CURRENT AND EMERGING TREATMENT STRATEGIES FOR MULTIPLE SCLEROSIS

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune disease that is characterized by central nervous system inflammation, demyelination, and axon loss. The clinical hallmarks of MS include a pattern of alternating relapses and remissions, and progression of permanent neurologic disability. Several subtypes of MS have been described on the basis of the initial clinical presentation and long-term course of disability. Longitudinal studies of the natural history of MS have identified several factors that are associated with poor prognosis, including greater disability at the time of evaluation, older age at onset, and a greater number of attacks during the first few years. Recent guidelines for the diagnosis of MS have incorporated magnetic resonance imaging (MRI) findings from the brain and spinal cord, which are also important prognostic markers early in the disease course. Steroids (eg, oral or intravenous methylprednisolone) have long been used to treat acute exacerbations of MS, although it is unclear whether they significantly alter the long-term course of the disease. Plasma exchange is effective treatment for attacks in some patients who do not respond to steroids. First-line disease-modifying treatments for MS include 3 formulations of interferon (IFN) β (subcutaneous IFNβ-1a administered 3 times/week; intramuscular IFNβ-1a administered once/week; and subcutaneous IFNβ-1b administered every other day) and glatiramer acetate. All of these agents have reduced relapses and MRI measures of disease activity in patients with relapsing MS. Some studies have suggested that more frequent, higher-dose IFNβ regimens may be superior to less frequent IFN administration. Because of the risk of potentially serious adverse events, natalizumab and mitoxantrone are usually reserved for patients who do not respond adequately to other treatments. Many new MS treatments are being evaluated in clinical trials, including oral immunomodulating agents and novel therapies that are intended to prevent neurodegeneration.


As described in the previous article, multiple sclerosis (MS) is an autoimmune disease that is characterized by perivascular infiltration of monocytes and lymphocytes, central nervous system (CNS) inflammation and demyelination, and progressive neuronal loss and CNS atrophy. MS typically begins with a period of alternating relapses and remissions, which is often followed by progressive and irreversible impairment of neurologic function. The clinical course of MS is individually quite variable. Most patients experience recurrent clinical symptoms in the early years. However, a minority experience progressive disability from the onset of MS, and a small number of other patients experience a single demyelinating event and then remain free of recurrences for years or even decades. Treatments that modulate the functioning of the immune system are the mainstay of
current MS disease-modifying therapy, and several new treatment options are in development.

**CLINICAL COURSE AND PROGNOSIS OF MS**

Several MS subtypes have been defined on the basis of the initial clinical presentation and long-term course. An advisory committee of the National Multiple Sclerosis Society developed standardized definitions of the 4 principal subtypes of MS, which are illustrated in Figure 1.\(^1\) The defining characteristic of relapsing-remitting MS (RRMS) is a pattern of clearly defined MS attacks, complete or partial return to baseline function after each attack, and the absence of disease progression between attacks. Recovery is often complete following early exacerbations but becomes less complete following later attacks. Primary progressive MS (PPMS) is defined by the gradual progression of disability from the initial onset of disease. Distinct relapses or remissions are absent, although plateaus or temporary minor improvements may occur. Secondary progressive MS (SPMS) begins with an initial period of relapses and remissions, which is followed by gradual progressive worsening with or without further relapses. Relapses during the early stages of SPMS are typically fewer in number and farther apart than in RRMS. Patients with progressive-relapsing MS (PRMS) exhibit gradual worsening of function from the onset of the disease, with superimposed acute relapses with or without full recovery.

Other MS subtypes have been proposed but are generally less well defined. The term “benign MS” has been used to describe a pattern of disease in which the patient remains fully functional many years after an acute MS episode.\(^1\) The precise criteria for benign MS are controversial, and different experts have used varying Expanded Disability Status Scale (EDSS) rating scores to define a benign course of MS. Benign MS is always a retrospective diagnosis, and it is not currently possible to prospectively identify individuals who will have a recurrence or progression-free long-term course. One recent analysis of the long-term course of benign MS found that individuals with EDSS scores of 2 or less 10 years after diagnosis are much less likely to experience disease progression and disability than patients with 10-year EDSS scores of 3 or more.\(^2\) However, this study and others have found that among individuals with EDSS scores lower than 3 with 10 or more years of disease duration, a significant proportion of the subjects were no longer considered benign after an additional decade.\(^3\) In a multivariate analysis, only the 10-year EDSS score was a significant predictor of 20-year outcomes.\(^2\) A rapidly progressing form of MS (malignant MS or Marburg syndrome) has also been described, which results in severe neurologic impairment or death within a relatively short period of time.\(^4,5\) An important trend in MS care over the last decade has been an increase in the use of disease-modifying therapies for patients with very early disease, including those with a single event suggestive of demyelination accompanied by additional lesions on magnetic resonance imaging (MRI) suggestive of MS (a presentation that has been referred to as a clinically isolated syndrome [CIS]).

Several studies have examined the natural history of MS or attempted to identify early risk factors of progression. In the pretreatment era, the median time to a disability level of 6 or worse (where unsupported mobility is lost) was 15 years, and 50% of patients transitioned to a progressive course by 10 years.\(^6\) In a population study in Olmstead County Minnesota, approximately 50% of patients with baseline EDSS scores of 3 to 5 required ambulatory assistance after 10 years, and approximately 50% of those with baseline EDSS scores of 6 to 7 were wheelchair confined or worse.\(^7\) Patients who initially have a relapsing-remitting course develop permanent disability more slowly than patients who initially present with progressive MS. However, once permanent disability develops, the rate of progression of disability is less affected by the presence or absence of additional relapses.\(^8\) These findings suggest that the 2 fundamental clinical phenomena of MS—remissions and progression—may be caused by distinct biologic mechanisms, or that progressive axonal degeneration is reflective of cumulative inflammatory initiated damage over long periods of time, or perhaps a combination of both, and that therapies that target MS exacerbations may not fully suppress the processes that cause permanent disability, particularly when applied to later stages of disease. Weinshenker et al examined the relationship between the time to progression to an EDSS score of 6 and several clinical variables in a large cohort of patients with RRMS.\(^9\) Significant independent predictors of more rapid disease progression included male sex, older age at onset, limb ataxia or impaired balance, brain stem or cerebellar involvement, number of attacks in the first 2 years, and higher EDSS score at baseline.
Patients with a remitting (rather than a progressive) course at onset had a more favorable prognosis, as did patients with longer intervals between the first 2 attacks. An analysis that combined the placebo groups from 4 large, randomized clinical trials of disease-modifying therapy found that predictors of eventual disease progression included higher baseline EDSS score, in addition to greater impairment of pyramidal and brain stem function. In a cohort study from Sweden that described prognostic factors in patients with MS who were followed for 25 years or more, Runmarker and Andersen found a similar set of factors that were associated with a less favorable long-term course, including a diagnosis of PPMS, older age, involvement of multiple CNS functional systems, more severe initial neurologic deficit, and fewer remissions. They found that the degree of neurologic deficits and particularly the involvement of multiple neurologic functions after 5 years were the most important prognostic factors, and that even among those with favorable prognostic factors, approximately 50% developed progressive MS. Factors that have been associated with benign MS include female sex, earlier age at onset, and EDSS lower than 2 after 10 years of disease duration. However, it is currently not possible to predict the clinical course for an individual patient, and these characteristics serve to aggregate patients into groups with more favorable or less favorable likely outcomes.

The clinical definitions of MS described previously were

**Figure 1. Principle Subtypes of MS**

Relapsing-remitting MS is characterized by clearly defined acute attacks with full recovery (A) or with sequelae and residual deficit upon recovery (B). Periods between disease relapses are characterized by lack of disease progression.

Primary progressive MS is characterized by disease showing progression of disability from onset, without plateaus or remissions (A) or with occasional plateaus and temporary minor improvements (B).

Secondary progressive MS begins with an initial relapsing-remitting course, followed by a progression of variable rate (A) that may also include occasional relapses and minor remissions (B).

Progressive-relapsing MS shows progression from onset but with clear acute relapses with (A) or without (B) full recovery.

MS = multiple sclerosis.

devised at a time when less information was available about the temporal course of structural alterations within the CNS of patients with MS, and the sensitivity of MRI for important disease events was not established. Consequently, the diagnosis of MS required demonstration of 2 or more clinically apparent episodes of demyelination. More recently, analyses of the CNS using MRI have revealed that the disease is more active than the clinical phenomenology would suggest, because patients with relapsing MS may experience 5 to 10 new lesions per year but only 1 to 2 clinical attacks. Revised MS diagnostic guidelines (the McDonald criteria) have been introduced that incorporate MRI as well as clinical events in the diagnosis of MS. A subsequent revision of the McDonald criteria clarified and expanded the application of MRI lesions of the spinal cord, further defined dissemination in space, and modified the definitional criteria for PPMS to make the criteria more useful. The McDonald criteria permit the diagnosis of MS with sufficiently high sensitivity and specificity on the basis of evidence of recurrent disease on MRI, even if there is no corresponding clinical event. This is important because considerable research has linked evidence of disease activity on MRI to eventual clinical outcomes. For example, one study of MRI at presentation in patients with CIS found that 88% of patients with abnormal brain MRIs progressed to clinically definite MS after 14 years, compared with only 19% of patients with normal brain MRIs at baseline. The same investigators found that the extent of MRI abnormalities in patients presenting with CIS was associated with their subsequent risk of disability up to 14 years later.

**TREATMENT OF MS**

The treatment of MS requires a coordinated program of pharmacologic and nonpharmacologic therapies to modify disease activity, relieve specific MS symptoms (eg, management of spasticity), and improve quality of life (eg, orthotics, psychosocial interventions, and rehabilitation). Although a discussion of symptomatic and nonpharmacologic interventions is beyond the scope of this article, these topics have been addressed in several recent reviews.

**TREATMENT OF ACUTE EXACERBATIONS**

Steroids have long been used to treat acute MS exacerbations. Early clinical trials demonstrated that patients with acute MS attacks recovered more quickly when they were treated with adrenocorticotropic hormone (ACTH) than with placebo. Intravenous (IV) methylprednisolone has largely replaced ACTH in contemporary practice. Methylprednisolone doses used in MS studies have varied from 500 mg to 2000 mg per day, and there is little consensus regarding the optimal dose. One study that compared oral administration of a cumulative total dose of approximately 600 mg over a 21-day period versus 1000 mg IV methylprednisolone daily for 3 days found that the 2 regimens produced similar improvement in MS relapses. The oral bioavailability of methylprednisolone is approximately 90%, and therefore, a slight dose adjustment would be required to attain an oral dose that is exactly equivalent to an IV dose.

It is controversial whether periodic administration of steroids alters the long-term course of MS. In one study, 88 patients with RRMS were randomized to single-blind treatment with pulsed IV methylprednisolone (1 g/day for 5 days, administered every 4–6 months for up to 2 years) versus IV methylprednisolone only during exacerbations. Patients who received the periodic steroids exhibited significantly less brain atrophy and fewer hypointense T1 lesions on MRI, and less progression of disability by EDSS in comparison to those treated only for clinical relapses. A study comparing high-dose versus low-dose IV methylprednisolone once every other month for patients with SPMS found no significant benefit for the study's primary end point (the proportion of subjects who sustained disability progression as measured by EDSS), although a secondary analysis (time to onset of sustained progression of EDSS disability) demonstrated delayed progression with high-dose methylprednisolone. A recent expert consensus report concluded that steroids have been shown to be beneficial for treatment of relapses, but there is insufficient evidence to conclude that they alter the natural course of the disease.

Plasma exchange is an effective salvage therapy for some patients whose acute relapses do not respond to steroids. In patients with severe MS episodes unresponsive to other therapy, plasma exchange produced moderate-to-marked improvement in approximately 40% of exacerbations. When the effectiveness of plasmapheresis in patients from this study in whom histopathologic samples were available was examined, all of the plasma-
pheresis responders had type 2 (antibody and complement-mediated) pathology. This latter study illustrates the concept that response to a therapy in MS may depend on a specific histopathologic subtype in addition to other factors not easily assessed in most patients before the initiation of treatment.

**DISEASE-MODIFYING THERAPIES**

First-line disease-modifying treatments include 3 formulations of interferon (IFN) β (IFNβ-1a for intramuscular administration, IFNβ-1a for subcutaneous administration, and IFNβ-1b) and glatiramer acetate (GA). Several randomized, double-blind, placebo-controlled clinical trials have demonstrated that all 4 of these agents significantly improve the symptoms of MS.

Although the specific and primary end points varied somewhat among the pivotal trials, randomized, placebo-controlled clinical trials have generally shown reductions in relapse rates and suppression of MRI activity with all of the IFNβ formulations, and some studies have also demonstrated significant effects on sustained disability and disease progression. Some evidence suggests that more frequent administration or higher IFNβ doses may be associated with better clinical outcomes. The Evidence of Interferon Dose-Response: European North American Comparative Efficacy study was a randomized, assessor-blinded comparison of 2 IFNβ dosing regimens: subcutaneous IFNβ-1a 44 µg 3 times per week versus intramuscular IFNβ-1a 30 µg once weekly. High-dose IFNβ was superior for several clinical and MRI outcomes during comparative treatment for 48 weeks with some patients treated for up to 2 years. As shown in Figure 2, patients in the high-dose group were significantly more likely to remain relapse free (odds ratio, 1.5; \( P = .023 \)), and they had a significantly longer time to first relapse (\( P = .0002 \)). High-dose IFNβ also produced significantly greater reduction in disease activity on MRI. When patients in the low-dose group were crossed over to high-dose IFN at the end of the blinded comparative treatment phase, relapse rates were reduced by approximately 50% compared to the prior study period whereas a 25% drop in annualized relapse rate was seen in those continuing on IFNβ-1a subcutaneous twice weekly. High-dose IFNβ was associated with a higher incidence of injection-site reactions (85% vs 33%; \( P < .001 \)) and neutralizing antibodies (26% vs 3%; \( P < .001 \)).

The Independent Comparison of IFNs study compared once-weekly IFNβ-1a 30 µg versus IFNβ-1b 250 µg administered every other day, for up to 2 years. In the blinded MRI analysis, 55% of subjects receiving the higher-dose IFNβ were free of new T2 lesions, compared to 26% of those on the once-weekly intramuscular dose. In an unblinded clinical analysis, the percentage of patients with relapses during 2 years of follow-up was significantly lower with high-dose IFN than with the lower dose (64% vs 49%; \( P = .03 \)).

It has been observed that neutralizing antibodies (NAbs) to IFNβ may develop in some treated patients, resulting in mitigation of some measures of efficacy as measured by relapse rates or MRI activity. In general, it appears that NAbs are least likely to occur with use of IFNβ-1a 30 µg intramuscular once weekly, and occur most commonly with IFNβ-1b 250 µg every other day subcutaneously. In some individuals, NAbs disappear over time despite continued use of IFNβ. Because of different methodologies in measuring NAbs and analyzing their effects, there is still controversy regarding indications for testing and actions to take when NAbs are present. This is reflected in differing recommendations by expert review panels.
The long-term effects of IFNβ have been examined in studies that have compared clinical outcomes for patients who were initially randomized to IFNβ therapy versus patients who were initially randomized to placebo but later crossed over to IFNβ treatment. For example, an analysis of data from the Prevention of Relapses and Disability by IFNβ-1a Subcutaneously in MS study demonstrated that patients who received early therapy with IFNβ-1a subcutaneous 44 µg 3 times weekly were less likely to demonstrate disability progression by EDSS than those taking placebo for 2 years and then active treatment for the next 2 years.\(^{40}\) In a subsequent follow-up, those beginning on active therapy continued to exhibit less disease progression and fewer relapses 7 to 8 years after enrollment into the study than patients who started therapy later.\(^{41}\) Analysis of patient data on follow-up as long as 16 years after initiation of treatment with IFNβ-1b demonstrated sustained improvement for patients who continued to receive IFNβ-1b in comparison with patients who discontinued treatment.\(^{42}\)

Randomized placebo-controlled clinical trials have demonstrated that early treatment with IFNβ for patients with CIS results in decreases in new MRI lesions and recurrent clinical events marking the conversion to clinically definite MS, and delays progression of disability.\(^{43,44}\) In the Betaferon/Betaseron in Newly Emerging MS for Initial Treatment study, patients with CIS were treated with IFNβ-1b or placebo until diagnosis with clinically definite MS, or for up to 2 years, after which patients could continue open-label treatment with IFNβ-1b. After a total of 3 years of follow-up, patients who were treated with early administration of IFNβ-1b exhibited significantly less risk of disability change by EDSS progression than patients for whom treatment was delayed until the onset of clinically definite MS.\(^{44}\) Over a 3-year follow-up period, confirmed progression on the EDSS rating scale was noted for 16% of patients in the early treatment group and 24% with delayed treatment ($P = .022$). An analysis of MRI outcomes from this study after 2 years of treatment also found significant reductions in the median number of newly active lesions (2 vs 5 for the IFNβ-1b and placebo groups, respectively; $P < .001$), in addition to reduced numbers of T2 and gadolinium (Gd)-enhancing lesions.\(^{45}\) Similar results on subsequent relapses and new MRI lesions were seen in a study using IFNβ-1a 30 µg once weekly compared to placebo.\(^{45}\)

Glatiramer acetate is composed of acetate salts of synthetic peptides that contain the amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine.\(^{46}\) GA binds to major histocompatibility complex and T-cell surface receptors, and shifts the cytokine profile of T cells to an anti-inflammatory pattern.\(^{47}\) In randomized, placebo-controlled clinical trials, GA has been shown to significantly reduce MS relapse rate, stabilize disease progression, and reduce the number of new Gd-enhancing and T2 MRI lesions.\(^{48,49}\) GA reduced the annualized relapse rate by approximately 30% during 3 years of double-blind administration and was associated with continued clinical stability by EDSS in those remaining on GA for up to 10 years.\(^{46,49,51}\) GA is usually administered at a dose of 20 mg per day. The results of a recent randomized, double-blind clinical trial suggested that a higher dose (40 mg) may be more effective for improving clinical outcomes and reducing MRI measures of disease.\(^{52}\)

**TREATMENT OF PATIENTS WITH WORSENING MS**

Many patients with MS exhibit continued relapses and deterioration of function despite treatment with currently available therapies. To date, no specific criteria have been validated for defining a suboptimal response to a disease-modifying therapy for MS. Several consensus groups have suggested that continuing relapses, particularly with incomplete recovery, worsening neurologic impairment, including the involvement of multiple functional pathways, and continued inflammatory lesions on MRI, may indicate the need to alter the current therapeutic regimen.\(^{53-55}\) Patients may respond suboptimally because treatment does not completely suppress inflammation or because inflammation is only one of several mechanisms that cause MS. Although the pathogenesis of MS includes inflammatory and neurodegenerative processes, current disease-modifying therapies act primarily by suppressing inflammation. In addition, treatment failure may be related to the formation of NABs as previously noted. Studies that have examined clinical or MRI outcomes have demonstrated that some cases of treatment failure in patients who are receiving IFNβ for MS may reflect antibody formation. It has been estimated that approximately 20% of patients who fail on IFN therapy are NAB-positive.\(^{56}\) Data from clinical trials of the all of the IFNβ agents demonstrated little
impact of NAb formation during the first 2 years of treatment, but increased disease activity in NAb-positive patients after 3 to 4 years. \(^{27}\) A modified formulation of IFNβ-1a subcutaneous has recently been developed with the objective of reducing the immunogenicity and improving the tolerability of IFNβ treatment. \(^{37}\) This reformulated IFNβ-1a does not contain human serum albumin or fetal bovine serum and has been shown to produce less proinflammatory cytokine stimulation and NAb than the conventional formulation in animal models and preliminary clinical testing.\(^{57}\)

Patients also may fail to respond to a particular therapy because of genetic variability. In a recent pharmacogenomic study, investigators conducted a genome-wide scan for candidate DNA variants that differed between IFN responders and nonresponders.\(^{58}\) Several genetic polymorphisms were identified that were associated with an increased likelihood of responding to IFN therapy, including genes that encode neuronal receptors for glutamate and γ-aminobutyric acid, in addition to heparan sulfate proteoglycans that are thought to participate in axon formation and regeneration.

Options for patients who are failing to respond adequately to treatment with an IFN or GA include changing the dose of the current IFNβ agent, switching between IFNβ and GA, or the use of natalizumab or mitoxantrone. Natalizumab is a monoclonal antibody against α4 integrin, a cell surface adhesion molecule that is important in leukocyte migration into the CNS. It is approved for the treatment of relapsing forms of MS. In the Natalizumab Safety and Efficacy in RRMS study, which examined the efficacy of natalizumab in more than 900 patients with relapsing MS during a 2-year period, natalizumab decreased the relapse rate by 68% and the risk of confirmed progression of disease by EDSS by 42% over 2 years. It also significantly improved several MRI measures of disease activity, including Gd-enhancing lesions, T2 lesions, and brain atrophy.\(^{69}\) Natalizumab was associated with 3 cases of progressive multifocal leukoencephalopathy (PML) during clinical trials in which it was given in conjunction with IFNβ-1a 30 µg intramuscular once weekly for MS,\(^{60,61}\) or in a patient with Crohn’s disease previously treated with immune suppressive agents.\(^{62}\) PML is a rapidly progressive viral demyelinating disease that is associated with infection and lysis of oligodendrocytes by reactivated JC virus in immunosuppressed patients.\(^{63}\) Natalizumab was temporarily withdrawn from the market while the clinical cohorts were reviewed for other cases. It has been released again for restricted clinical use, and no new cases of PML have been reported to date. As a consequence of the risk of PML, natalizumab is generally recommended for patients who have not responded to or who cannot tolerate other MS therapies and is not administered in conjunction with other immunomodulatory agents.\(^{64}\)

Mitoxantrone is an antineoplastic agent that is approved for worsening forms of relapsing MS (ie, worsening RRMS, SPMS, or PRMS). In clinical trials of patients with SPMS or with very active MS, mitoxantrone reduced the rate of progressive disability by EDSS, improved ambulation, and reduced the likelihood of new relapses.\(^{55,66}\) Mitoxantrone has been associated with an increased risk of cardiotoxicity, and serial monitoring of cardiac ejection fraction is recommended before each dose.\(^{67}\) The risk of cardiotoxicity increases with the total cumulative mitoxantrone dose particularly when the cumulative dose exceeds 100 mg/m². The maximum approved mitoxantrone dose, for MS is 140 mg/m². Mitoxantrone has also been associated with infrequent toxic leukemias and is generally reserved for patients with worsening forms of relapsing MS despite other treatments.

**EMERGING STRATEGIES FOR MS THERAPY**

Several new treatments are in development but are not yet approved for MS. Alemtuzumab is a humanized monoclonal antibody against the CD52 cell surface molecule, which is present on T and B lymphocytes.\(^{68}\) Administration of alemtuzumab induces complement-mediated lysis of lymphocytes and has been shown to significantly improve early RRMS, producing an even greater beneficial effect than IFNβ-1a in one study.\(^{69}\) It has the potential to cause autoimmune-mediated adverse effects, including autoimmune thyroid disease and thrombocytopenia. Rituximab, a monoclonal antibody that selectively depletes CD20+ B lymphocytes, was recently evaluated in a phase II clinical trial of patients with MS.\(^{70}\) Compared with placebo, rituximab significantly reduced the proportion of patients with relapses, in addition to the number of new Gd-enhancing lesions over 72 weeks of follow-up.\(^{71}\) Therapies that target the interleukin (IL)-12/IL-23 family of inflammatory cytokines have been proposed as a potential treatment
strategy for MS, and a monoclonal antibody directed against IL-12/IL-23 has been examined in a phase I study. Daclizumab is a monoclonal antibody directed against the IL-2 receptor. It has been shown in a small initial series to result in stabilization or improvement in patients with RRMS or SPMS with continued relapses and active MRI lesions despite treatment with IFNβ.

Several agents are being developed for oral administration. Oral cladribine, a purine analogue with lymphootoxic activity, has been examined in several clinical trials for progressive forms of MS, and may be the first oral MS therapy to enter the clinic. Other oral therapies are at earlier stages of development. Fingolimod interacts with sphingosine-1-phosphate 1 receptors, which are thought to mediate movement of lymphocytes from lymphoid tissues. In a phase II clinical trial, oral fingolimod significantly reduced relapse rate and the number of Gd-enhancing lesions after 6 months. BX 471 is an oral agent that interrupts the activity of CC chemokine receptor 1 chemokines, which regulate the migration of immune cells. Chemokine receptors have been proposed as a potentially important target in autoimmune disorders, including MS, and BX 471 is currently being evaluated in early stage clinical trials for MS and other indications. Oral fumaric acid derivatives (eg, BG-12) are thought to induce apoptosis in activated T lymphocytes, downregulate cellular adhesion molecules, and induce Th2-like cytokine release from T-helper cells. Administration of oral fumaric esters to patients with MS and contrast-enhancing MRI lesions at entry was found to reduce the number and volume of contrast-enhancing lesions during open-label therapy. Oral fumaric esters are currently in phase III clinical trials. Teriflunomide is a dihydroorotate dehydrogenase inhibitor that blocks pyrimidine synthesis in rapidly dividing cells (including T lymphocytes), resulting in anti-inflammatory effects. Teriflunomide has been shown to reduce active MRI lesions in a phase II clinical trial with a trend toward clinical relapse rate and reduced EDSS progression. Teriflunomide is now in phase III clinical trials. Laquinimod is a synthetic compound related to roquinimex that inhibits inflammatory disease in animal models of MS. In a phase II study, laquinimod reduced the mean number of new contrast-enhancing lesions by 44% compared to placebo over 24 weeks. Further clinical studies are planned. MBP-8298, a synthetic peptide incorporating sequences of myelin basic protein, is hypothesized to induce immune tolerance to the dominant epitope of this myelin protein. It is being tested in patients with SPMS. Vaccination strategies using irradiated lymphocytes or T-cell receptor peptides are also being tested in patients with MS and other autoimmune disorders.

As noted previously, the pathogenesis of MS includes CNS inflammation and neurodegeneration, yet the available treatment strategies for MS work primarily by modulating immune dysfunction. Strategies to prevent or reverse neurodegeneration are generally at earlier stages of development. Neurotoxicity caused by the excitatory neurotransmitter glutamate or by activation of membrane sodium channels has been described in several neurologic disorders and may contribute to axonal injury in MS. Glutamate receptor or sodium channel antagonists have been proposed as potential therapies for MS, but are at early stages of clinical development.

**CLINICAL TRIAL DESIGN AND OUTCOME MEASUREMENT**

Conclusions about differences in efficacy or safety between therapies can best be made when treatments are directly compared within the same trial, yet few head-to-head comparisons of MS treatments have been conducted. Several factors make it difficult to compare the effectiveness of different MS therapies based on results from different studies and to compare recent studies with those that were conducted in the past. Clinical trials of MS therapies conducted over the last 2 decades have varied considerably in specific therapeutic strategies and patient populations enrolled, making it difficult to compare the results of studies with one another. The availability of effective therapies for MS affects subjects likely to enter newer placebo-controlled clinical trials, and the growing trend toward earlier therapy over the last decade—including the use of disease-modifying therapies for patients with CIS—may alter the disease characteristics of patients who now enroll in MS studies. Participants with more severe or active MS may be less likely to enroll in current trials, in which they may receive a placebo, resulting in substantially better outcomes (eg, lower relapse rates) for placebo-treated patients in newer studies.

These lower event rates would make it more difficult to demonstrate treatment effects between groups,
resulting in the need for larger and more expensive clinical trials. A significant challenge for future research will be to design and validate outcome measures that are predictors of the future course of disease and that can be used in smaller numbers of patients or over a shorter period of time.

CONCLUSIONS

Although the clinical course of MS varies considerably from patient to patient, long-term studies have identified several clinical factors that predict the clinical course. Steroids improve acute MS exacerbations, but it is unclear whether they significantly improve the long-term course of illness. First-line disease-modifying therapies for patients include GA and 3 formulations of IFNB, all of which have been shown to reduce relapses and improve other clinical outcomes in patients with relapsing MS. Natalizumab and mitoxantrone also are effective for patients with relapsing MS, but are generally used as second-line therapy because of the increased risk of serious adverse events. Emerging treatment options for MS include oral therapies and monoclonal antibodies directed at new targets to favorably alter immune-mediated damage. Novel treatments that specifically target mechanisms that cause neurodegeneration are under active investigation.

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