Multiple Sclerosis

Therapeutic Update

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Therapy for multiple sclerosis (MS) is undergoing rapid changes. We discuss recent developments in the therapy of MS, failures as well as successes, and consider some newer approaches. Multiple sclerosis, a multifocal, initially remitting-relapsing, and in some cases primarily progressive, inflammatory central nervous system immune-mediated demyelinating disease, with some axonal involvement, is currently the most common disabling neurologic disease of young people in North America and Europe. Although much is known about the pathogenesis, there is no cure and the disease must be managed long-term. Recently, there have been a number of advances in the treatment of MS.

There are several dimensions to the therapy of MS: treatment of the underlying disease (treatment of relapses, prevention or modulation of relapses, and prevention of progression) and treatment of the effects of the disease (treatment of symptoms and provision of support). Since there is limited information available about what determines the tempo of the underlying disease, advances in the prevention of relapses and progression have been few, and most have occurred recently. Given that there are a series of pathogenetic steps in the formation of an inflammatory demyelinating plaque, there are several approaches to treating and preventing relapses. We concentrate on the therapy of the underlying disease in this article rather than symptom management.

PREVENTION OF RELAPSES AND ACCUMULATION OF DEFICIT

There is no therapy that completely prevents relapses in MS, although there are several that reduce the frequency (and severity) of relapses and probably delay or reduce accumulation of deficit. Some of these medications are already on the market, while others are investigational only. Some that showed promising results or a hint of efficacy in pilot trials have recently been shown to have no efficacy.

INTERFERONS

Several type I interferons have been shown to reduce the frequency of relapses. The original rationale for the use of type I interferons was as antiviral agents in what was thought by some to be a viral disease. In addition, some investigators reported that cells of patients with MS did not produce sufficient amounts of interferon in cell culture. The interferons are known to have multiple immunomodulatory actions, and this is likely their mechanism of action, rather than any antiviral effect. Two are approved by the Food and Drug Administration for use in the United States for patients with MS, interferon beta-1b and interferon beta-1a, and these are on the market.

Interferon beta-1b (Betaseron, Berlex, Richmond, Calif) has been shown to reduce the frequency of relapses by about 30% in a trial involving 372 patients divided into a placebo group, a low-dose group (0.05 mg every other day subcutaneously), and a high-dose group (0.25 mg every other day subcutaneously). Patients had at least 2 relapses in the 2 years before enrollment (Table). The annual number of relapses was 1.27, 1.17, and 0.84 in the placebo, low-dose, and high-dose groups. In a companion study, measuring disease activity by the number of new lesions appearing on magnetic resonance imaging (MRI), there were 80% fewer active scans in the treated group (combined low- and high-dose inter-
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<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Study Subjects</th>
<th>EDSS Score</th>
<th>Annualized Relapse Rate</th>
<th>Patients Progressing, %†</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>Low</td>
<td>Placebo</td>
</tr>
<tr>
<td>Interferon beta-1b (2-y results)</td>
<td>372</td>
<td>0.0-5.5</td>
<td>0.84</td>
<td>1.05</td>
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<tr>
<td>Interferon beta-1b (5-y results)</td>
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<td>Glatiramer acetate</td>
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<td>1.34</td>
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</tbody>
</table>

*EDSS indicates Extended Disability Status Scale; ellipses, not applicable.*

†Progression was not defined in the same way.

‡High dose vs placebo.

The burden of disease, defined by the total area of the brain occupied by lesions, was 22% less in the treatment group compared with the placebo group. However, there was, at the end of 2 years, no significant difference in the Extended Disability Status Scale (EDSS) between the groups. Defining a sustained (3-month) increase of EDSS score by at least 1.0 step as progression, 46% of the placebo group progressed after a median of 46 months, while 35% of the high-dose group did so. This difference was not statistically significant although in a 5-year follow-up study a trend to less disability was noted (Table). However, the number of patients remaining in the controlled study for 4 or 5 years precluded the likelihood of detecting any statistically valid differences.

It was found that 38% of patients had developed neutralizing antibodies to the drug, and that these patients seemed to have much less benefit. In the patients who did not develop such antibodies, the decreased rate of relapse and the beneficial effect on the MRI were sustained for 4 to 5 years (Table). However, in patients who developed neutralizing antibodies to the drug, there was no significant difference in the EDSS between the groups. Defining a sustained (3-month) increase of EDSS score by at least 1.0 step as progression, 46% of the placebo group progressed after a median of 46 months, while 35% of the high-dose group did so. This difference was not statistically significant although in a 5-year follow-up study a trend to less disability was noted (Table). However, the number of patients remaining in the controlled study for 4 or 5 years precluded the likelihood of detecting any statistically valid differences.

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A study of the efficacy of interferon beta-1b in reducing the gradual increase of deficit (progression) in secondary progressive disease was halted in Europe because of the demonstration of efficacy in patients treated with the drug for 2 years. In this study 718 patients with MS with demonstrated secondary progression were randomized to subcutaneous injections every other day of 0.25 mg of interferon beta-1a (358 patients) or placebo (360 patients) for 3 years. The primary outcome variable was time from initiation of drug to deterioration of the EDSS score by 1.0 point in those entering the study with an EDSS score of 3.5 to 5.5 and by 0.5 point in those with an initial EDSS score of 6.0 to 6.5. In the placebo group, 49.8% had confirmed progression, while only 38.9% of patients in the treatment group progressed (P = .008). The mean number of days to progression was 549 in the placebo group, compared with 893 in the treatment group. Secondary outcome variables were also measured. A parallel study is still ongoing (as of this writing) in North America.

The adverse effects of the drug include local injection reactions, a flu-like syndrome (myalgias, fever, and malaise), and depression. Elevations of liver enzymes can also occur as can abnormalities in red and white blood cell and possibly also platelet counts. These are often mild and require no change in dosage. In some patients, a reduction in dosage, or discontinuation of the drug, may be required. In post-Food and Drug Administration approval experience, increase in spasticity has been anecdotally observed. Interferon beta-1b should not be used if the patient is actively and severely depressed, if the patient is pregnant or intends to become pregnant, or if the patient is hypersensitive to any of the components of the drug.

Interferon beta-1a (Avonex, Biogen, Cambridge, Mass), which differs from interferon beta-1b by a single amino acid residue substitution and by being glycosylated, was investigated in a trial comparing the accumulation of deficits in patients receiving therapy and placebo, as the primary outcome. In this study, 301 patients with relapsing-remitting MS (EDSS score, 1.0-3.5) were randomized to treatment (30 µg intramuscularly once a week) or placebo. Progression (a sustained increase of at least one step in the EDSS score for 6 months) occurred in 21.9% of treated patients, compared with 34.9% of patients receiving placebo at 104 weeks. Magnetic resonance imaging indexes of disease activity measured by gadolinium enhancement were also reduced in the treatment group although the volume of disease by T2 weighting did not differ from placebo. The exacerbation rate was a secondary outcome variable in this study. The placebo group had an average of 0.90 exacerbations per year, while the treatment group had only 0.61, which was a statistically significant difference (P = .002). The exacerbation rate was derived from the subset of patients who had completed 104 weeks of follow-up by the end of the study, so that the figure given is an extrapolation from a Kaplan-Meier analysis. The lesion volume defined on T2 weighting decreased in both groups, but the decrease was not significantly different between baseline and second year in the treatment group. Almost all the decrease in lesion volume was between baseline and the first year in the treatment group; there was virtually no further decrease be-
between the first and second years. Furthermore, the lesion volumes were not statistically significantly different ($P = .36$) in the second year between the treatment and placebo groups. Adverse effects significantly more common in the treatment group included flulike symptoms, muscle aches, fever, and chills, but the incidence of depression was the same in the 2 groups.

Several studies on higher doses of interferon beta-1a are underway. The results of 1 study on higher doses of interferon beta-1a (Rebif, Ares-Serono International SA, Geneva, Switzerland) were recently published. In this study, 68 patients with remitting-relapsing MS were randomized to 11 µg (3 MIU) or 33 µg (9 MIU) of interferon beta-1a subcutaneously 3 times a week for 6 months. There was no placebo control group in this trial. Magnetic resonance imaging activity was the primary outcome, and clinical relapse rate was the secondary outcome. The patients received monthly brain MRI scans for 6 months before starting the drug to establish a baseline, and again for the next 6 months. The mean number and volume of enhancing lesions per month before starting the drug were compared with the MRI activity after the drug was started, in each group independently. On average the low-dose and high-dose groups had approximately 3.1 and 3.2 relapses in the 2 years before the study. Both groups had significant reduction of the MRI activity as well as relapse rate, although the final EDSS scores were not significantly reduced, compared with the initial EDSS scores in either group. There was no clear dose response, although the study was not powered to detect this. Preliminary results from the 2-year follow-up in this study have been published in abstract form.5 The dropout rate was low. The annualized relapse rates were 0.78 in the low-dose and 0.42 in the high-dose groups, with a trend to statistical significance ($P = .06$). The 2-year relapse-free proportions were 33% in the low-dose group and 59% in the high-dose group ($P = .04$). The changes in lesion volume on both T1- and T2-weighted images were the same in both groups, suggesting that there is a dissociation between the clinical and MRI outcomes when measured by volume, a measure of disease burden, a similar finding with interferon beta-1a (Avonex).

The results of a second higher-dose study are available. In the Prevention of Relapses and Disability in Multiple Sclerosis (PRISMS) study,10 560 patients with relapsing-remitting disease, with at least 2 relapses in the previous 2 years, were randomized into 1 of 3 arms: placebo (187 patients); interferon beta-1a (Rebif), 22 µg (6 MIU) (189 patients) or 44 µg (12 MIU) (184 patients) subcutaneously 3 times a week for 2 years. The primary outcome variable was the number of relapses, while severity of relapses, deficit accumulation, and MRI disease activity and T2-lesion burden were secondary outcome variables. The average number of relapses per patient was 2.56 in the placebo group, 1.82 in the low-dose (22 mg; $29\%$ reduction from placebo), and 1.73 in the high-dose (44 mg) group (32$\%$ reduction from placebo). These decreases in the number of relapses were statistically significant, with $P < .005$ for either treatment group compared with placebo. There was no formal statistical comparison between the 2 dose groups, however, although there appeared to be a dose-response effect in the summarized data. The mean number of months to progression was 11.9, 18.5, and 21.3 in the placebo, low-dose, and high-dose groups, respectively, with the results statistically significant ($P < .05$) between either of the treatment groups compared with placebo. For the patients with high baseline EDSS score, only the high-dose group achieved a statistically significant ($P < .05$) delay in progression. The MRI burden of disease (defined by volume of lesions on T2-weighted images) increased by 10.9$\%$ in the placebo group and decreased by 1.2$\%$ and 3.8$\%$ in the low- and high-dose groups, respectively ($P < .0001$) for either group compared with placebo.

**GLATIRAMER ACETATE (FORMERLY COPOLYMER-1)**

A mixture of tetrameric oligopeptides of random composition of alanine, tyrosine, glutamate, and lysine, glatiramer (formerly known as copolymer-1) (Copaxone) was noted to suppress experimental allergic encephalomyelitis in an animal model of MS.11 The exact mechanism(s) of action is unknown. After a smaller trial of 50 patients, glatiramer acetate was used in a trial of 252 patients (EDSS score, 0-5.0) with relapsing-remitting MS divided into treatment and placebo groups. The drug was given at a dose of 20 mg subcutaneously every day.12 The annual rate of relapses in the treatment group was 30$\%$ less than that in the placebo group (Table). However, serial MRI surveillance of disease activity was not extensively done. An extension study13 shows that the effect on relapses persists. There is also some evidence of benefit on disability. The drug is well tolerated, with a transient, mild systemic reaction consisting of flushing, chest tightness with palpitations and dyspnea, and anxiety being reported in 15$\%$ of patients. No abnormal hematologic or chemical tests were noted and local injection reactions were modest. This is a class B pregnancy drug, so that while it is not recommended for use in pregnant patients, it may represent less risk to young women of childbearing age, especially if pregnancy is being considered or if the patient is not practicing a highly effective method of birth control.

Since there has been no trial directly comparing interferon beta-1a, interferon beta-1b, and glatiramer acetate with each other, and because of differences in patient populations and other aspects of study design, it is difficult to comment on their relative efficacies. A trial to look at the combined effect of glatiramer and interferon beta-1a is in the planning stages.

**OTHER AGENTS**

Immunosuppression is an approach long used in the treatment of MS. It has not been successful because of the toxicity, nonselective nature, and unimpressive efficacy of the agents when studied in placebo-controlled trials. Methotrexate has shown only modest short-term efficacy in a single study, and higher doses are being explored when the low-dose regimen fails. Other immunosuppressive and immunomodulatory agents achieving little or no apparent efficacy include total lymphoid irradiation, cladribine, mitoxantrone, sulfasalazine, acyclovir, and oral bovine myelin. Recent studies on intravenous (IV) immunoglobulin demonstrated a beneficial effect.
effect on the relapse rate and gadolinium-enhancing lesions, but not on EDSS. However, this therapy is expensive. At our institution, the cost of 1 year’s IV immunoglobulin therapy, for the drug alone, without administration or other nursing costs, exceeds the cost of a year’s therapy with interferon beta-1a, interferon beta-1b, or glatiramer by more than 3 times. In addition, IV immunoglobulin therapy is not without risk. Roquinimex and anti-CD3 monoclonal antibodies were found to be too toxic. Other modalities currently in trials include phosphodiesterase inhibitors, vaccines using whole T cells and T-cell receptor fragments, and bone marrow transplants. However, relapses have been well documented to occur after bone marrow transplant.14

TREATMENT OF RELAPSES

Various strategies for treatment of relapses are available based on known and proposed pathogenetic steps of the formation of an inflammatory demyelinating plaque. These include prevention of adhesion of immunologically active cells to endothelium, prevention of the passage of active cells across the blood-brain barrier by inhibiting enzymes that are crucial to affecting the breach, suppression of the effect of inflammatory mediators, suppression of other activities of inflammatory cells including glial cells, and suppression of the inflammatory response by up-regulating anti-inflammatory cytokines. Although corticosteroids have a proven place only in the treatment of acute relapses, the other modalities discussed in this section may not be similarly limited.

ORAL CORTICOSTEROIDS

It has become standard practice to treat major MS relapses with high-dose IV methylprednisolone, while a short course of low-dose oral prednisone has been used for mild or moderate relapses. In the optic neuritis treatment trial comparing the response of acute optic neuritis with IV methylprednisolone, low-dose oral prednisone, or placebo (457 patients), patients in the IV methylprednisolone arm had slightly better visual recovery at 6 months than those in the oral prednisone and placebo arms, but this advantage had disappeared at 1 year.13 In a more recent study,16 patients with an acute MS relapse were randomized to either IV methylprednisolone or low-dose oral methylprednisolone. There was no significant difference in any outcome measure at any time point. In a double-blind, placebo-controlled trial comparing high-dose IV methylprednisolone with high-dose oral prednisone, there was no difference in the final outcome between the 2 groups.17 However, the trials are not totally comparable, involving different disease presentations, different patient groups and numbers, and different outcomes. Furthermore, the power of these latter 2 trials to detect significant differences between the different groups was rather low. Given the conflicting data, it is likely that the current practice of using high-dose IV corticosteroids for major relapses and low-dose oral prednisone for minor relapses will continue.

Other modalities for the treatment of individual relapses are in clinical trials and include monoclonal antibodies against adhesion molecules, matrix metalloproteinase inhibitors, platelet-activating factor inhibitors, tumor necrosis factor alpha inhibitors, and anti-inflammatory cytokines.

SUMMARY AND FUTURE DIRECTIONS

There are currently several new agents on the market specifically approved for the treatment of MS by the Food and Drug Administration, and others are available for off-label use, although the latter are not generally in use for various reasons including equivocal efficacy, toxicity, and expense. Others are available for investigational use only (anti-adhesion molecule antibodies, T-cell vaccines, platelet-activating factor inhibitors, matrix metalloproteinase inhibitors, monoclonal anti-T-cell antibodies), and it is too early to be able to say much about their efficacy. There are numerous potential targets of therapy, and more are found as the basic immunology of the disease continues to be explored. New therapeutic strategies are likely to evolve in the near future, as the disease continues to be studied. Therapy for MS is in an active, dynamic flux, and there is reason for cautious optimism.

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