ABSTRACT

The development of slowly progressive neurologic deficits in patients with multiple sclerosis (MS), either starting from disease onset or after a cycle of relapses and remissions, is a vexing clinical problem for patients and physicians alike. Whereas current disease-modifying therapies have made significant inroads in blunting the long-term effects of relapsing-remitting MS, these same treatments have shown limited clinical effectiveness for patients with either primary progressive MS (PPMS) or secondary progressive MS (SPMS). More aggressive immunosuppressive regimens have been tried in these patients, but toxicity and complications often detract from their effectiveness over time. At the same time, there are exciting new treatment approaches being developed for patients with all forms of MS, and research being conducted on the therapeutic frontiers in this disease is focused on both reducing toxicity and improving long-term effectiveness. This article will review the diagnostic and therapeutic challenges presented by PPMS and SPMS; then it will turn to a discussion of the latest treatment interventions being tested in clinical trials. We hope to paint a picture of both the complex challenges facing clinicians who care for patients with progressive MS, but also show that the future remains bright with regard to new treatment options. (Adv Stud Med. 2008;8(8):284-292)

MULTIPLE SCLEROSIS: THERAPEUTIC FRONTIERS AND PROGRESSIVE DISEASE*

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Multiple sclerosis (MS), a central nervous system (CNS) disease characterized by the confluence of inflammation, demyelination, and gliosis, can be relapsing-remitting or progressive in its clinical course. On average, MS is twice as common in women as in men, with a typical age of onset between 20 and 40 years. Relapsing-remitting MS (RRMS) accounts for roughly 85% of all cases at initial diagnosis. This phase of disease is characterized by discrete neurologic attacks that often evolve over a period of days to weeks, followed by clinical remission. Though affected individuals usually recover after each attack and become stable before relapsing again, this is not always the case. Thus, nearly 50% of patients who become gait-impaired during an attack do not recover fully, leading to accumulating disability.¹

Most patients with RRMS eventually enter a progressive phase of deterioration known as secondary progressive MS (SPMS), which may occur at any point during the disease. Within 15 years of diagnosis, approximately 50% of patients develop SPMS. In contrast to the gradual transition from RRMS to SPMS, some 15% of patients with MS experience progressive disease from onset. In general, patients with primary
progressive MS (PPMS) are somewhat older at diagnosis (approximately 40 years old) and deteriorate more rapidly. Fewer than 5% of patients have what is referred to as progressive relapsing MS (PRMS), an overlap disorder between RRMS and PPMS. Patients with PRMS experience superimposed relapses against the backdrop of relentlessly progressive disease from onset.\(^1\) Irreversible disability is an end result of all forms of MS and may occur following an incomplete remission of a relapse or from slow insidious progression.\(^2\) Current research suggests that these 2 causes of disability may be distinct and should be targeted separately in order to achieve maximal therapeutic efficacy over the long term.\(^3\)

Despite their efficacy in RRMS, current disease-modifying therapies (DMTs), including interferon (IFN) \(\beta\) and glatiramer acetate (GA), for the most part have not proven themselves particularly useful in delaying the accumulation of disability in the progressive phases of disease. Thus, there continues to be an unmet therapeutic need in slowing the degeneration that is believed to occur in progressive forms of MS. Indeed, once patients progress to SPMS—a state in which accumulated disability likely reflects irreversible axonal loss—options are limited.

**Revising the Diagnostic Criteria for PPMS**

Currently, there are 15 to 20 compounds being developed for the treatment of MS, and some focus has shifted to advancing therapeutic options for the treatment of progressive disease.\(^4\) Indeed, in the first 5 years of the 21st century, the diagnostic paradigm for progressive MS shifted, as reflected by the modified McDonald criteria. Since their original publication in 2001, the core features of the revised criteria have remained constant, with a focus on objective clinical findings, dissemination of lesions in space and time, and use of paraclinical measures to expedite and enhance the accuracy of the diagnostic process. In 2005, however, the International Panel on the Diagnosis of MS reconvened to modify diagnostic criteria based on newly available evidence. One area of focus was on the criteria used in the diagnosis of PPMS.\(^5\)

To summarize, a diagnosis of PPMS no longer absolutely requires evidence of oligoclonal immunoglobulin G bands with immunofixation in cerebrospinal fluid (CSF) as the main criteria. Rather, emphasis returned to 1 year of disease progression in conjunction with magnetic resonance imaging (MRI)-based signs of progression (Table).\(^5\)

**Diagnosis of SPMS**

Diagnosing SPMS can be challenging because the transition from RRMS does not generally occur at one fixed point in time. Although MRI results can be helpful at this stage, they can also be misleading. For example, the number of gadolinium (Gd)-enhancing lesions tends to decrease in patients with RRMS as they transition to SPMS and becomes low as the disease advances. Still, decreases in Gd-enhancing lesions can also occur in response to treatment with DMTs and focal enhancement can still occur in the clinical setting of progression. Furthermore, the average burden of brain T2-hyperintense lesions tends to be higher in patients with SPMS than in those with RRMS, and focal spinal cord lesions also tend to accumulate. Likewise, a greater degree of brain and spinal cord atrophy is seen in SPMS than in RRMS.\(^6\) However, accumulating clinical disability is the defining feature of SPMS and almost always trumps MRI findings as the basis for diagnosis. Therefore, a careful clinical history remains the most important tool to identify the SPMS transition.

<table>
<thead>
<tr>
<th>Table. Revised Criteria for Diagnosis of PPMS</th>
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<tr>
<td><strong>Original McDonald Criteria (2001)</strong></td>
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<tr>
<td>Dissemination in space by MRI evidence of 1 of the following: • ≥9 T2 brain lesions, or • ≥2 cord lesions, or • 4–8 brain lesions and 1 cord lesion, or • Positive VEP with 4–8 MRI lesions, or • Positive VEP with &lt;4 brain lesions plus 1 cord lesion and</td>
</tr>
<tr>
<td>Dissemination in time by MRI or continued progression for 1 year</td>
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<tr>
<td>CSF = cerebrospinal fluid; IgG = immunoglobulin G; MRI = magnetic resonance imaging; PPMS = primary progressive multiple sclerosis; VEP = visual evoked potential.</td>
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THE NATURAL HISTORY OF RELAPSING AND PROGRESSIVE MS AND IMPLICATIONS FOR INTERRUPTING THE UNDERLYING DISEASE PROCESSES

One of the major goals of the McDonald criteria is to provide a clinical basis for earlier therapeutic intervention in patients with MS, with the assumption that early treatment delays subsequent disability. In an early observational study of the natural history of MS (before the widespread use of DMTs), patients with RRMS and PPMS were followed for their rate of disease progression and to determine what effect, if any, relapses had on progression over time. Here, the primary outcome measure was time to progression of disease based on the Kurtzke Expanded Disability Status Scale (EDSS).

Among the 1844 subjects analyzed, 85% had RRMS and 15% had PPMS at onset. The median time from first symptom to an EDSS score of 4 in the RRMS group was 11.4 years (95% confidence interval [CI], 10.5–12.3 years). This level of disability (EDSS 4) occurred in most patients with PPMS almost from the time of onset, a difference that was highly significant (P < .001). On the other hand, both patients with RRMS and those with PPMS moved from EDSS scores of 4 to 6 and from 6 to 7 at nearly identical rates. Likewise, when rates of disability progression between patients with PPMS and those with SPMS were compared, both populations showed identical findings regardless of whether patients had superimposed relapses or not. Taken together, these data show that there seems to be a notable dissociation between relapses and progression of irreversible disability, suggesting that the 2 disease manifestations may occur through independent mechanisms.

In terms of whether the former begets the latter, a more recent observational cohort study followed 1504 patients with RRMS for up to 7 years for the effect of IFNβ on disease progression. Although not a randomized, controlled clinical trial, data from this study suggested that treated patients (n = 1103) progressed to SPMS significantly slower than untreated individuals (n = 401). Thus, it is possible to infer that the natural history of conversion to progressive MS may be delayed by the early initiation of a DMT. Understanding these natural history data is crucial to determining whether a given treatment intervention really has an impact on the course of disease in SPMS.

AN EVIDENCE-BASED REVIEW REVEALS A LACK OF GOOD TREATMENT OPTIONS FOR PRIMARY-PROGRESSIVE DISEASE

Treatment of PPMS has been a particular challenge in the MS field. Prior studies have been small, owing in large part to the infrequent nature of PPMS. However, in a 3-year, randomized, double-blind, placebo-controlled trial, the PROMISE study evaluated 943 patients with PPMS treated with GA (20 mg/day) or placebo. Patients between the ages of 30 and 65 with EDSS scores between 3 and 6.5 were enrolled. The primary endpoint was a 1-point progression in EDSS score for subjects with baseline EDSS scores of 3 to 5, and a 0.5-point progression for subjects with baseline scores of 5.5 to 6.5. These score changes had to be sustained for at least 3 months. The number of enhancing lesions and volume of T2 lesions on annual cranial MRI scans were also analyzed as part of the secondary analysis. Although significant GA treatment effects were demonstrated on MRI-monitored lesion enhancement and total plaque burden, the drug had no demonstrable effect to delay the accumulation of clinical disability over time compared to placebo.

Because study investigators observed a relatively slow rate of progression in placebo-treated subjects, several post-hoc analyses were undertaken as part of their effort to improve sensitivity in order to detect potential treatment differences. In one such analysis of male patients (n = 455), GA significantly delayed time to sustained progression of accumulated disability compared with placebo. Based on analysis of second-interim data (reflecting at least 2 years of treatment), a total of 61.6% of male GA-treated patients remained progression free, compared with 49.1% of placebo-treated patients (hazard ratio, 0.71 [95% CI, 0.51–0.98; P = .039]). These data imply that there may be a role for the use of GA in men with PPMS.

AN EVIDENCE-BASED REVIEW OF THERAPIES USED IN SPMS

Oral Methotrexate

In a 2-year, randomized, double-blind, placebo-controlled trial, 60 patients with progressive MS were randomized to receive a weekly dose of oral methotrexate (7.5 mg) or placebo. Patients between the ages of 21 and 60 were enrolled and stratified into 2 groups according to EDSS score (3–5.5 [n = 19] and 6–6.5 [n = 41]). Treatment failure was defined by means of a composite...
outcome measure comprised of the following components: EDSS, Ambulation Index (AI), Box and Block Test (BBT), and the 9-Hole Peg Test (9HPT). Overall, methotrexate-treated patients had a significantly lower incidence of sustained progression compared with placebo patients (51.6% vs 82.8%, P = .011).16

Univariate analysis of individual parameters (EDSS, AI, 9HPT, and BBT) showed significant methotrexate-related treatment benefits in the 9HPT parameter for methotrexate-treated patients with SPMS (P = .007) and also all patients who had EDSS scores of 6 or higher at baseline (P = .017). This was not the case for the other individual parameters, however, though there was a trend favoring methotrexate treatment in the group analysis (P = .157). The implication of a treatment-related benefit in the 9HPT parameter is that upper-extremity function, a parameter that is not reflected by the EDSS, may benefit from treatment with methotrexate.10

Differences in outcomes were sustained for 2 years, during which time there was no significant toxicity, though in general, long-term methotrexate use is associated with bone marrow suppression, hepatotoxicity, interstitial pulmonary fibrosis, and teratogenicity. Admittedly, methotrexate-related benefits are modest, but there is some efficacy.

**INTERFERON β**

The efficacy of IFNβ-1b for the treatment of patients with SPMS was explored in a 3-year, randomized, double-blind, placebo-controlled trial conducted by the European Study Group on IFNβ-1b in SPMS.2 A total of 718 patients with baseline EDSS scores between 3 and 6.5 were randomized to placebo or IFNβ-1b administered in doses of 8 million IU subcutaneously every other day throughout the study. This study showed that there was a significant difference in confirmed progression of disability in favor of IFNβ-1b (P = .0008) as measured by a 1-point increase sustained for 3 months on the EDSS for patients with baseline scores of 3 to 6 and a 0.5-point increase for patients with baseline scores of 6 to 6.5 that became apparent starting 9 to 12 months after enrollment and that continued for 2 to 3 years in the intention-to-treat analysis. With respect to confirmed progression, 49.8% of placebo-treated patients progressed, compared with 38.9% of IFNβ-1b–treated patients (P = .0048)—a 21.7% reduction. By month 12, time to becoming wheelchair bound was significantly delayed by up to 9 months in IFNβ-1b–treated patients (P = .0129). Additionally, the mean annual relapse rate was reduced overall by approximately 30% (P = .002), and time to first relapse was prolonged in the IFNβ-1b group (644 days vs 403 days, P = .003) compared with the placebo group.2

Results from the 3-year, randomized, placebo-controlled trial conducted by the North American Study Group on IFNβ-1b in SPMS were not as encouraging as those obtained by their European counterparts. Thus, North American researchers did not find any significant difference in progression of disability in IFNβ-1b–treated patients with SPMS compared with placebo-treated control patients. The study included a total of 939 patients with baseline EDSS scores of 3 to 6.5, who received placebo or 1 of 2 doses of IFNβ-1b (250 µg or 160 µg/m² of body surface area) administered subcutaneously every other day. The primary outcome measure was time to progression of 1 or more EDSS point with a baseline score of 3 to 5.5, or 0.5 EDSS points if baseline score was 6 to 6.5.11

There was no difference in the comparison of time to confirmed EDSS progression between the pooled IFNβ-1b group and the placebo group (P = .71). However, there was a significant treatment effect on the annual relapse rate for the pooled IFNβ-1b group and the 250-µg group, with a 36% reduction among all IFNβ-1b–treated subjects and a 43% reduction for the 250-µg group. In addition, there was a significant treatment-associated benefit in T2-weighted lesion area, with a median change from baseline to end point of 10.9% in the placebo group, compared with 0.4% in the 250-µg group and 0.8% in the 160-µg/m² group (P < .0001 vs placebo in both groups). There was also a 71% reduction in newly active lesions in the combined treatment group compared with placebo (P < .001). Despite its proven use in treating RRMS, IFNβ-1b did not have a treatment effect on the progression of disability in patients with SPMS.

Ultimately, differences between outcomes in the European and North American studies were attributed to differences in the baseline characteristics between subjects in the 2 studies. A consensus statement of the 2 study groups suggested that IFNβ-1b provides therapeutic effect on disability progression in patients who remain in the inflammatory phase of their disease.12

**MITOXANTRONE**

This phenomenon of only a subset of patients with SPMS responding to therapy was reinforced in the
MIMS (Mitoxantrone in SPMS) study, a randomized, placebo-controlled trial of 194 patients between the ages of 18 and 55 with SPMS or worsening RRMS, in which patients were randomized to placebo, mitoxantrone 5 mg/m², or mitoxantrone 12 mg/m² intravenously every 3 months for 24 months. Mitoxantrone, a synthetic anthrancenedione antineoplastic agent, has various immunosuppressive properties, including the capacity to inhibit T-cell activation, diminish B-cell antibody production, and deactivate macrophages. In the MIMS study, baseline EDSS scores were between 3 and 6.5. The primary end point was a multivariate composite of 5 parameters, including change in EDSS scores, change in AI, adjusted total number of treated relapses, time to first treated relapses, and change in standardized neurologic status at 24 months. EDSS deterioration of 1 point or more occurred in 8% of mitoxantrone-treated patients, compared with 25% of placebo-treated patients \( (P = .013) \). There was also a significantly higher percentage of mitoxantrone-treated patients who did not relapse during the study period, compared with placebo-treated patients \( (P = .021) \). These treatment effects were associated with the 12-mg/m² dose, but not the 5-mg/m² dose. The mean increase in the number of T2-weighted lesions in the mitoxantrone group was 0.29, compared with 1.94 in the placebo group \( (P = .03) \). Once again, patients who gained the most therapeutic benefit in this study were those with more inflammatory disease. The mean change in EDSS scores of patients treated with mitoxantrone 12 mg/m² who had not experienced relapses before treatment \( (n = 188) \) was 0.13, compared with 0.67 in placebo-treated patients. In patients who had relapsed before treatment \( (n = 140) \) and were still in the inflammatory stage of disease, the mean change in EDSS score was 0.5, compared with -0.22 in patients treated with mitoxantrone. In the United States, mitoxantrone (12 mg/m² administered intravenously every 3 months) is the only US Food and Drug Administration (FDA)-approved therapy for worsening RRMS, PRMS, and SPMS.\(^1\)

Use of mitoxantrone should be time limited, due to the cardiotoxicity associated with long-term usage. Potential cardiac-related problems include cardiomyopathy, reduced ventricular ejection fraction, and irreversible congestive heart failure. There is also a significantly increased risk of leukopenia, which affected 19% of patients in MIMS who received the 12-mg/m² dose of mitoxantrone \( (P < .05) \). As a result of its risk profile, a cumulative dose beyond 140 mg/m² is not recommended, which translates into roughly 2 to 3 years of therapy. In many cases, mitoxantrone is most appropriate for patients who have failed other therapies.

**Cyclophosphamide**

Other cytotoxic treatments have some utility in the treatment of patients with progressive MS, although the benefits are often counterbalanced with substantial toxicity and risk. In a study of 256 patients with progressive MS, patients were randomized to receive cyclophosphamide using 2 different induction regimens, either with or without outpatient boosters of 700 mg/m² every other month for 2 years. Most patients not given boosters continued to progress; however, time to treatment failure (as reflected by EDSS scores) beyond 1 year of therapy was significantly prolonged among those patients who received ongoing treatments \( (P = .03) \). This benefit of sequential cyclophosphamide treatments was also significantly tied to the patient’s age; those 40 years or younger had a much better response \( (P = .003) \) compared to those older than 40 years \( (P = .97) \).

**Intravenous Immunoglobulin**

Certain therapies known to be effective in treating RRMS have proven to be ineffective in slowing the degeneration associated with SPMS. In the ESIMS (European Study on Intravenous Immunoglobulin in MS), 318 patients with SPMS were randomized to intravenous immunoglobulin (IVIG) at a 1-g/kg per month dose as part of a 27-month, placebo-controlled, double-blind study. IVIG treatment had no treatment effect on time to confirmed EDSS progression; the annual relapse rate was 0.46 in both treatment groups. Moreover, the T2 lesion load stayed the same in both groups, though there was a significantly lower rate of brain atrophy progression in IVIG-treated patients compared with placebo-treated patients. In contrast to the overall lack of treatment effect in patients with SPMS, IVIG lowers the relapse rate, improves disability, and reduced Gd-enhancing lesions on MRI in patients with RRMS.\(^1\)

**The Role of Community Neurologists Treating Patients with Progressive MS: Making Real-Life Treatment Decisions in an Imperfect World**

Despite the lack of good treatment options with robust efficacy and a sound safety and tolerability profile for patients with SPMS, neurologists must still work...
with patients to optimize outcomes and attempt to stave off disability for as long as possible. When a group of community neurologists \((n = 47)\) was surveyed about their clinical opinions and treatment practices as they relate to patients with progressive MS, 46% of respondents cited IFNβ-1b as their agent of choice for the long-term treatment of progressive MS. Another 17% chose GA, whereas 15% chose mitoxantrone. Only 4% indicated that they use methotrexate as their treatment agent of choice for patients with SPMS, and less than 5% of respondents chose any of the following: azathioprine, natalizumab, IVIG, pulse corticosteroids, or combination therapy. None of the respondents cited cyclophosphamide as their agent of choice. It was noteworthy that not one neurologist who responded to the survey would recommend to their patients that they not receive treatment, nor were they willing to treat symptoms only. Overall, physicians appeared determined to treat patients with available agents.

**Promising Experimental Pipeline: Update on Novel Therapies for Progressive MS**

Much of the focus in recent MS research has been on gaining more insight into the mechanisms underlying the progressive nature of the disease and developing directed therapies to slow the rate of disability and degeneration, while minimizing side effects. Various types of agents are being developed, including injectables, agents that are administered intravenously, and oral agents. Although drug development is driven by different therapeutic principles, on the broadest level, the goal is to interrupt the cascade of immune activation-related events that eventually lead to destruction of the myelin sheath and the underlying axon.

**Injectables**

An autologous attenuated T-cell vaccine, which is in development as an injectable therapy, is being developed and tested based on the immune response principle. Application of this principle involves screening patients for reactivity to myelin proteins and then extracting these myelin reactive T cells (MRTCs), expanding these ex-vivo, irradiating the cells, and reinjecting them in doses of 30 to 45 million cells per injection in order to use these irradiated MRTCs as a target antigen and induce a suppressor cell response. The theory is that there is a defect in the number of regulatory suppressor T cells in MS, and MRTCs are free to attack the CNS. However, induction of an immune response directed at the irradiated expanded pool of MRTCs should lead to an increase in suppressor T cells to help restore balance in the CNS between myelin-reactive lymphocytes and suppressor lymphocytes. Though this is a highly experimental therapy and there are no data yet, a 52-week, 150-subject, double-blind, placebo-controlled, randomized trial is under way in patients with clinically isolated syndrome and RRMS. Results are due in 2008.

Another injectable in development for the treatment of MS is commonly used to inhibit solid-organ graft rejection. Daclizumab is a mouse humanized monoclonal antibody against CD25 that targets and binds to interleukin (IL)-2 receptor, which blocks the binding of IL-2, a pro-inflammatory cytokine found on activated T cells. In a phase II study of 10 patients with RRMS or SPMS who had failed IFN therapy, there was a 78% treatment-associated reduction in contrast-enhancing lesions on MRI after 7 months of therapy \((P = .004)\). Patients also experienced significant treatment-related improvements in the Scripps Neurological Score \((4.35\%, P = .048)\) and the 9HPT \((4.79\%, P = .006)\). The main safety and tolerability issues were nausea and diarrhea, but they were not considered major. Daclizumab is administered subcutaneously every 2 weeks. Results from the CHOICE trial, a randomized, placebo-controlled trial, examined daclizumab or placebo added to IFNβ therapy in 230 patients with RRMS. There was a statistically significant reduction in new or enlarged Gd+ \((72\%)\) at 24 weeks in the 2-mg/kg group compared to placebo \((P = .004)\). A secondary end point indicates that daclizumab revealed a trend in reducing the annualized relapse rate compared to placebo (an approximately 35% reduction), but these observations did not reach statistical significance.

**Intravenous Agents**

MBP8298 is a synthetic peptide that was designed to replicate the most common target autoantigen on the myelin sheath (Figure 1). Its mode of action is based on the principle of antigen-specific tolerance induction. Patients with progressive MS have higher myelin basic protein reactive antibodies in their CSF. When injected intravenously into patients with MS, MBP8298 binds to the major histocompatibility molecules, which anergizes, or turns off, the myelin reactive lymphocytes, suppresses the MS-related autoimmune response, and restores immunologic tolerance. As a result, CSF autoantibodies are suppressed.
In a 24-month randomized, double-blind, placebo-controlled phase II trial involving 32 patients with PPMS or SPMS and baseline EDSS scores between 3 and 7.5, patients randomized to MBP8298 received 500-mg injections every 6 months. Although there were no significant differences between drug-treated and placebo-treated patients with respect to changes in EDSS scores in the overall group analysis, subgroup analysis of human leukocyte antigen (HLA) haplotypes DR2 and DR4 (n = 20) showed treatment-related benefits in patients treated with MBP8298. Both HLA-DR2 and -DR4 are MS-linked alleles, which are carried by 60% to 70% of individuals with MS, compared with only 30% of the general population. Time to progression of disability as reflected by EDSS scores was 78 months in the DR2/DR4 subgroup, compared with 18 months in placebo-treated patients (P = .004). There were no significant side effects noted during the study; however, patients required the 5-minute intravenous treatment every 6 months in order to sustain treatment-related benefits. Currently, there is a phase III, placebo-controlled trial under way, and additional data are expected within a year.

Another monoclonal antibody that is being tested in patients with MS is rituximab, which is already used for the treatment of lymphoma. Rituximab targets a protein expressed on B lymphocytes—CD20—which leads to the depletion of B cells (Figure 2). In a 48-week, placebo-controlled, phase II trial involving patients with RRMS, 85% of patients were relapse free at 24 weeks, compared with 65% of placebo-treated patients—a 58% reduction in relapses (P = .023). There was also a 91% relative reduction in Gd+ lesions in treated patients (P < .001). There is a substantial safety database on rituximab because it has been used to treat hundreds of thousands of patients. The most common safety-related problems associated with rituximab in general are infusion reactions, tumor lysis syndrome in lymphoma-treated patients, and progressive multifocal leukoencephalopathy (PML). Researchers suspect that the 2 reported cases of PML, both of which occurred in patients with lupus, may have been associated with treatment with other immunosuppressive agents, suggesting that treatment-naïve patients may be less likely to experience treatment-related PML. Currently, rituximab is being tested in patients with PPMS in phase III trials. Rituximab is a promising therapeutic, but may eventually be replaced by ocrelizumab—the fully humanized version of rituximab, a chimeric murine/human monoclonal antibody.

Alemtuzumab is a humanized monoclonal antibody that targets CD52 on T cells, B cells, monocytes, and eosinophils. Blocking CD52 results in selective long-term depletion of mature potentially autoreactive lymphocytes, leading to profound inhibition of...
inflammatory CNS activity. In a 3-year, phase II trial involving 334 patients, patients received 1 or 2 doses of alemtuzumab (12 mg/day or 24 mg/day intravenous daily for 5 days once per year) or IFNβ-1a subcutaneous. After 2 years there was a 75% reduction in risk of relapse ($P < .00328$) and 65% reduction in the risk of progression of clinical disability ($P < .01194$) in patients treated with alemtuzumab compared with those treated with IFNβ-1a. There are notable safety concerns associated with alemtuzumab, including Grave’s disease, Goodpasture’s syndrome, and immune-related thrombocytopenic purpura (ITP). There was a 3% incidence of ITP in the phase II study, which led to one death. Though the trial was stopped, investigators are currently collecting safety and efficacy data, but not dosing patients. The US FDA has approved further trials with a greater safety oversight, and phase III trials are planned.17

**Oral Agents**

There are promising drugs in the pipeline that may provide long-awaited oral treatment options for patients with MS. Fingolimod (FTY720) targets the sphingosine-1 phosphate receptor located on activated T cells. Blockade of this receptor prevents activated T cells from migrating out of the lymph nodes into the CNS. This sequestering action prevents new inflammatory T cells from leaving the peripheral lymph nodes and entering the circulation (Figure 3). In a randomized, placebo-controlled, phase II trial, 281 patients with RRMS received daily doses of 1.25-mg or 5-mg fingolimod. After the first 6 months of treatment, there was a 50% reduction in clinical activity and an 80% reduction in Gd+ lesions on MRI in patients treated with fingolimod, compared with patients treated with placebo. Two-year data reflected a continued treatment effect: 75% to 77% of treated patients were still relapse free. Both doses of fingolimod had similar efficacy in treating RRMS-related symptoms, yet there were no significant changes in EDSS during the short study period. There were safety concerns that arose during the trial, notably transient bradycardia with the first-dose administration. Other adverse events seen in transplant clinical trials have included macular edema, increased airway resistance, and dermatologic risks that could lead to skin cancer. Investigators relied on built-in safety features, including 6-hour on-site monitoring after first-dose treatment. However, investigators are testing lower doses in order to address the safety issue, while maintaining a treatment effect. Phase III trials are currently enrolling study subjects.20

Laquinimod is an orally active synthetic immunoregulator; however, its precise mode of action has not yet been clearly elucidated. In animal models, laquinimod suppressed CD4+ cells and macrophages, resulting in reduced leukocyte infiltration in the CNS. In a 24-week, phase II, randomized, placebo-controlled study of 209 patients with RRMS, treatment with 0.3-mg doses of laquinimod resulted in a 44% reduction in the mean cumulative number of active lesions compared with placebo ($P < .05$). There were no significant adverse events or safety issues. Phase III trials are currently being initiated.21

Cladribine is a synthetic oral agent engineered to exploit the specific enzymatic degradation of deoxynucleotides in lymphocytes. It is currently in development as an add-on therapy to IFNβ-1b. However, it is being studied both for its potential use as add-on therapy and as monotherapy for patients with RRMS. Data from these trials are forthcoming.22

BG-12, an oral fumarate, has been used for treating severe chronic psoriasis in Germany and was investigated in a phase II trial in which patients with MS received 1 of 3 doses of BG-12 (120 mg, 360 mg, or 720 mg) or placebo. Statistically significant results were seen in patients treated with the 720-mg dose. This treatment group had a 69% reduction in the...
mean number of Gd-enhancing lesions ($P < .001$) as measured from weeks 12 to 24 of the study. They also had a 48% reduction in new or newly enlarging T2-hyperintense lesions at 6 months, compared to baseline ($P < .001$). Phase III trials are currently under way, including a monotherapy placebo-controlled trial and a comparison study with GA.

**AN EVOLVING THERAPEUTIC PARADIGM**

The IFNs and GA were considered the first true DMTs for the treatment of MS and have radically changed the treatment paradigm for RRMS. Nonetheless, once patients transition to progressive MS, treatments become less effective and options are limited. Although currently available DMTs can strongly reduce inflammation, which plays a less significant role in progressive MS than in RRMS, they have not been able to prevent the progressive loss of neurons and axons, and the accumulation of disability that accompanies progressive disease. In the face of this challenge, researchers have been developing new agents and testing agents used in other areas of autoimmune disease and oncology for the treatment of MS. The advent of these agents—vaccines, injectables, intravenous agents, and oral agents—may one day change the landscape of treatment of this progressive disease. At the moment, neuronal repair and remyelination represent the ultimate long-term disease-modification goals. In the near term, however, having therapeutic options that allow clinicians to slow the pace of accumulated disability in patients with a progressive disease is a worthy, and realistic, aspiration.

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