information on only a limited part of the overall disease course. Lengthy placebo-controlled studies are impractical because patients whose condition is deteriorating withdraw from them, making the studies less informative. Lengthy open-label studies do not provide definitive evidence about the efficacy of MS treatment, since patients who are doing well elect to continue receiving drug therapy, while patients whose condition is deteriorating stop drug therapy.
to try something else. This results in observer bias favoring long-term efficacy.

Despite their limitations, the studies suggest that available disease therapies are likely to have a beneficial effect on long-term disability, and this might translate into cost-effective treatment. The current cost of the drugs is $8000 to $10,000 per patient annually, which represents approximately 25% of the estimated per-patient annual cost attributed to MS.1 Long-term cost-benefit analyses are needed.

THE FUTURE OF CONTROLLED CLINICAL TRIALS FOR MS THERAPY

Are Placebo-Controlled Trials Justified?

Placebo-controlled trials for RRMS therapy are now impractical in regions of the world where effective disease-modifying agents are readily available. Furthermore, placebo-controlled trials for RRMS therapy are ethically questionable because of convincing evidence for meaningful, albeit partial, therapeutic benefits. The role of placebo-controlled trials is less clear in patients with SPMS, with the emergence of effective therapies. A published study demonstrated statistically significant but clinically modest benefits of low-dose oral methotrexate therapy for patients with chronic progressive MS,42 and recently completed studies have demonstrated the efficacy of IFN-β-1b therapy and mitoxantrone therapy for patients with SPMS. As results from these and other studies are published, placebo-controlled studies for patients with SPMS will become less practical and more ethically questionable. Since no therapy has demonstrated any benefit for primary progressive MS, placebo-controlled studies for this disease category are well justified.

Can We Improve Clinical Outcome Measures for Future Trials?

An international consensus conference on MS outcome measures pointed out limitations of traditional scales for MS clinical trials and indicated the need for new assessment systems that are multidimensional, quantitative, and include evaluation of cognition.43 Based on the report from this conference, the National Multiple Sclerosis Society appointed a task force to recommend improved clinical outcome measures. The task force recommended functional composites consisting of simple quantitative tests of neurologic function.4445 A 3-part composite that was recommended46 is currently being tested as an outcome measure in therapeutic trials. It remains to be seen whether quantitative functional composites will prove to be advantageous compared with traditional measures, such as the relapse rate and the EDSS score.

What Is the Relative Role of MRI Compared With Clinical Measures in MS Therapy Trials?

The relationship between MRI abnormalities and clinical disease activity in patients with RRMS is weak. The rate of detection of new gadolinium-enhanced MRI brain lesions is 5 to 10 times higher than the rate of clinical relapses,3337 indicating that most new MRI lesions are clinically silent. Similarly, the relationship between the volume of hyperintense T2-weighted lesions and the EDSS score is also weak.23 However, it has been demonstrated that patients with RRMS have measurable amounts of ongoing cerebral atrophy,37 which is also poorly reflected in traditional clinical measures. These findings raise the possibility that in the relapsing-remitting stage of MS, the disease process is subclinical to a substantial degree. The principal concern in this regard is that disability progression occurs only after a threshold of irreversible tissue injury has been surpassed.3648 This concept provides a rationale for using MRI measures as outcomes in clinical trials, particularly for patients with RRMS, in whom the neurologic outcomes are imprecise and insensitive to the underlying pathology. Studies are needed to validate traditional and newer MRI markers, such as brain and spinal cord atrophy, as primary outcome measures.

Can We Design Methods to Reliably Test MS Drug Therapies in Combination?

With the advent of partially effective therapies, active arm comparison studies will be needed to make further progress in the field of MS drug therapy. To date, however, no studies have been reported in which drug therapies were tested in combination. Designs for such studies must be developed, and increasingly sensitive and precise outcome measures will be required to achieve practical sample sizes.

Can Therapeutic Interventions Be Rationally Designed to Target Specific Pathogenic Mechanisms?

Most completed and ongoing clinical trials are based on the concept that MS is caused by autoreactive T cells that initiate injury to myelin in the central nervous system. Interventions range from highly specific inhibition of the tri-molecular complex to more global forms of immunosuppression. However, recent histopathologic studies49 suggest that the pathologic characteristics vary significantly among individual patients, raising the possibility that therapy may need to be individualized. Additionally, data indicate that axons and myelin are targets of the pathologic process, providing a rationale for neuroprotective or neurotrophic factors in future clinical trials. Ultimately, improved understanding of pathogenic mechanisms will be needed for selecting rational interventions.

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REFERENCES