

Review Article

Drug Therapy

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MANAGEMENT OF MULTIPLE
SCLEROSIS

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MULTIPLE SCLEROSIS is a common disease of the central nervous system affecting approximately 1 million young adults, mostly women, worldwide.¹ It is characterized by episodic neurologic symptoms that are often followed by fixed neurologic deficits, increasing disability, and medical, socioeconomic, and physical decline over a period of 30 to 40 years.

For most of the 20th century, multiple sclerosis was considered untreatable. In 1982, the Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society of the United States sponsored the first international workshop on therapeutic trials.² This workshop served to usher in an era of activism and optimism that has substantially replaced widespread therapeutic nihilism and skepticism about the feasibility of clinical trials in multiple sclerosis.

There have been a number of important advances since the international workshop.^{3,4} The Expanded Disability Status Scale achieved widespread use as a single measure of the severity of multiple sclerosis.⁵ Magnetic resonance imaging (MRI) was invented, applied to multiple sclerosis,⁶ and quickly established as a sensitive marker of the pathologic process. Large multicenter clinical trials were completed,⁷⁻¹⁴ and monographs on clinical trials were published.^{15,16} The Food and Drug Administration (FDA) approved interferon beta-1a (Avonex, Biogen, Cambridge, Mass.), interferon beta-1b (Betaseron, Berlex Laboratories, Richmond, Calif.), and glatiramer acetate (Copaxone, Teva Marion Partners, Kansas City, Mo.) for pa-

tients with relapsing–remitting multiple sclerosis. As a result of these advances, effective therapies are now available, and clinical trials of other promising therapies are under way.

DISEASE CHARACTERISTICS
RELATED TO TREATMENT DECISIONS

The goal of therapy in patients with multiple sclerosis is to prevent relapses and progressive worsening of the disease. Spontaneous recovery is rare when neurologic deficits have persisted for longer than six months, and there are no known therapies that promote regeneration and reverse fixed neurologic deficits. Therefore, disease-modifying therapy should be considered before neurologic deficits have persisted longer than six months. Decisions in individual patients should be based both on the course of the patient's disease and on the probability of severe disabling disease.

A standardized nomenclature to describe the course of multiple sclerosis (Table 1) was developed by consensus.¹⁷ The most common pattern at onset is relapsing–remitting disease, but it becomes secondary progressive disease over time in more than 50 percent of patients. Approximately 10 percent of patients have primary progressive multiple sclerosis. They tend to be older at onset (40 to 60 years of age) and commonly have a progressive myelopathy. Patients with primary progressive multiple sclerosis have fewer gadolinium-enhanced lesions on cranial MRI scans and fewer inflammatory changes in cerebrospinal fluid than patients with secondary progressive multiple sclerosis.¹⁸ Progressive relapsing multiple sclerosis is a very uncommon pattern of disease. The vast majority of patients have relapsing–remitting multiple sclerosis during the early years and secondary progressive multiple sclerosis later. Patients with relapsing–remitting multiple sclerosis have the best responses to treatment, whereas patients with progressive disease are less responsive to treatment.

Disease-modifying therapy should be considered early in the course for patients with an unfavorable prognosis. The unfavorable prognostic markers related to more rapid worsening of disease that are listed in Table 2 can be used to select patients for treatment.¹⁹⁻²² Patients who have multiple cranial MRI lesions at the time of their first symptoms are much more likely to have major disability later on.²³ Therefore, in addition to the clinical features, the findings on cranial MRI are useful in selecting patients for early treatment. Approximately 10 percent of patients have relatively benign disease, however, so not every patient should receive disease-modifying therapy.

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DESIGN OF CLINICAL TRIALS

Relation between Treatment Strategies and Pathogenesis

Various lines of research support the hypothesis that multiple sclerosis is an autoimmune process occurring in genetically susceptible persons after an environmental exposure. The geographic heterogeneity of the disease and the widely varying prevalence rates in different ethnic populations suggest interplay between environmental and genetic factors. The observation that common viral infections can precipitate relapses led to the concept that viruses can trigger autoimmune demyelination in susceptible persons.²⁴ No specific pathogen has been reliably linked to multiple sclerosis, however, so none of the current treatment approaches are targeted at microbial pathogens. The children of patients with multiple sclerosis have an increased risk (30-fold to 50-fold) of multiple sclerosis.²⁵ Studies of twins and adopted children suggest that the increased risk is largely genetic.²⁶ Candidate-gene and whole-genome screening suggests that multiple weakly acting genes interact to determine the risk of multiple sclerosis.²⁷⁻²⁹

Most current therapeutic approaches are based on the hypothesis that multiple sclerosis is an organ-specific autoimmune disease. Inoculation of susceptible animals with myelin proteins results in a relapsing–remitting, inflammatory, demyelinating central nervous system disease called experimental autoimmune encephalomyelitis. Experimental autoimmune encephalomyelitis can be transferred to unimmunized animals through activated T cells that recognize small fragments of myelin proteins.³⁰ These pathogenic T cells use a restricted array of genes for T-cell–antigen receptors. Molecular strategies that interrupt the interaction between myelin protein peptides and pathogenic T-cell receptors are effective in acute experimental autoimmune encephalomyelitis.³¹ Human T cells that recognize myelin antigens also have restricted use of T-cell receptors, prompting attempts to eliminate pathogenic T cells with antibodies or vaccination.³² To date, however, evidence of a unique immunologic abnormality in patients with multiple sclerosis is lacking. In particular, T cells that recognize myelin can be isolated with similar frequencies from patients with multiple sclerosis and normal subjects. Furthermore, as autoimmune diseases progress, self-peptides are released from the target organ, increasing the diversity of the T-cell response. This phenomenon, termed “epitope spreading,” occurs in animals with chronic experimental autoimmune encephalomyelitis^{33,34} and in patients with multiple sclerosis³⁵ and may limit simple treatment strategies based on blocking the recognition of autoantigen.

The lesions of multiple sclerosis resemble those induced by delayed hypersensitivity, containing inflammatory cytokines, activated T cells, and mononuclear

TABLE 1. CLINICAL CATEGORIES OF MULTIPLE SCLEROSIS.

DISEASE CATEGORY	DEFINITION
Relapsing–remitting	Episodes of acute worsening with recovery and a stable course between relapses
Secondary progressive	Gradual neurologic deterioration with or without superimposed acute relapses in a patient who previously had relapsing–remitting multiple sclerosis
Primary progressive	Gradual, nearly continuous neurologic deterioration from the onset of symptoms
Progressive relapsing	Gradual neurologic deterioration from the onset of symptoms but with subsequent superimposed relapses

TABLE 2. PROGNOSTIC MARKERS THAT PREDICT MORE SEVERE MULTIPLE SCLEROSIS.

Progressive disease from the onset of symptoms
Motor and cerebellar signs at presentation to neurologist
Short interval between the first two relapses
Poor recovery from relapse
Multiple cranial lesions on T ₂ -weighted MRI at presentation

phagocytes.^{36,37} These elements, shown in Figure 1, are all potential targets for intervention. Function-related T-cell surface molecules can be down-regulated with antibodies. Cytokine-based therapies, such as those involving soluble receptors for tumor necrosis factor α or immunosuppressive cytokines such as transforming growth factor β or interleukin-10, may potentially be effective. The inflammation of the central nervous system may also be sensitive to intervention directed against leukocyte and cerebrovascular endothelial adhesion molecules or chemokines, which mediate the migration of leukocytes into the central nervous system. In both multiple sclerosis and experimental autoimmune encephalomyelitis, myelin antibodies are concentrated in the central nervous system, and demyelinating antibodies in experimental autoimmune encephalomyelitis synergize with T-cell–effector mechanisms.⁴⁷ Pathogenic antibodies are also potential therapeutic targets.

Controlled Clinical Trials

Therapeutic advances in multiple sclerosis are dependent on clinical trials because of the highly variable and unpredictable course of the disease and the difficulty in precisely measuring neurologic disability. The Expanded Disability Status Scale,⁵ the most widely used outcome measure in clinical trials of multiple sclerosis, is an ordinal rating scale ranging from 0 to 10, in increments of 0.5, with higher scores reflecting increasing severity. The fact that there is a single score for each patient at each time point makes study design and statistical analysis relatively simple, but

Circulating autoreactive T cells are activated by stimulation with superantigens,³⁸ molecular mimicry,³⁹ or unknown mechanisms. Once activated, these autoreactive cells traverse the blood–brain barrier to enter the central nervous system. Perivascular antigen-presenting cells provide the signals necessary to result in the activation and clonal expansion of these autoreactive T cells and the secretion of proinflammatory cytokines by them. The cytokines, including tumor necrosis factor and interferon- γ , induce astrocytes and leukocytes to secrete chemokines⁴⁰ and stimulate the expression of adhesion molecules by endothelial cells. Activated microglia and macrophages damage myelin internodes.⁴¹ Proinflammatory cytokines may directly inhibit nerve conduction, leading to neurologic dysfunction. Immunosuppressive cytokines (not shown) inhibit the inflammatory process, leading to neurologic recovery. The putative mechanisms of action of the therapeutic effects of interferon beta, as indicated by the numbers, include inhibition of the proliferation of autoreactive T cells (1)⁴²; inhibition of the expression of major-histocompatibility-complex class II molecules,⁴³ leading to reduced antigen presentation within the central nervous system (2); inhibition of metalloproteases,^{44,45} leading to reduced migration of T cells into and through the central nervous system (3); and induction of immunosuppressive cytokines,⁴⁶ leading to resolution of the inflammatory process (4).

as clinical relapses.⁵⁰ Preliminary evidence of the efficacy of treatments on the basis of MRI findings will probably serve as the basis for future trials, and all will include serial MRI as an important secondary outcome measure.

Corticosteroids are the mainstay of treatment for acute relapses of multiple sclerosis. Corticosteroids have immunomodulatory and antiinflammatory ef-

fects that restore the blood–brain barrier, reduce edema, and may possibly improve axonal conduction. Corticosteroid therapy shortens the duration of the relapse and accelerates recovery, but whether the overall degree of recovery is improved or the long-term course is altered is not known.^{51–53} Corticotropin was demonstrated to help recovery from relapse,⁵² but it has been largely replaced by high-dose intravenous methylprednisolone, because the latter has a more rapid onset of action, produces more consistent benefits, and has fewer side effects.^{52,54} For moderate-to-severe relapses, 1000 mg of methylprednisolone per day by intravenous infusion for 3 to 5 days followed by 60 mg of oral prednisone per day, with tapering of the dose over a period of 12 days, accelerates neurologic recovery.

In the Optic Neuritis Treatment Trial, 457 patients with acute optic neuritis were randomly assigned to receive 1000 mg of intravenous methylprednisolone per day for 3 days followed by 1 mg of oral prednisone per kilogram of body weight per day for 11 days; 1 mg of oral prednisone per kilogram per day for 14 days; or oral placebo. The rate of recovery of vision was significantly faster in the intravenous-methylprednisolone group, with the greatest benefits in patients with visual acuity of 20/50 or worse at entry,⁹ but there were no significant differences between groups in visual outcome at six months. Prednisone therapy increased the risk of new episodes of optic neuritis in either eye, and intravenous methylprednisolone reduced by approximately 50 percent the risk of an attack leading to the diagnosis of multiple sclerosis during the two-year follow-up.⁵⁵ This effect was most evident in patients at highest risk for subsequent relapse — those with multicentric brain lesions on MRI at entry into the study. After three years, differences between the treatment groups were no longer significant,⁵⁶ suggesting that intravenous methylprednisolone delayed but did not stop the development of multiple sclerosis after optic neuritis. These results have led to the widespread use of intravenous methylprednisolone for patients with optic neuritis and abnormal findings on MRI of the brain. The results also renewed debate over whether intravenous methylprednisolone has long-term benefits for patients with multiple sclerosis. A clinical trial is under way to determine whether pulsed doses of intravenous methylprednisolone given every other month slow disease progression in patients with moderate disability and secondary progressive multiple sclerosis.

Interferon Beta

Interferon beta is the treatment of choice for patients with relapsing–remitting multiple sclerosis. Two forms of recombinant interferon beta — 1a and 1b — have been approved by the FDA and European regulatory agencies. Interferon beta-1a is a glyco-

syated, recombinant mammalian-cell product, with an amino-acid sequence identical to that of natural interferon beta. Interferon beta-1b is a nonglycosylated recombinant bacterial-cell product in which serine is substituted for cysteine at position 17.

Interferon beta-1b was tested in a multicenter trial involving 372 patients with relapsing–remitting multiple sclerosis and mild-to-moderate disability. Treatment consisted of either 8 million units (250 μ g) or 1.6 million units (50 μ g) of interferon beta-1b or placebo given by subcutaneous injection every other day for up to five years. As compared with treatment with placebo, treatment with the higher dose reduced the relapse rate by 31 percent, increased the proportion of patients who were relapse-free (27 percent vs. 17 percent), and reduced by a factor of 2 the number of patients who had moderate and severe relapses.⁸ There was no difference in the proportion of patients in whom disability increased or in changes in the disability scores between treatment groups. The patients in the placebo group had a mean increase of 17 percent in the area of the lesions on T₂-weighted MRI at three years, as compared with a mean decrease of 6 percent in the patients given high-dose interferon beta-1b. There was also a significant reduction in disease activity, defined as the finding of new or enlarging lesions in serial MRIs.⁵⁷ The MRI findings in this study were pivotal in obtaining FDA approval for interferon beta-1b and initiated the era in which MRI has a key role in assessing therapeutic responses in patients with multiple sclerosis.

Interferon beta-1a was tested in a multicenter trial involving 301 patients with relapsing–remitting multiple sclerosis and mild-to-moderate disability. Treatment consisted of weekly intramuscular injections (6 million units [30 μ g]) or placebo for up to two years.^{7,58} The principal outcome was the length of time to the progression of disability, defined as a decrease from base line of at least 1.0 point on the Expanded Disability Status Scale that persisted for at least six months. Treatment with interferon beta-1a, as compared with placebo, significantly lowered the probability of progression of disability⁷ and of severe disability.⁵⁹ In addition, patients treated with interferon beta-1a for two years had a reduction of 32 percent in the annual rate of relapse, and had fewer gadolinium-enhanced lesions on MRI. The favorable effect of interferon beta-1a on gadolinium-enhanced lesions, confirmed in a separate study with interferon beta-1b,⁶⁰ suggests that interferon beta inhibits new lesion formation.

Both types of interferon beta are usually well tolerated. The most common side effects are influenza-like symptoms for 24 to 48 hours after each injection, and these usually subside after two to three months of treatment. Injection of interferon beta-1b causes redness, tenderness, swelling, and occasionally, necrosis at the injection site. Interferon beta-1b

TABLE 3. IMPORTANT UNRESOLVED QUESTIONS RELATED TO INTERFERON BETA THERAPY IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS.

When should therapy be started?
How long should therapy be continued?
Can the dose be individualized to achieve maximal therapeutic benefit?
What are the therapeutic mechanisms of action of the drug?
What are the long-term benefits?
Which preparation of interferon beta is clinically superior?

can also cause slight elevations in serum aminotransferase concentrations, leukopenia, or anemia, and a few patients have become depressed or have had worsening of preexisting depression. Interferon beta-1b—neutralizing activity was detected in serum samples from 38 percent of patients by the third year of treatment⁶¹ and correlated with decreased efficacy of therapy.⁶² Serum interferon beta-1a—neutralizing activity was found less often — in 14 percent of patients after one year and 22 percent after two years.⁷

Although interferon beta therapy is effective, important questions remain (Table 3). A risk-benefit analysis must be done in each patient. The cost of therapy, currently approximately \$8,000 to \$10,000 per year, and the uncertain long-term risks may outweigh the benefits in patients with mild multiple sclerosis and a favorable prognosis. Whether long-term therapy should be started at the time of the first attack and what constitutes the optimal duration of therapy are not known. In a study of recombinant interferon alfa-2a (Roferon-A, Hoffmann-LaRoche, Nutley, N.J.) in patients with relapsing-remitting multiple sclerosis, relapse occurred when therapy was stopped after six months,⁶³ suggesting the need for more prolonged therapy. The final report from the interferon beta-1b study⁶¹ suggested that patients continued to respond to treatment for five years, a finding that supports the value of long-term therapy, but the high dropout rate (greater than 50 percent) may have biased the results in favor of long-term therapy. Specific indications to stop therapy were steady progression of disability over a period of six months or treatment with three courses of corticotropin or corticosteroids for acute relapses during a one-year period.⁶⁴ The appearance of serum interferon beta—neutralizing antibodies should prompt alternative therapy, particularly in patients with disease progression.⁶⁵

The variable biologic response to interferon beta suggests that the dose could be individualized. Side effects of the interferon beta-1b correlate with body-surface area,⁶¹ but there are no established methods to individualize the dose for maximal efficacy. Figure 1 shows the putative sites of action of interferon beta in patients with multiple sclerosis. Clarifying the mechanisms most closely linked to efficacy might lead to

better methods to individualize treatment, particularly if the therapeutic effect could be monitored easily.

The best preparation of interferon beta and the long-term benefits of such therapy remain controversial. Both interferon beta-1a and interferon beta-1b reduce the relapse rate and disease activity on MRI, but interferon beta-1a appears to be better tolerated. In addition, interferon beta-1a results in less progression of disability,⁷ suggesting that long-term therapy will lessen the eventual impact of the disease.

Glatiramer Acetate

Glatiramer acetate is a mixture of random synthetic polypeptides composed of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine in a molar ratio of 6.0:1.9:4.7:1.0. It was synthesized as an immunological mimic of myelin basic protein, a putative autoantigen in multiple sclerosis. After glatiramer acetate was found to inhibit experimental autoimmune encephalomyelitis, a small trial suggested efficacy in patients with relapsing-remitting multiple sclerosis.⁶⁶ It was subsequently tested in a trial involving 251 patients with relapsing-remitting multiple sclerosis and mild-to-moderate disability. Treatment consisted of daily subcutaneous injections of 20 mg of glatiramer acetate or placebo for two years.¹⁴ The annualized relapse rate, the primary end point, was 29 percent lower in the glatiramer acetate group, and the proportion of patients who did not have a relapse was higher (34 percent vs. 27 percent). A greater proportion of patients in the glatiramer acetate group had an improvement of 1.0 point or more in their score on the Expanded Disability Status Scale (25 percent vs. 15 percent), and fewer had worsening of disability (21 percent vs. 29 percent). The most common side effect was mild reactions at the injection site, which occurred in 90 percent of patients given glatiramer acetate; 15 percent had brief episodes of flushing, chest tightness, shortness of breath, palpitations, and anxiety after one or more injections. Serum antibodies to glatiramer acetate also developed, but the presence of these antibodies had no effect on the clinical benefit. MRI scans, which were obtained at only one of the study sites, showed little change over the course of the study.⁶⁷

Glatiramer acetate was approved by the FDA in 1996. It represents an alternative to interferon beta therapy for patients with relapsing-remitting multiple sclerosis and may be most useful for patients who become resistant to interferon beta treatment owing to serum interferon beta—neutralizing activity.

Azathioprine

Azathioprine, a purine analogue, depresses both cell-mediated and humoral immunity. A meta-analysis of five randomized, double-blind, placebo-controlled trials supported the conclusion that oral azathioprine (2 to 3 mg per kilogram per day) reduces

the rate of relapse in multiple sclerosis⁶⁸ but has no effect on the progression of disability. The concern that prolonged azathioprine therapy may increase the risk of non-Hodgkin's lymphoma or skin cancer⁶⁹ was not confirmed in a case-control study.⁷⁰ Azathioprine should be considered in patients with relapsing-remitting multiple sclerosis who do not respond to therapy with interferon beta or glatiramer acetate. Azathioprine may be useful in patients with Devic's disease,⁷¹ a variant of multiple sclerosis affecting the optic nerves and cervical spinal cord, or in those with recurrent inflammatory myelitis.⁷²

Intravenous Immune Globulin

Intravenous immune globulin has been used successfully in neuroimmunologic disorders, including acute and chronic inflammatory demyelinating polyradiculopathy and myasthenia gravis, but its role in patients with multiple sclerosis is not yet clear. In a study of 150 patients with relapsing-remitting multiple sclerosis who were treated with intravenous immune globulin (150 to 200 mg per kilogram per month) or placebo for two years, there was less worsening in the scores on the Expanded Disability Status Scale in the group given immune globulin, but the differences between groups were small. The number of relapses and the annual relapse rate were also lower in the immune globulin group. However, the treating physicians were aware of the treatment assignment, which could have biased the results.

PROGRESSIVE MULTIPLE SCLEROSIS

Investigators have only recently made a clinical distinction between secondary progressive multiple sclerosis and primary progressive multiple sclerosis, and most studies have not distinguished between these two forms of chronic progressive multiple sclerosis. Treatment for chronic progressive multiple sclerosis has usually consisted of nonspecific immune suppression and has been of only moderate benefit.

Methotrexate

Methotrexate inhibits dihydrofolate reductase. Low-dose oral methotrexate is relatively nontoxic and effective in rheumatoid arthritis and psoriasis, presumably by inhibiting both cell-mediated and humoral immunity or as a result of its antiinflammatory effects. Sixty ambulatory patients with chronic progressive multiple sclerosis and moderate-to-severe disability were treated with methotrexate (7.5 mg weekly) or placebo for two years.⁷³ As compared with placebo, methotrexate significantly reduced sustained worsening, according to a composite measure of outcome that included the Expanded Disability Status Scale, the Ambulation Index,⁷⁴ and two tests of arm function. The methotrexate-treated patients had less disease progression, and patients with secondary progressive multiple sclerosis benefited most.^{73,75} The

clinical benefits were considered moderate, but toxicity was minimal. Because there are no nontoxic alternative treatments for patients with chronic progressive multiple sclerosis, low-dose oral methotrexate should be considered for those with progressive deterioration.

Cyclophosphamide

Cyclophosphamide is an alkylating agent with potent cytotoxic and immunosuppressive effects. In several controlled but unblinded trials, high-dose intravenous cyclophosphamide with or without subsequent booster injections was effective in patients with chronic progressive multiple sclerosis.^{74,76,77} However, one trial failed to demonstrate benefit.¹⁰ In this trial, the examining neurologist was unaware of the treatment assignments, and the patients wore bathing caps to mask the alopecia induced by cyclophosphamide. Cyclophosphamide has many side effects in addition to alopecia, including nausea and vomiting, hemorrhagic cystitis, leukopenia, myocarditis, infertility, and pulmonary interstitial fibrosis. Treatment with cyclophosphamide may be most appropriate for patients with rapidly progressive disease who do not respond to less toxic alternatives such as methotrexate.⁷⁸

Cyclosporine

Cyclosporine is a potent immunosuppressive drug that inhibits several steps in the activation of T cells. In a multicenter U.S. study, 550 patients with chronic progressive multiple sclerosis were given oral cyclosporine (initial dose, 7 mg per kilogram per day) or placebo for two years.¹¹ The length of time before patients became dependent on a wheelchair was slightly longer in the cyclosporine group, but nephrotoxicity occurred in 84 percent of cyclosporine-treated patients, and hypertension was also frequent. The moderate clinical benefits of cyclosporine appear to be outweighed by its toxicity.

FUTURE DIRECTIONS

Long-term placebo-controlled trials may no longer be ethically justifiable in patients with relapsing-remitting multiple sclerosis, given the evidence of the efficacy of interferon beta and glatiramer acetate. Comparisons between treatments are needed but will require very large samples, lengthy studies, and more sensitive outcome measures.^{49,79} Analyses of cost effectiveness and the quality of life^{80,81} will be increasingly important as more therapeutic options become available.

There are many potential new therapies, and it is not clear how best to screen them. Effectiveness in experimental autoimmune encephalomyelitis has been considered a prerequisite, but many therapies that are effective in experimental autoimmune encephalomyelitis are not useful in patients with multiple

sclerosis. Using serial gadolinium-enhanced MRI scans to screen therapies for efficacy has been recommended,⁷⁹ but such an approach has the potential of screening out treatments that might alter a different stage of the pathologic process.

Specific forms of immune suppression are based on deleting or inhibiting autoreactive pathogenic T cells. This approach may be limited by the heterogeneity and complexity of myelin determinant recognition in patients with established multiple sclerosis.³⁵ Nevertheless, ongoing trials are testing the efficacy of a T-cell-receptor vaccine,^{32,82} myelin peptides conjugated to major-histocompatibility-complex molecules,⁸³ and oral myelin,⁸⁴ all of which are thought to inhibit myelin-reactive T cells. Studies of nonspecific immunomodulation with linomide, transforming growth factor β , and soluble tumor necrosis factor-receptor are under way and are planned for interleukin-10. Remyelination strategies are largely at a preclinical stage, although the efficacy of intravenous immune globulin is being tested in patients who have fixed neurologic deficits.⁸⁵ In the future, glial-cell transplantation⁸⁶ or treatment with recombinant growth factors⁸⁷ could be used to stimulate regeneration and functional recovery.

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