Multiple Sclerosis: Update on Treatment

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The last decade of the 20th century witnessed the evolution of new treatments for many neurologic disorders, arguably none more than for multiple sclerosis (MS). The development of pharmacologic agents for MS paralleled advances in the understanding of disease pathophysiology, in neuroimmunology, and in neuroimaging. Whereas a truly comprehensive examination of the neuroscience of MS is beyond the scope of this article, a thorough investigation of recent strides in pharmacotherapy of the disease is possible. Consequently, this article will provide a general overview of MS, focusing on current concepts and practice involving therapeutic intervention.

AN OVERVIEW OF MULTIPLE SCLEROSIS
Epidemiology and Etiology

An immune-mediated, inflammatory, demyelinating disease of the central nervous system (CNS), MS is a major cause of neurologic disability in young adults. In the United States, there are approximately 250,000 to 400,000 persons who have MS, with a female-to-male ratio of 2:1.[1] Although MS was previously thought to be primarily a disease of CNS myelin, recent neuropathologic studies have confirmed historical evidence of axonal injury in both the early and late stages of the illness.[2]

Classifications

MS is classically described as a CNS white matter disorder disseminated in time and space that presents as a relapsing-remitting illness in 80% to 85% of patients.[1,3] Approximately one half of individuals with relapsing-remitting MS (RRMS) will develop secondary progressive MS (SPMS), with a slow accumulation of disability, within 10 years of the disorder's initial presentation.[4,5] In 15% to 20% of patients, the MS course is described as primary progressive, with insidiously advancing impairment and no clear-cut relapses.[1,3] More rarely, patients with primary progressive MS develop occasional acute or subacute episodes of neurologic dysfunction; this disease subtype is termed progressive-relapsing MS.[5]

Symptoms and Signs

MS attacks are accompanied by neurologic symptoms and signs lasting at least 24 hours; discrete relapses are separated by no fewer than 30 days.[6] The clinical manifestations of MS are protean, and only their temporal evolution suggests the presence of the disease. Common symptoms include diminished visual acuity (resulting from optic neuritis), diplopia, dysarthria, sensory disturbances, trigeminal neuralgia, weakness and clumsiness of limbs, Lhermitte's sign (ie, an electric-like sensation radiating along the spine and into the arms and legs on neck flexion), urinary incontinence, constipation, and neuropsychiatric disturbances (eg, memory impairment, euphoria, impaired information processing). Neurologic signs typically found on examination include an afferent pupillary defect, optic atrophy, nystagmus, internuclear ophthalmoplegia, spasticity, absent superficial abdominal reflexes, decreased vibratory sensation in the lower extremities, truncal ataxia, intention tremor, and Babinski's sign.

Diagnosis

Diagnostic tests used to establish a clinical diagnosis of MS include brain and spinal cord magnetic resonance imaging (MRI), analysis of somatosensory evoked potentials, and analysis of cerebrospinal fluid to detect increased amounts of immunoglobulin or oligoclonal bands. Brain MRI is the most sensitive diagnostic tool for MS; it can discriminate between active and inactive disease activity (on the basis of the appearance and number of MS plaques) in over 90% of patients. MRI abnormalities indicating the presence or progression of MS include hyperintense white matter signals on T2-weighted and fluid-attenuated inversion recovery images; gadolinium enhancement of active lesions; hypointense "black holes" (representing gliosis); and brain atrophy on T1-weighted studies.[1,7,8] Serial MRI studies documenting lesion activity are a much more sensitive indicator of disease progression and have become an important part of outcome measurement in therapeutic trials.

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Table 1. Current Disease-Modifying Therapies for Multiple Sclerosis

Agent	Disease Classification	Dosage	Adverse Effects
Interferon beta-1b (Betaseron)	RRMS, SPMS*	8 million IU subcutaneously, every other day	Flu-like syndrome, injection site reaction, depression,[†] menstrual irregularity
Interferon beta-1a			
Avonex	RRMS	30 μg intramuscularly weekly	Flu-like syndrome
Rebif[‡]	RRMS	22 or 44 μg subcutaneously every other day	Flu-like syndrome
Glatiramer acetate (Copaxone)	RRMS	20 mg subcutaneously daily	Postinjection syndrome (ie, chest pain, palpitations, flushing anxiety), injection site reaction
Mitoxantrone	RRMS, SPMS	12 mg/m^2 body surface area intravenously every 3 mo for 2 y (maximum: 100 mg/m^2)	Alopecia, nausea, menstrual disorders, leukopenia, cardiomyopathy

RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

*Consensus is lacking regarding the effectiveness of Betaseron for SPMS.

[†]Effect postulated but as yet unproved.

[‡]Available in Europe and Canada only.

THERAPEUTIC PRINCIPLES IN MULTIPLE SCLEROSIS

The management of MS comprises 3 separate but parallel pathways: disease modification, symptomatic treatment, and rehabilitation. Disease-modifying agents affect the natural history of MS. Symptomatic therapies target the clinical manifestations of MS. Rehabilitation involves designing adaptive strategies to ameliorate the dysfunction and disability associated with MS. The appropriate interventions must be made on an individual basis.

Disease-Modifying Therapy

MS is a chronic disease. Natural history studies have shown that more than 50% of patients with RRMS will develop SPMS after 10 years.[1] Half of the patients with RRMS will require an aid for ambulation within 15 to 23 years of disease onset.[3] As recently as the early 1990s, MS was considered untreatable by most physicians, and disease modification therapy was limited to episodic courses of corticosteroids for MS relapses. Since 1994, the US Food and Drug Administration (FDA) has approved 4 agents for patients with RRMS or SPMS: interferon beta-1a, interferon beta-1b, glatiramer acetate, and mitoxantrone (**Table 1**). These medications have revolutionized the approach to patients with MS and have transformed MS into a very treatable illness.

Corticosteroids. The use of corticosteroids in MS is generally limited to the short-term treatment of acute exacerbations, although the possible role of these agents in maintenance therapy is under study. Corticosteroids generally hasten the time to recovery from a clinically significant relapse. There is, however, no consensus on the optimal formulation, dosage, route of administration, or duration of treatment. One randomized study[9] comparing the effects of orally administered methylprednisolone (48 mg daily for 1 week, followed by a 2-week taper) and intravenously administered methylprednisolone (1000 mg daily for 3 days) found no difference in neurologic recovery at 4 weeks. Brusaferri and Candelise[10] conducted a meta-analysis of clinical trials of corticosteroids of various preparations in the treatment of acute relapses of MS and optic neuritis. They concluded that although corticosteroids produced significant improvement in disability at 30 days compared to placebo, there was no statistical difference compared with placebo at longer follow-up. The short-term benefits of corticosteroids were seen with either low or high doses.

Many neurologists favor a 3- to 7-day course of intravenously administered methylprednisolone (500 to 1000 mg daily) followed by an oral taper of prednisone for approximately 10 to 14 days.[1] Moreover, given the results of the Optic Neuritis Treatment Trial,[11] clinically disabled MS patients with acute optic neuritis should receive corticosteroids intravenously rather than by the oral route alone.

Interferon beta. Three interferon beta products have been approved for the treatment of MS in the United States and/or Europe. These recombinant agents differ in mode of production, chemical structure, route of administration, and dosage. Each has been shown to reduce the relapse rate, disability progression, and MRI evidence of activity in RRMS. Their benefit in SPMS, however, has not yet been clearly established.

The precise mechanism of action of interferon beta in RRMS is not completely known. Interferon beta binds to surface receptors on lymphocytes, monocytes, and endothelial cells, resulting in a cascade of nuclear events that modulate proinflammatory and anti-inflammatory cytokine production, antigen presentation, and T-cell trafficking across the blood-brain barrier.[1,12] These cellular activities take place in the peripheral circulation.

Interferon beta-1b (Betaseron), a nonglycosylated recombinant product derived from *Escherichia coli*, was the first FDA-approved medication for RRMS. It differs from natural interferon-β by a single amino acid substitution. In a 2-year multicenter, double-blind, placebo-controlled study of 372 ambulatory patients with RRMS, 8 million IU (MIU) of interferon beta-1b administered subcutaneously every other day was found to decrease the annual exacerbation rate from 1.27 to 0.84 ($P = 0.0001$), a reduction of 32%.[13] An intermediate dose of interferon beta-1b (ie, 1.6 MIU) was also significantly effective compared with placebo but less so than the higher dose. Patients in the high-dose arm of the study had less severe exacerbations and were more likely to be exacerbation free during the investigation. An accompanying study that analyzed brain MRI scans for lesion activity showed a significant reduction in both disease burden and disease activity in patients treated with 8 MIU interferon beta-1b compared with placebo at the end of 3 years. The placebo group had a mean increase in lesion load of 17.1%, whereas the interferon beta-1b group had a mean reduction of 6.2% ($P = 0.002$).[14] In a 5-year analysis of the original patient cohort, the benefits of interferon beta-1b on relapse rate were maintained. Although fewer patients taking interferon beta-1b had confirmed disability progression after 5 years, this result did not reach statistical significance.

Interferon beta-1b has also been studied in patients with SPMS, but results have been conflicting. In a multicenter, randomized, double-blind, placebo-controlled trial of 718 patients with SPMS, the European study group found that patients treated with 8 MIU of interferon beta-1b every other day had a significant delay in time to confirmed disability progression ($P = 0.0008$).[15]

Unfortunately, a second North American study of interferon beta-1b in SPMS failed to show a similar clinical benefit.[16] Thus, the role of interferon beta-1b in the treatment of SPMS remains controversial.

Interferon beta-1a (Avonex, Rebif), a naturally sequenced glycosylated recombinant mammalian product, has also been approved by various agencies for the treatment of RRMS. Intramuscularly administered interferon beta-1a (Avonex) is available in the United States, Canada, and Europe; subcutaneously administered interferon beta-1a (Rebif) is not yet approved for use in the United States.

In a randomized, placebo-controlled, double-blind study of 301 patients with RRMS, weekly intramuscular administration of interferon beta-1a (Avonex) at a dosage of 30 μg was shown to significantly slow accumulation of clinical disability over 104 weeks.[17] In this study, the primary outcome variable—time to sustained worsening of disability—was defined as time to an increase of 1.0 on the Kurtzke Expanded Disability Status Scale that persisted for at least 6 months. Disability progression occurred in 34.9% of the placebo group and 21.9% of interferon beta-1a recipients ($P = 0.02$), representing a 37% reduction in sustained disability accumulation. Weekly intramuscular administration of interferon-1a also significantly reduced the rate of exacerbations (18%) as well as gadolinium enhancement of lesions on brain MRI studies.[17]

In a 2-year multinational randomized trial of 560 patients with RRMS, subcutaneously administered interferon beta-1a (Rebif) at dosages of 22 μg and 44 μg 3 times weekly reduced relapse rates over 1 and 2 years by 27% and 33%, respectively.[18] Both doses prolonged time to first relapse, and patients in either treatment group were significantly more likely to be relapse free. Moreover, accumulation of sustained disability and MRI evidence of disease was decreased in both treatment arms. A dose effect was detected on all outcome measures.

Interferon beta-1a also was shown to be beneficial in patients with a first isolated demyelinating event (eg, optic neuritis, partial transverse myelitis, brainstem-cerebellar syndrome) and MRI evidence of prior subclinical demyelination.[19] Such patients are at high risk to develop clinically definite MS within 3 years.[11,20,21] In the Controlled High Risk Avonex Multiple Sclerosis study,[19] patients with monophasic demyelinating syndromes who were treated with weekly intramuscular administration of interferon beta-1a at a dosage of 30 μg had a 44% reduction in risk for developing clinically definite MS compared with placebo ($P = 0.002$) during the 3-year trial.

Another randomized, double-blind trial of interferon beta-1a (Rebif) was conducted in Europe by Comi and colleagues.[22] In this study, 308 patients with a first demyelinating event (either unifocal or multifocal) and a brain MRI showing 3 or more white matter lesions typical of MS were given either interferon beta-1a 22 μg subcutaneously weekly or placebo for 2 years. Fewer patients in the interferon beta-1a group converted to clinically definite MS, compared with the placebo group (34% versus 45%, respectively; $P = 0.047$), by the end of the study. The time at which 30% of patients developed clinically definite MS was 569 days in the beta inferon-1a group and 252 days in the placebo group. There was also a modest but significant reduction in relapse rate in patients receiving interferon beta-1a, compared with patients receiving placebo (33% versus 43%, $P = 0.045$). The number of new lesions and the lesion load detected on MRI was also significantly lower in the interferon beta-1a group.

Because both of these studies were of relatively short duration, it is not possible to determine whether initiating treatment in the early phase of MS affects long-term accumulation of neurologic disability. It does appear, however, that administration of low-dose interferon beta-1a in patients in the earliest stages of MS has at least short-term benefits. Follow-up analysis of patients in these trials may help clarify issues concerning more long-term benefits of early initiation of therapy in this population.

Interferon beta in all its formulations is associated with a number of adverse events, including flu-like symptoms, depression, menstrual irregularities, injection-site reactions, and increased spasticity.[23] The flu-like symptoms tend to abate after several months[1,13] and usually respond to acetaminophen, ibuprofen, or prednisone administration. Alternatively, to reduce adverse effects, interferon beta can be initiated at one quarter to one half the recommended dose and then gradually titrated to full dosage. The most commonly reported laboratory abnormalities in patients taking interferon beta are leukopenia and elevated liver enzyme levels; these irregularities usually reverse with temporary cessation of therapy.[23] Neutralizing antibodies to interferon beta develop in 12.5% to 38% of patients and may lessen therapeutic efficacy.[13,17,18]

Glatiramer acetate. Glatiramer acetate (Copaxone), formerly known as *copolymer 1*, is a mixture of synthetic polypeptide chains consisting of 4 amino acids: L-glutamate, L-lysine, L-alanine, and L-tyrosine. Glatiramer acetate (GA) was originally developed as an analogue to myelin basic protein and was found to modify or suppress experimental autoimmune encephalo-

myelitis, the animal model of MS. Subsequent studies confirmed its usefulness in the treatment of MS.[24]

Johnson and colleagues[24] reported clinical benefits of GA in a randomized, multicenter, placebo-controlled trial of 251 patients with RRMS. Patients given GA 20 mg subcutaneously daily had a 2-year relapse reduction of 29%, compared with those given placebo. GA patients were more likely to be relapse free, although this parameter did not reach statistical significance. Patients in the treatment arm had significantly improved scores on the Kurtzke Expanded Disability Status Scale, whereas patients in the placebo arm had worsened scores at the end of the study. In a 12-month extension study, GA continued to favorably affect relapse rate and disability progression.[25] Finally, in a 6-year open-label study involving 208 patients from the original cohort, Johnson and colleagues[26] reported a sustained relapse rate reduction of 0.23; 69.3% of patients who received GA for 5 or more years were neurologically stable, according to scores on the Kurtzke Expanded Disability Status Scale.

The effects of GA on disease activity detected by MRI have subsequently been confirmed as well. Comi and colleagues[27] randomized 239 patients with RRMS to receive either daily subcutaneous administration of GA 20 mg or placebo; each patient underwent monthly brain MRI and clinical evaluation for 9 months. Patients in the treatment arm had a mean reduction of 29% in gadolinium-enhancing lesions ($P = 0.003$), which was the primary outcome measure. GA was also associated with significant decreases in new lesions and lesion volume during the study period.

GA is well tolerated. The most common adverse effect is an injection-site reaction, consisting of mild erythema and induration.[24] More rarely, GA may be associated with a postinjection syndrome characterized by a variable combination of chest tightness, flushing, dyspnea, palpitations, and anxiety.[24] This systemic reaction is sporadic and unpredictable and was reported at least once in 15% of patients; no more than 7 recurrences in any single patient was described.[24] The reaction typically occurs within minutes of an injection and resolves spontaneously within 30 seconds to 30 minutes. This systemic reaction is not associated with cardiac or other organ abnormalities.

The mechanism of action of GA in MS is unknown. Proposed immunomodulatory activities include (1) inhibition of myelin-reactive T cells by blocking human leukocyte antigen, (2) T-cell receptor antagonism, and (3) induction of anti-inflammatory T–helper 2 cells.[28,29]

Mitoxantrone. Mitoxantrone (MTX) is an anthracenedione used for the treatment of numerous malignancies. It has demonstrated efficacy in patients with

both RRMS and SPMS, although the results of a major study have only been published in abstract form.[30,31] In a multicenter, double-blind, placebo-controlled trial, 194 patients were randomized to receive quarterly intravenous infusions of MTX 12 mg/m² body surface area, MTX 5 mg/m², or placebo for 2 years. Both doses of MTX had a favorable effect on relapse rate, time to first exacerbation, disability progression, and MRI-detected lesion activity.[30,31] Treatment was generally well tolerated; alopecia, urinary tract infections, nausea, and vomiting were the most common adverse events reported. Yet, because cumulative dosages of MTX above 140 mg/m² are associated with cardiomyopathy, its long-term use in patients with MS will likely be limited. Although MTX has received FDA-approval for treating worsening RRMS and SPMS, further recommendations regarding its use await publication of peer-reviewed data.

Other agents. Other immunosuppressive agents also have a reported benefit in cases of MS. In addition to the first-line therapies already discussed (Table 1), azathioprine, methotrexate, intravenously administered immunoglobulin, plasmapheresis, and cyclophosphamide have shown some efficacy in both relapsing and progressive forms of the disorder.[1,12,32–34] Although these agents have been supplanted by the newer medications, they continue to be used; their potential effectiveness as adjunctive therapies, in combination with interferon beta or GA, awaits further study.

Practical considerations in disease modification therapy. There is growing consensus that disease modification therapy should commence early in patients with RRMS.[1,35] This belief has developed from the outcomes of a multitude of natural history studies, therapeutic trials, MRI data, and neuropathologic analyses. In essence, it is hypothesized that starting immunomodulatory treatment during the early inflammatory phase of disease will delay the onset of irreversible axonal loss that predominates in the later stages of MS; however, confirmation of this theory has not been established.

The clinician managing patients with RRMS has few studies available comparing interferon beta and GA when deciding initial therapy. Furthermore, the long-term efficacy and safety of interferon beta and GA remain unknown. The choice of treatment is frequently determined by a combination of physician preference and patient tolerance to adverse drug events.

Although interferon beta-1a, interferon beta-1b, and GA have each been shown to favorably affect relapse rate, disability progression, and MRI activity, there is emerging evidence that all agents and all dosages are not equally efficacious. Several studies comparing interferon beta-1a at weekly dosages ranging from 22 μg to 144 μg[17,36] have shown a dose effect on both clinical and MRI measures, as was previously shown for interferon beta-1b.[13,14] In a 12-month prospective, open-label study comparing interferon beta-1a (Avonex), interferon beta-1b (Betaseron), and GA (Copaxone), relapse rate reduction was statistically significant in only the interferon beta-1b and GA patient groups.[37] Given these data, it seems possible that patients with more active RRMS—that is, those with more frequent exacerbationhs or more incomplete remissions—may respond more favorably to GA, interferon beta-1b, or high-dose interferon beta-1a than to low-dose interferon beta-1a. Low-dose interferon beta-1a or GA may be reasonable options in patients with isolated demyelinating syndromes or less active RRMS.

Another factor influencing choice of immunomodulatory treatment is patient tolerance of adverse drug effects. Both low-dose interferon beta-1a and GA are better tolerated than high-dose interferon beta-1b. Interferon beta-1a and interferon beta-1b are both associated with the formation of neutralizing antibodies, but the clinical relevance of these antibodies remains uncertain.

Patients whose disease progresses while they are taking a primary immunomodulatory agent pose a difficult dilemma. None of the new drugs halt disease activity, and relapses are expected to continue, albeit at lesser frequency. Some patients taking interferon beta may benefit from switching to GA. Alternatively, increasing the weekly interferon beta dosage may be helpful, although this step might also produce intolerable adverse effects. Institution of therapy with an immunosuppressive drug such as mitoxantrone, either alone or in combination with other agents, may also be considered.

Symptomatic Therapy

Patients with MS experience a variety of secondary symptoms that result from neurologic dysfunction, including neuropathic pain, spasticity, fatigue, cerebellar tremor, and neurogenic bladder. Neuropathic pain (eg, dysesthetic limb pain, trigeminal neuralgia) may be ameliorated with gabapentin, phenytoin, or carbamazepine.[1,38] Spasticity may be lessened with orally administered agents such as baclofen, tizanidine, or diazepam. Patients with refractory spasticity may benefit from intrathecal injection of baclofen delivered by a surgically implantable programmable pump.[39] Disabling fatigue may be managed with pemoline, amantadine, or modafinil.[1,40] Although cerebellar outflow

tremor rarely responds to medication, carefully select-ed MS patients may benefit from stereotactically target-ed chronic thalamic stimulation.[41] Finally, neurogenic bladder disturbances such as urinary frequency and in-continence can be treated with anticholinergic agents and intermittent catheterization; vigilant monitoring for urinary tract infection is essential because of the high incidence of bladder dysfunction in MS.

Future Directions in MS Therapy

Despite the development of evidence-based disease-modifying therapy for MS, more effective agents still must be found. None of the current medications halts disease progression or reverses the pathophysiologic effects of demyelination. Possibly, any "cure" for MS must await better elucidation of the disease mechanism.

Effective treatments for MS will ultimately need to focus not only on reducing inflammation and demyeli-nation but also on preventing axonal injury (neurode-generation) and promoting remyelination (neural re-pair). Potential immunomodulatory agents include anticytokines, a T-cell vaccine, and inhibitors of costim-ulation molecules, matrix metalloproteinases, or adhe-sion molecules.[1] Neuroprotective strategies may in-clude using blockers of oxidative reduction and nitric oxide synthesis. Neural repair approaches most likely will encompass inhibition of antibody-mediated demy-elination and apoptosis, transplantation of oligoden-droglial stem cells, and administration of nerve growth factors.[42] Finally, bone marrow transplantation is under investigation for patients with highly aggressive disease.

It is unlikely that any single agent or class of agents will be effective in all phases of the MS disease process. Thus, the management of MS in the future will most likely involve combinations of therapies with different mechanisms of action. The ultimate goal will be to develop treatments that will not only halt disease pro-gression but also restore neurologic function.   **HP**

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