Pharmacology and Therapeutics

Principles to Practice

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MULTIPLE SCLEROSIS

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OVERVIEW

Multiple sclerosis (MS) is a complex disease of the central nervous system (CNS) with the potential to cause significant physical and emotional disability. Approximately 350,000 Americans are currently diagnosed with MS, and the direct and indirect costs associated with the disease are about $14 billion per year.[1] MS is the most common nontraumatic cause of neurologic disability in early to middle adulthood. There is an inherent variability from patient to patient with regard to disease course and severity. Some patients experience frequent exacerbations with escalating disability while others have a relatively benign course. Most commonly the disease begins with episodic relapses that are separated by periods of remission. In the later stages of the disease, many patients will develop slowly progressive neurologic disability. Most evidence points to an immune-mediated pathophysiology involving B and T lymphocytes, macrophages, and microglia. According to this hypothesis, an autoimmune response against CNS myelin is initiated, leading to demyelination and axonal injury. To date, the most effective therapies have been immunosuppressant and immunomodulatory drugs. While none of the approaches can be described as curative, the presently approved drugs have led to significant reductions in relapse rates and disability.

INTRODUCTION

Epidemiology

The typical age of onset for MS is between 20 and 40. The disease is unusual before adolescence, but onset has been described as young as age 2 and as old as age 74. The ratio of affected women to men is between 1.7:1 and 2.5:1, although the ratio is more even at older ages of onset. Several important epidemiologic observations have been made about the geographic distribution of MS. In both the northern and southern hemispheres, the prevalence of the disease increases with increasing distance from the equator. There is also a difference in risk for different ethnic groups, independent of latitude. For example, England and Japan are at the same latitude, but the prevalence of MS differs significantly in the two countries (85 per 100,000 for England versus 1.4 per 100,000 in Japan). Caucasians tend to have the highest risk, while lower risk is seen in people of African or Asian descent. The highest prevalence is seen in the northern United States, southern Canada, northern Europe, and southern Australia. The southern United States and southern Europe have a moderate prevalence. The lowest prevalence is seen in Japan, China, Latin America, and equatorial Africa. Migration studies have also added to our understanding of the relationship between geography and risk of MS. Children born to parents who migrated from a low- to a high-risk area had an increase in their risk of developing MS, and vice versa.[2] By analyzing the ages of migrants, it was suggested that one's environmental risk was determined by about age 15.[2] This has led to hypotheses that the risk of MS is partly determined by viral exposures during childhood. Recent data suggest that the incidence of MS may be increasing, especially in women, although issues regarding ascertainment and diagnosis make these studies challenging.

Genetics

In addition to environmental factors, genetics influences the risk of developing MS. Family clusters are known to occur. Twin studies have found that the monozygotic twin of an MS patient has about a 30% chance of developing MS. Dizygotic twins have a risk that is similar to that of any sibling of an MS patient, about 2% to 5%. The risk in children of MS patients is slightly lower than for siblings. Second- and third-degree relatives of an MS patient also carry some elevated risk. Genetic studies have found the strongest association with the major histocompatibility complex (MHC), particularly the HLA-DRB1 locus. More recently, two additional genes were identified in genome-wide scans,[3] the interleukin-2 receptor alpha gene and the interleukin-7 receptor alpha gene. The fact that all three genes are part of the immune system serves as an important confirmation of the autoimmune nature of this disease.

Clinical Features

MS has classically been separated into four different subtypes: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing MS (Fig. 46-1). Relapsing-remitting MS (RRMS) is the most common clinical subtype, representing about 85% of patients at diagnosis. It is marked by intermittent exacerbations that may partly or completely resolve over weeks to months. These relapses are separated by periods of clinical stability. However, patients may continue to experience symptoms from prior relapses that healed incompletely. After a variable period of time, a majority of RRMS patients will enter a secondary progressive phase of the disease (SPMS). SPMS patients experience a slowly progressive worsening of disability that may or may not have superimposed relapses. About 10% to 15% of patients will

have a primary progressive course (PPMS), marked by slowly progressive worsening from the outset without relapses. A small number of patients are labeled as having progressive relapsing MS. These patients begin with a progressive course but develop one or more relapses. Patients who have had a single demyelinating event, but do not yet meet criteria for MS, are referred to as having a clinically isolated syndrome.

MS can present with a large number of symptoms possibly referable to the CNS. The symptoms may be transient and often difficult to describe. Classic MS symptoms include unilateral blurred vision with brow pain on lateral eye movement, weakness, numbness, paresthesias, pain, imbalance, double vision, bladder and bowel dysfunction, impaired coordination, fatigue, depression, cognitive impairment, heat intolerance, and sexual dysfunction. On exam, common signs include visual impairment, brainstem dysfunction, nystagmus, dysarthria, spasticity, hyperreflexia, weakness, sensory loss, and ataxia. Several paroxysmal phenomena can be associated with MS, including tonic spasms, trigeminal neuralgia, and myokymia. New clinical symptoms are thought to result from new areas of inflammation and demyelination, while the acquisition of long-term disability is more related to axonal damage.[4,5]

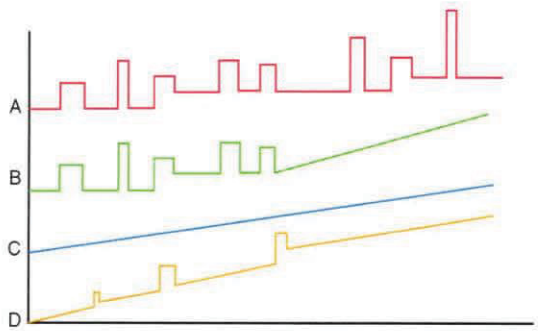

FIGURE 46-1 • A diagrammatic representation of disability by time for different subtypes of MS. A, Relapsing-remitting MS. **B,** Secondary progressive MS. **C,** Primary progressive MS. **D,** Progressive relapsing MS.

Diagnosis

The diagnosis of MS can be challenging as there is no single test with adequate sensitivity or specificity and there are several potential mimics. MS was classically diagnosed by the identification of lesions attributable to the CNS white matter that were separated in time and space with objective findings on neurologic exam and no better explanation.[6] However, the advent of magnetic resonance imaging (MRI) has significantly changed how the diagnosis is made. Currently, the most widely used diagnostic criteria are the McDonald criteria, which were last revised in 2005 (Table 46-1).[7] These criteria endorsed the use of MRI as a surrogate marker for defining separation in time and space.

Brain MRI in MS classically shows lesions that are hyperintense on T2-weighted sequences (Fig. 46-2). Lesions are frequently in the periventricular white matter, often extending perpendicular to the ventricle. Lesions of the corpus callosum are common in MS, as are lesions in the subcortical white matter, cerebellum, brainstem, and spinal cord. Newer imaging techniques are also identifying an increased number of lesions in the cortex. Acute lesions will often enhance with gadolinium, indicating active inflammation with blood-brain barrier (BBB) breakdown. Areas of hypointensity on T1 sequences are also seen. T1 hypointensity is observed transiently in acute lesions. However, when it is present chronically, it likely represents an area of significant axonal damage. Disability correlates more strongly with the T1 hypointensity volume than the volume of T2 hyperintensities. With time, the accumulating axonal damage will often manifest as global cerebral atrophy. Only about 5% to 10% of lesions seen on MRI are associated with clinical symptoms. Gray matter lesions are also common in MS, but are not well seen on conventional MRI.

TABLE 46-1 REVISED MCDONALD CRITERIA

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks; objective clinical evidence of 2 or more lesions	• None
2 or more attacks; objective clinical evidence of 1 lesion	• Dissemination in space, demonstrated by: →MRI *or* →2 or more MRI-detected lesions consistent with MS plus positive CSF *or* →Await further clinical attack implicating a different site
1 attack; objective clinical evidence of 2 or more lesions	• Dissemination in time, demonstrated by: →MRI *or* →Second clinical attack
1 attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	• Dissemination in space, demonstrated by: →MRI *or* →2 or more MRI-detected lesions consistent with MS plus positive CSF *and* • Dissemination in time, demonstrated by: →MRI *or* →Second clinical attack
Insidious neurologic progression suggestive of MS	• One year of disease progression (retrospectively or prospectively determined) *and* • Two out of three of the following: a. Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive visual evoked potentials) b. Positive spinal cord MRI (2 or more focal T2 lesions) c. Positive CSF

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; MS, multiple sclerosis.
From Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 2005;58:840-846.

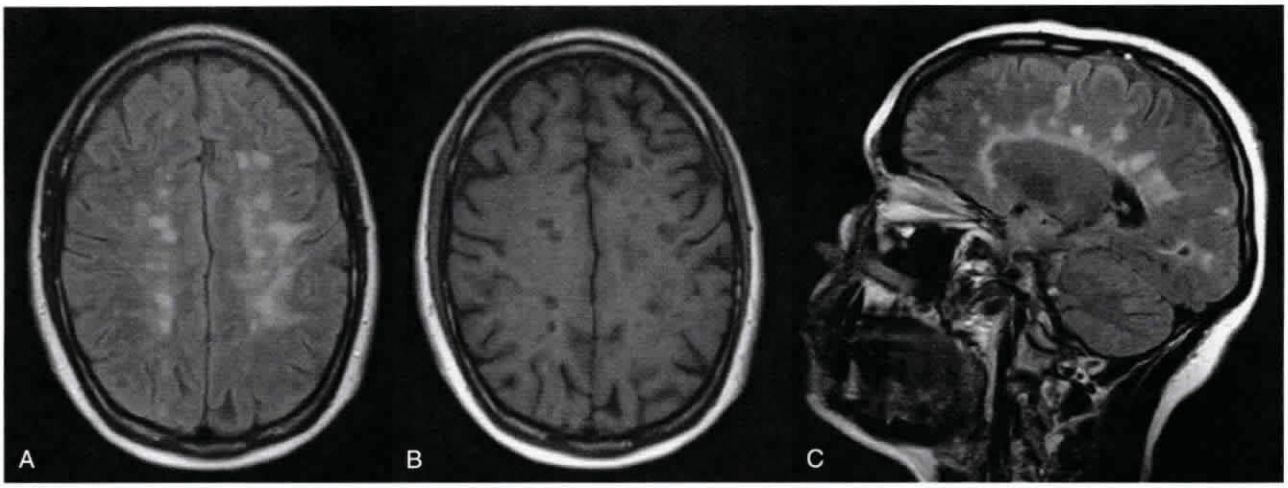

FIGURE 46-2 • Brain MRI of a patient with MS. A, Axial fluid-attenuated inversion recovery (FLAIR) image showing multiple hyperintensities. **B,** Axial T1-weighted image at the same level. Some of the areas of FLAIR hyperintensity are also hypointense on T1-weighted images. **C,** Sagittal FLAIR image showing periventricular hyperintensities.

In the past, a cerebrospinal fluid (CSF) exam was a common part of the MS diagnosis. The presence of an elevated protein, oligoclonal bands, or an elevated immunoglobulin G index is supportive of the diagnosis. Although CSF analysis is still important in some cases to rule out other diagnoses such as infections, it is often unnecessary in routine cases. Evoked potentials of the visual, auditory, or somatosensory pathways can be helpful in some cases to detect subclinical lesions that cannot be seen on MRI.

PATHOPHYSIOLOGY

Classically, MS has been described as an immune-mediated demyelinating disease affecting the brain, spinal cord, and optic nerves.[8] Recent research has reemphasized the concomitant presence of both gray matter pathology and extensive axonal damage in the brains of patients diagnosed with MS.[9,10] The exact cause(s) of MS have not been determined, but a combination of genetic and environmental factors coalesces in some people to lead to demyelination and axonal damage. One theory is that certain viruses may share sequence homology with myelin proteins and, through molecular mimicry, mediate aberrant activation of cross-reactive T cells. Viruses may also cause bystander activation through release of cytokines or stimulation of antigen-presenting cells. It is possible that MS is actually a syndrome of various related diseases that cause episodic demyelination and neuronal damage. Four pathologic subtypes of MS have been described, as discussed later, confirming a variety of immunopathogenetic mechanisms involved in different types of MS. While most of these types have an immune-mediated component, there are some aspects of MS that may be independent of the immune system. For example, the degeneration of chronically demyelinated axons that occurs in the secondary progressive phase of the disease appears to be noninflammatory. To date, the only successful treatment strategies for MS have involved immunomodulatory or immunosuppressive approaches, supporting the role that the immune system plays. Moreover, these therapies generally are effective only during the relapsing-remitting phase, the most inflammatory phase of the disease.

Pathologic examination of the CNS in patients with MS typically identifies an inflammatory response involving cellular and humoral immune systems. Whether or not the immune system begins by recognizing a foreign antigen and then strays against self or begins by recognizing self-antigens is unknown. Fundamental to the classic description of MS pathogenesis is the inappropriate disruption of the BBB. Normally, the BBB is composed of specialized endothelial cells with an intricate network of tight junctions. Functionally, the BBB significantly restricts the diffusion of molecules from the periphery into the CNS. Disruption of the BBB by immune cells in MS is responsible for gadolinium-enhancing lesions on MRI and "attacks" in MS patients. Lymphocytes are able to migrate across the BBB via a series of adhesion molecule interactions. Critical to this process is a connection between very late antigen-4 (VLA-4) on lymphocytes and monocytes and its ligands vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells and fibronectin in the basement membrane.[11] Presumably, once effector cells from the immune system have gained access to the CNS, they secrete a cascade of cytokines that lead to demyelination and ultimately axonal damage (Fig. 46-3).

Numerous studies have analyzed the relative role that $CD4^+$ and $CD8^+$ T cells play in disease pathogenesis. Epidemiologic studies and mouse models have linked MS to MHC class II genes, which present antigens to $CD4^+$ T cells.[12-14] Thus, $CD4^+$ T cells have been of interest for years. The production of tumor necrosis factor (TNF) from $CD4^+$ T cells correlates with the number of T2-hyperintense lesions on MRI.[15] While autoreactive T cells have been identified in patients with MS and in healthy volunteers, the $CD4^+$ T cells are functionally different in patients with MS. Specifically, they tend to be more differentiated and have a higher level of T helper cell type 1 (Th1) phenotypes in patients with MS compared to controls.[16] Yet, therapy directed against $CD4^+$ T cells made only a small difference in patients treated in clinical trials.[17,18] Therapy that depleted both $CD4^+$ and $CD8^+$ T cells, however, led to a reduction in disease activity.[19-21] The role of T helper type 17 (Th17) cells in MS is less clear. This newly described subset of T cells has been implicated in an animal model of MS, experimental autoimmune encephalomyelitis, and interleukin (IL)-17 expression can be seen in MS brain-infiltrating cells.

Several studies have identified the potential role of $CD8^+$ T cells in MS. Genetic studies have implicated various MHC class I genes as being associated with increased risk of MS while some MHC class I genes are protective.[22,23] Persistence of autoreactive $CD8^+$ T cells in the CSF of patients with MS has been described.[24] In mouse studies, $CD8^+$ T cells have been shown to potentiate immune-mediated demyelinating disease.[25] Yet, there are also data that suggest a possible neuroprotective role for self-reactive $CD8^+$ T cells.[26] While $CD4^+$ T cell production of TNF-α has correlated with the number of T2-hyperintense lesions on MRI, certain $CD8^+$ T cell populations have been negatively correlated with T1-hypointense lesions.[15,27]

In one study, a systematic review of biopsies and autopsy specimens from MS patients identified four distinct pathologic patterns.[28] Two patterns were noteworthy for T-cell infiltrates and preservation of oligodendrocytes, with one pattern additionally having deposition of

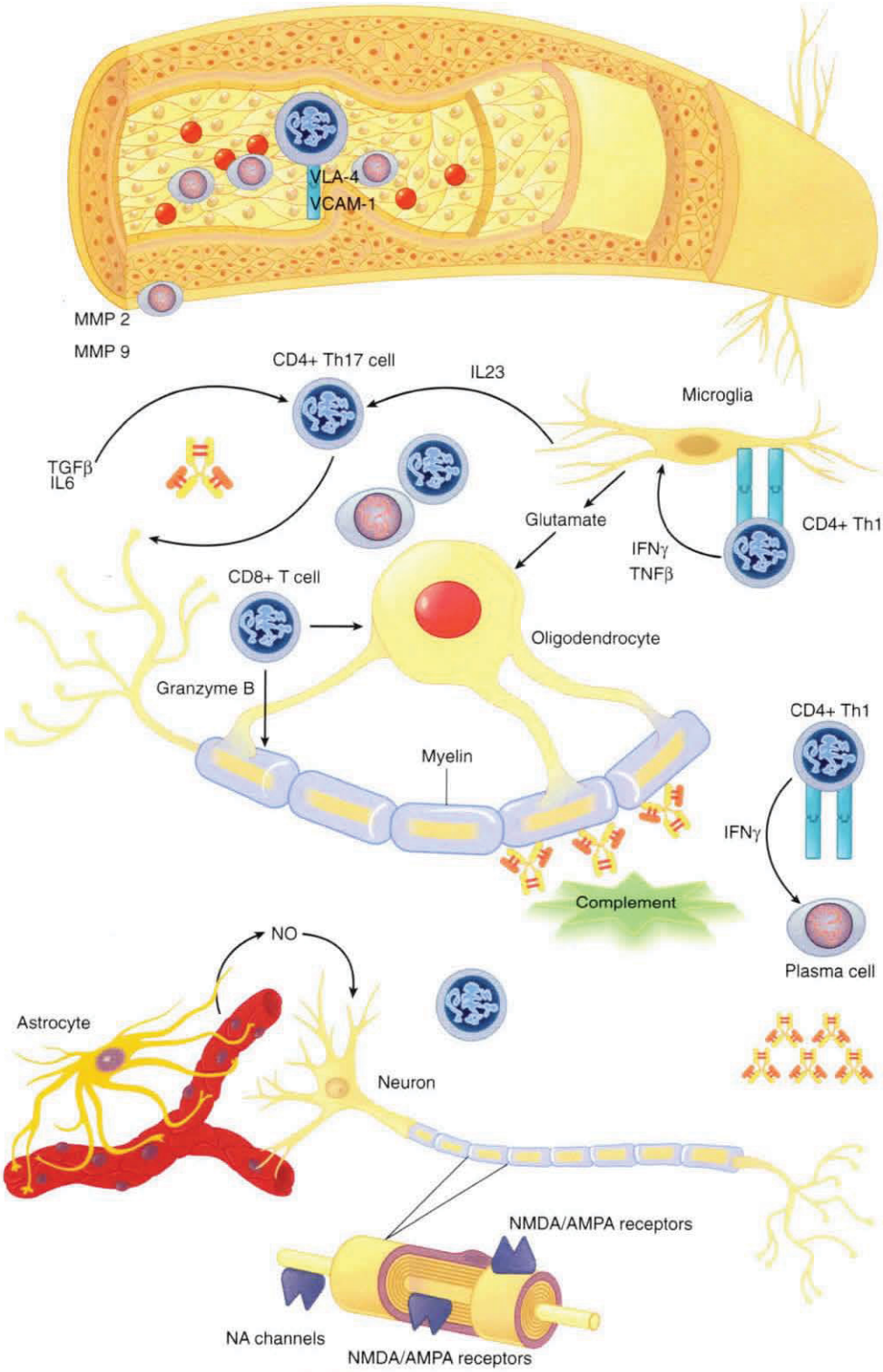

FIGURE 46-3 • Pathogenesis of MS.

antibodies and complement. A third pattern was notable for a T-cell infiltrate without antibody deposition, but there was a loss of myelin-associated glycoprotein in tissues and oligodendrocyte apoptosis with preserved myelin around veins and venules. Finally, the fourth pattern was notable for T-cell inflammation, but also oligodendrocyte cell death. This research identified heterogeneous pathology between patients with MS, but the findings within each individual patient were homogeneous. Presumably, these patterns represent various forms of MS, but only one form is occurring in any given patient at one time. However, the selection bias that is inherent in this study (patients presenting for biopsy or autopsy) could account for some of the homogeneity, and other groups have not confirmed these patterns in their MS brain tissue examinations.

Clinically, patients may experience new symptoms in the setting of new inflammation and demyelination affecting clinically eloquent parts of the CNS. Often the inflammation resolves partly, and there can be partial remyelination with varying degrees of gliotic scarring and axonal damage. Much of the disease accumulates in a silent manner and is not evident until compensatory mechanisms begin to break down, years into the disease process. Thus, progression of disability occurs slowly with time but becomes most noticeable after years of accumulated axonal damage.[4] Therapeutic possibilities include immunomodulatory, immunosuppressive, neuroprotective, and neuroreparative strategies.

THERAPEUTICS AND CLINICAL PHARMACOLOGY

Goals of Therapy

There are two types of therapies for MS: disease-modifying therapies (DMTs) and symptomatic treatments. All of the DMTs currently approved by the U.S. Food and Drug Administration (FDA) for MS act by immunomodulation or immunosuppression. These treatments are effective at reducing the frequency of disease relapses and decreasing the number of new lesions seen on MRI in RRMS. Some have also been shown to delay the accumulation of disability. While these immunomodulatory treatments are beneficial in relapsing-remitting patients, they have not been proven effective in SPMS or PPMS. Immunomodulation is probably ineffective in progressive MS because the nerve damage in these groups is less dependent on inflammation. Consequently, there is a major need for treatments for progressive MS patients.

While the DMTs decrease the incidence of new relapses, they are not helpful in repairing damage that has already occurred. Prior relapses often leave patients with residual symptoms. A number of medications are available to help these MS-related symptoms. Alleviating pain, spasticity, bladder dysfunction, depression, and anxiety makes up a significant portion of the care offered to patients with MS.

Therapeutics by Class

Immunomodulators

Interferons. The first drug specifically approved for use in relapsing MS was interferon beta-1b (Betaseron in North America/Betaferon in Europe). Subsequent to that, two different preparations of interferon beta-1a were released (Avonex and Rebif). While the interferon beta-1a preparations are identical to human interferon-β in terms of amino acid sequence and glycosylation, interferon beta-1b is produced in bacterial cells, has a few amino acid changes, and is not glycosylated. All of the interferons are FDA approved for RRMS and are therefore not recommended for PPMS or SPMS without relapses.

Mechanism of Action. A variety of mechanisms of action have been proposed for beta interferons. First, immunologically, there is a down-regulation of $CD80^+$ B cells in patients treated with interferon beta.[29] This protein is responsible for co-stimulation of T cells and leads to Th1-type cytokine secretion. Interferon beta also suppresses the expression of interferon-γ–induced MHC class II antigens on antigen-presenting cells.[30,31] Several studies have demonstrated a direct effect on T cells, including suppression of matrix metalloproteinases (MMPs) and promotion of the production of anti-inflammatory cytokines such as IL-4 and IL-10.[32-34] These processes complement each other and lead to an overall shift in T-cell cytokine profiles, favoring a T helper cell type 2 (Th2) response over Th1.[33]

A complementary immunomodulatory effect of interferon beta is that it alters the permeability of the BBB, making it more difficult for autoreactive T cells to enter the parenchyma.[35,36] Clinically, patients on interferon beta have markedly fewer gadolinium-enhancing lesions.[37-40] Reducing the ability of reactive immune cells to enter the CNS would lower the number of new demyelinating lesions and axonal damage. The mechanisms underlying this effect likely relate both to direct immune effects on T cells (decreased MMP production and T-cell activation) and direct effects on endothelial cells. This includes shedding of VCAM-1 into a soluble circulating form that may saturate T-cell ligands and decrease cell migration across the BBB.[41]

Interferon beta also has potential neuroprotective qualities. T cells from patients treated with interferon beta stimulate human brain endothelial cells to secrete nerve growth factor. This protein may play a role in protecting axons from inflammation-mediated damage.[42]

Dosing. The three preparations of interferon beta vary in their dose and route of administration. Interferon beta-1b (Betaseron/Betaferon) is administered every other day via a subcutaneous injection at a dose of 250 mcg. One version of interferon beta-1a (Avonex) is administered intramuscularly once a week at a dose of 30 mcg. The other version of interferon beta-1a (Rebif) is administered subcutaneously three times a week at a dose of either 22 or 44 mcg per injection. Dose titration is recommended for the subcutaneous formulations to decrease the chance of side effects at the onset of therapy. There have been a series of large-scale, double-blind, placebo-controlled trials of these medications in RRMS.

The specific biologic activity is not readily comparable between the different interferon beta preparations. A variety of bioassays are used to quantify interferon beta activity.[43] One strategy utilizes a series of biomarkers that quantify the antiviral effects of interferon beta. Markers such as MXA protein, neopterin, and 2′,5′-oligoadenylate synthetase can be measured in vitro and in vivo and used to compare the relative biologic activity of the three interferons.

Clinical Efficacy. Pivotal studies have found that interferon beta reduces relapse rates by approximately a third and the appearance of new lesions on MRI by approximately 50% to 70%.[40,44-46] Two head-to-head trials have compared low-dose (Avonex) and high-dose (Betaseron/Betaferon or Rebif) interferons to determine whether or not there is a dose-dependent effect. These trials identified a more robust effect of higher dose interferon, especially early on in therapy.[47,48] There is evidence to indicate that interferon can lose its clinical efficacy if a patient develops persistently high titers of neutralizing antibodies.[49,50] This may explain why the higher efficacy of high-dose interferons wanes over time when compared to low-dose interferon.

Adverse Effects. Clinically, patients taking interferon injections may experience a variety of potential side effects. The most common are flulike symptoms including fever, chills, muscle aches, and fatigue. These symptoms are usually self-limited and diminish with successive doses. They can be managed with the use of prophylactic acetaminophen and/or ibuprofen or naproxen taken 1 hour before an injection and are a rare cause of discontinuing medication. Taking the medicine at bedtime can also be useful so that the patient is asleep during the peak period of side effects. Patients utilizing a subcutaneous route of administration have an increased potential for developing site reactions in the skin when compared to the intramuscular injection route. Injection site necrosis can be seen in patients using subcutaneous interferon beta[51] but is rare now with proper injection technique. Some data have linked the use of interferon to an increased rate of depression.[52,53] Drops in peripheral blood counts in all cell lines have been seen, and interferons have rarely caused severe hepatic injury. Consequently, it is advised that patients have their complete blood count with differential, platelet count, blood chemistries, and liver function tests checked periodically. Patients taking Rebif or Betaseron are advised to have these tests at 1, 3, and 6 months after initiation of therapy and

periodically thereafter. Avonex patients are advised to have monitoring at least every 6 months. Thyroid function should also be monitored every 6 months, and a pregnancy test should be sent before starting therapy in women of childbearing age. Other rare adverse effects observed with interferon beta are seizures, cardiomyopathy, menstrual irregularities, and autoimmune disorders (especially thyroid dysfunction).

Glatiramer Acetate. Glatiramer acetate (Copaxone) is a collection of peptides randomly formed from four amino acids (alanine, glutamate, lysine, and tyrosine) combined in a molar ratio of 4.2 : 1.4 : 3.4 : 1.0. The peptides have lengths ranging between 40 and 100 residues. This compound has sequence homology with myelin basic protein and was originally tested as an agent for inducing demyelination in mice. Instead, the compound offered protection for mice with experimental autoimmune encephalitis. Glatiramer acetate is FDA approved for reducing the frequency of relapses in RRMS.

Mechanism of Action. After injection, glatiramer acetate binds MHC class II molecules and is presented to T lymphocytes. Glatiramer acetate biases T cells toward a Th2 $CD4^+$ T-cell profile.[32,54,55] In mice these glatiramer acetate–reactive T cells can be isolated from the CNS and may both ameliorate inflammation and promote neuroprotection and repair via the release of growth factors such as brain-derived neurotrophic factor (BDNF).[32,56-58] Further evidence implicates a shift in peripheral immune system–derived T cells, including upregulation of $CCR7^+$ T central memory $CD4^+$ cells and of $CD8^+$ T cells in response to glatiramer acetate therapy[59,60] (Fig. 46-4).

Beyond effects on T cells, there is in vitro and in vivo evidence that glatiramer acetate exerts an effect on antigen-presenting cells. Monocytes alter their cytokine expression in response to glatiramer acetate, increasing IL-10 levels and decreasing IL-12 levels.[61] Thus, glatiramer acetate–treated monocytes promote a Th2 type T-cell response. Furthermore, there is evidence to indicate the monocyte activity is inhibited by glatiramer acetate, as evidenced by diminished CD25, CD69, and TNF-α expression.[62] These effects may play a direct role in the drug's clinical activity.

Finally, more recent evidence supports a possible role for glatiramer acetate in promoting neuroprotection. The T cells generated by treatment produce BDNF, which promotes neuronal survival.[57,63,64] While this feature is not unique to glatiramer acetate–treated T cells, animal models suggest that these T cells are uniquely primed to migrate to sites of injury within the CNS and promote repair.[65,66]

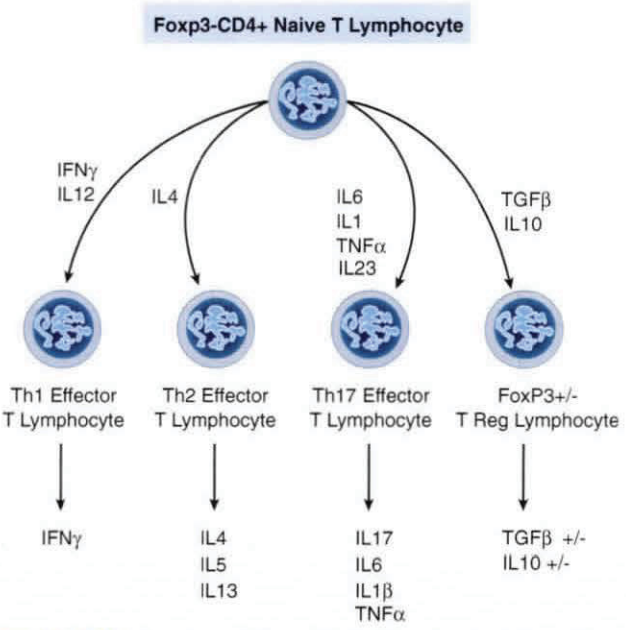

FIGURE 46-4 • The differentiation of $CD4^+$ T lymphocytes. (Adapted from Weaver CT, Harrington LE, Mangan PR, et al. Th17: an effector CD4 T cell lineage with regulatory T cell ties. Immunity 2006;24:677-688.)

Dosing. Glatiramer acetate is administered as a daily subcutaneous injection of 20 mg. Dose titration is not needed. The available data on pharmacokinetics are very limited.

Clinical Efficacy. The clinical benefit of glatiramer acetate was proven in a double-blind, placebo-controlled trial where the outcomes were relapse rate and disability progression.[67] Further studies also identified a benefit as measured by MRI parameters (a reduction in the number of enhancing lesions and T2-hyperintense lesions).[68] Currently, the combination of interferon and glatiramer acetate is being studied to determine whether the efficacy of each would be additive.[69] There have been no convincing data indicating that the development of antibodies against glatiramer acetate are clinically relevant.[70]

Adverse Events. Tolerability of daily glatiramer acetate injections is quite good. Unlike interferon, there are no flulike side effects, but, because of the subcutaneous nature of the injection, site reactions are common. Patients may experience lipoatrophy at injection sites, causing dimpling of skin.[71] About 10% of patients experience an idiosyncratic reaction shortly after injection of the drug, characterized by chest tightness, shortness of breath, palpitations, and flushing. It is a self-limited event that does not require intervention.[72] It does not represent an allergic reaction, and patients are able to take their next dose with little risk of recurrence. Some study patients experienced this once while others had several episodes. Occasional transient chest pain without the other associated symptoms has also been observed, but it does not appear to have any important clinical sequelae. Routine blood monitoring is not needed, but, as with all of the DMTs, women of childbearing age should have a pregnancy test before beginning therapy.

Natalizumab. Natalizumab (Tysabri) is a humanized monoclonal antibody that was FDA approved for use in MS in November 2004.[73] Subsequent to its release, two patients who had been enrolled in the combination natalizumab and interferon beta-1a (Avonex) trial developed progressive multifocal leukoencephalopathy (PML), a serious viral brain infection, and one died. Subsequently, a third patient with PML was discovered postmortem. That patient had been exposed to four doses of natalizumab and several other chronic immunosuppressive medications for Crohn's disease. This prompted the voluntary withdrawal of natalizumab from the market while a safety analysis could be completed. Natalizumab was re-released for use as monotherapy in the summer of 2006 under a monitoring program designed to identify potential PML cases early. The FDA has approved natalizumab for use in relapsing forms of MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. It is recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies.

Mechanism of Action. Natalizumab is a humanized monoclonal antibody that binds to the α4 chain of the VLA-4 integrin dimer on the cell surface of all leukocytes except neutrophils. Normally, VLA-4 binds to targets such as VCAM-1 on the surface of activated vascular endothelium. Natalizumab interferes with this interaction and thereby prevents migration of leukocytes across the BBB to sites of inflammation. This is believed to lead to decreased CNS inflammation and demyelination.

Dosing. Natalizumab is administered as a 300-mg intravenous (IV) infusion every 4 weeks. Steady state levels are reached approximately 24 weeks after monthly dosing, and the mean half-life of the drug is 11 days. Dosing in renal or hepatic insufficiency has not been studied.

Clinical Efficacy. Two large, randomized, double-blind, placebo-controlled studies of natalizumab have been published.[73,74] One was a study of natalizumab monotherapy (AFFIRM) and the other was a study of natalizumab in combination with interferon beta-1a (SENTINEL). The AFFIRM trial found a 42% reduction in the risk of sustained disability progression after 2 years in the natalizumab group compared to placebo.[73] In the natalizumab group, the annualized relapse rate was reduced by 68% and the number of new or enlarging T2 hyperintensities was reduced by 83%.[73] The mean number of

gadolinium-enhancing lesions was also reduced significantly with natalizumab (92% reduction).

Adverse Events. The greatest concern about the use of natalizumab is the risk of developing PML. In the Phase III studies, the risk was found to be approximately 1 in 1000 patients. However, the three patients that developed PML were all treated with other immunomodulating drugs, so the risk of PML in monotherapy may be lower. The two MS patients who were diagnosed with PML developed it after 2 years of treatment. The patient with Crohn's disease who developed PML received 8 months of treatment. It is not known whether early detection of PML and discontinuation of the medication will help new cases. Unfortunately, the mortality rate for PML is high and there are no effective treatments. The real rate of PML with natalizumab in clinical practice will not be known for several years. As required by the FDA-mandated safety program, patients receiving natalizumab who develop new neurologic symptoms or signs need to be evaluated by a neurologist and have a brain MRI performed to help rule out PML.

Complications of natalizumab therapy go beyond possible PML. Patients can have immediate infusion-related reactions (2%), which are common to almost all therapeutic monoclonal antibodies. These include chest tightness, shortness of breath, urticaria, and rarely anaphylaxis. Patients on natalizumab had a higher rate of headaches and urinary tract infections when compared to placebo.[73,75] Persistent antibodies to natalizumab were seen in 6% of patients treated in trials and were associated with decreased efficacy of the drug.[76] Periodic monitoring of liver function is recommended with this treatment. Natalizumab remains a very potent and well-tolerated therapeutic option for MS. However, due to a still unknown risk of PML, it is prudent to limit natalizumab use to patients with more aggressive forms of relapsing MS who do not respond to first-line treatments.

Immunosuppressants

Mitoxantrone. Mitoxantrone (Novantrone) is a synthetic intercalating chemotherapeutic agent that is used in the treatment of MS. It has shown efficacy in RRMS and subsets of SPMS.[77-79] It is FDA approved for reducing neurologic disability and/or frequency of clinical relapses in SPMS, progressive relapsing, and worsening RRMS. Of note, it is the only FDA-approved treatment for SPMS. Mitoxantrone is also approved for use in the treatment of acute nonlymphocytic leukemia and for pain related to advanced hormone-refractory prostate cancer. This drug has significant potential toxicities, including cardiotoxicity, myelosuppression, and risk of leukemia. Consequently, it is reserved for use in patients with aggressive disease.

Mechanism of Action. Mitoxantrone readily crosses the BBB and inhibits DNA replication and RNA synthesis in leukocytes.[80] It also inhibits topoisomerase II, interfering with DNA repair.[81] The effect in MS, beyond a global immunosuppressive effect, might be related to its demonstrated specificity for antigen-specific T cells.[82] Mitoxantrone may also have effects on monocytes, inhibiting their ability to migrate across the BBB.[83] Finally, there are also data indicating that mitoxantrone interferes with antigen-presenting cell function.[84]

Dosing. The FDA-approved dose for mitoxantrone is 12 mg/m^2 IV every 3 months. However, one clinical trial also used a mitoxantrone dose of 20 mg IV monthly combined with a monthly dose of methylprednisolone.[85] The drug is eliminated in a three-compartment model with half-lives of 6 to 12 minutes, 1.1 to 3.1 hours, and an elimination half-life of 23 to 215 hours.[86] It is 78% bound to plasma proteins and is excreted in urine and feces either as unchanged drug or as inactive metabolites. Mitoxantrone should not be used in MS patients with hepatic impairment because its clearance is significantly reduced in these patients. It is also contraindicated in patients with a left ventricular ejection fraction (LVEF) less than 50% or patients whose cumulative lifetime dose is greater than 140 mg/m^2.

Clinical Effects. In a pivotal study, mitoxantrone was tested on patients who had a measurable worsening of disability in the prior 18 months. This was either a stepwise worsening in RRMS patients or a gradual progression of disability in patients with SPMS (with or without superimposed relapses). When dosed at 12 mg/m^2 every 3 months for 24 months, mitoxantrone decreased the number of relapses and decreased the chance of having disability progression compared to placebo.[87] A second trial gave mitoxantrone 20 mg IV and methylprednisolone 1 g IV monthly or methylprednisolone alone for 6 months to patients with very active disease based on clinical and MRI criteria.[88] The group receiving monthly mitoxantrone and methylprednisolone had fewer new enhancing lesions on MRI compared to the methylprednisolone-alone group. Relapse rate and mean disability scores also improved in the mitoxantrone group.

Adverse Effects. There are two major potential complications of mitoxantrone therapy: cardiomyopathy and leukemia. Congestive heart failure (CHF) can occur during therapy or months to years after discontinuation of mitoxantrone. In cancer patients receiving up to 140 mg/m^2, the risk of CHF was estimated at 2.6%.[86] The risk of an asymptomatic decrease in LVEF is likely higher. It is recommended that all MS patients receiving mitoxantrone have evaluation of their ejection fraction by echocardiogram or multigated radionuclide angiography at baseline and before each dose of mitoxantrone. MS patients with a clinically significant drop in LVEF or an LVEF below 50% should not receive mitoxantrone. Contraindications to use include prior history of cardiovascular disease, history of mediastinal radiotherapy, previous use of anthracyclines or anthracenediones, and concomitant use of cardiotoxic drugs. The cardiac toxicity is dose related, prompting the mandated lifetime maximum dose of 140 mg/m^2.

The other major concern is a risk of secondary acute myelogenous leukemia, which has been seen in 0.25% of MS patients treated with mitoxantrone.[86] Myelosuppression is seen with this treatment, typically beginning 8 to 14 days after a single large dose and persisting for 4 to 10 days. Other potential side effects include nausea, alopecia, changes in menstrual cycle, amenorrhea, urinary tract infections, and transaminitis. Prior to each dose, a complete blood count, platelet count, and liver function tests should be checked. The medication should not be administered to patients with an absolute neutrophil count less than 1500 cells/mm^3 or a platelet count less than 100,000/mm^3. Due to potential teratogenic effects of mitoxantrone, women of childbearing age should have a pregnancy test prior to each dose of mitoxantrone. The potential complications and relatively limited clinical benefit have diminished the use of mitoxantrone under this protocol. Yet, there are several ongoing studies examining the usefulness of mitoxantrone as an inducing agent in regimens for RRMS.[89] These studies are determining whether a lower dose of mitoxantrone prior to starting an injectable DMT will improve clinical outcomes.

Corticosteroids. Corticosteroids dampen the inflammatory cellular response and cytokine cascade through a variety of mechanisms that are incompletely understood. Cytokines are proteins released by inflammatory cells that can amplify the immune response as well as mediate direct damage to the nervous system.[90,91] Corticosteroids suppress gene expression and secretion of many of the proinflammatory cytokines implicated in MS.[92,93] Second, corticosteroids stop T cells and B cells from activating by interfering with cell signaling.[94] Third, corticosteroids decrease the extravasation of immune cells into the CNS by suppressing MMPs and adhesion molecules.[95] Finally, corticosteroids actually have proapoptotic effects on activated immune cells.[96] The effects of corticosteroids are not limited to peripheral immune cells. Corticosteroids may decrease BBB permeability by suppressing adhesion molecule expression on endothelial cells, and suppressing effector functions of glial cells in the CNS. Both pro- and antiapoptotic effects of corticosteroids on neurons have been reported.[97]

Clinical indications for using corticosteroids in MS are controversial. There is compelling evidence from large trials that a pulse of high-dose IV corticosteroids can accelerate the recovery from a relapse.[98] The most widely cited study of corticosteroids in demyelinating disease is the Optic Neuritis Treatment Trial.[99] This study was a double-blind, placebo-controlled trial that enrolled patients with a first episode of isolated optic neuritis. The three groups were (i) IV corticosteroids (methylprednisolone 250 mg IV every 6 hours for 3 days) followed by an oral prednisone taper, (ii) an oral prednisone taper in isolation, and (iii) oral placebo. Over 450 patients were followed prospectively to track visual recovery and risk of other episodes of demyelination. While the long-term outcomes for all three groups were

similar, patients receiving IV corticosteroids had a faster recovery. Another observation from this study was that patients who received only oral corticosteroids had the highest rate of recurrent optic neuritis. Thus, when relapses of demyelinating disease occur, the usual course of treatment involves a pulse dose of IV corticosteroids with or without an oral taper. Only small clinical studies have been performed analyzing the potential role of corticosteroids in long-term disease management.[100] While some data have supported the use of quarterly pulses of corticosteroids, longer term, controlled studies will be required to validate these findings. Potential adverse effects of acute treatment with corticosteroids include elevated blood pressure, hyperglycemia, insomnia, mania or psychosis, and weight gain. Additional adverse effects of long-term treatment include risk of peptic ulcers, infections, and osteoporosis.

Cyclophosphamide. Cyclophosphamide (Cytoxan) is an alkylating agent that is used to treat malignancies and some autoimmune conditions. Cyclophosphamide has also been used to treat MS, although it is not FDA approved for this indication. A 1983 study randomized patients with severe, progressive MS to IV cyclophosphamide plus adrenocorticotrophic hormone (ACTH), ACTH alone, or plasma exchange with ACTH and oral cyclophosphamide.[101] The study was neither blinded nor placebo controlled. It found that 80% of patients treated with IV cyclophosphamide plus ACTH had stabilized at 1 year compared to 20% in the group treated with ACTH alone. Other studies of cyclophosphamide in progressive MS have been negative.[102,103] Subgroup analyses determined that younger patients with a shorter duration of progressive disease and an inflammatory component to their disease as evidenced by MRI or clinical activity may be more likely to respond to cyclophosphamide.[104] Several small, open-label studies have also used monthly pulses of cyclophosphamide in RRMS patients with continued disease activity while on interferon beta or glatiramer acetate.[105-108] At doses varying from 500 to 1500 mg/m^2 IV monthly, these studies have shown benefits on both MRI and clinical outcomes.

Possible adverse effects seen with cyclophosphamide include infertility, amenorrhea, alopecia, cardiotoxicity, infections, and secondary malignancies. Hemorrhagic cystitis is more commonly associated with long-term oral cyclophosphamide treatment; however, patients receiving cyclophosphamide should be adequately hydrated. A complete blood count and urinalysis should be performed periodically to monitor the white blood cell count and to rule out hematuria. A pregnancy test should be sent prior to initiation of therapy.

Azathioprine. Azathioprine (Imuran) is a purine analogue that is used for posttransplantation immunosuppression, rheumatoid arthritis, and other autoimmune conditions. It is not FDA approved for MS, but it is used commonly in Europe in MS patients, partly because it is relatively inexpensive. An evidence-based review concluded that azathioprine was helpful in patients who experience frequent relapses.[109] An open-label clinical trial studied the effect of adding azathioprine to interferon beta-1b in patients experiencing an exacerbation or disease progression while on interferon beta.[110] Patients were maintained on interferon beta-1b and titrated up to a goal dose of 3 mg/kg of azathioprine as tolerated. However, only 1 of the 15 patients was able to tolerate the full dose of azathioprine. MRI scans on the combination therapy had 65% fewer gadolinium-enhancing lesions when compared to baseline scans in the same patients when they were on interferon beta monotherapy. The authors found that a total white blood count less than 4800 was the best predictor of MRI response.

Possible adverse effects with azathioprine include myelosuppression, gastrointestinal side effects, infections, elevated transaminases, and secondary malignancies. At the onset of therapy, patients should have a complete blood count and pregnancy test. The blood count should then be monitored weekly for the first month, twice monthly for the second and third months, and then monthly. About 0.3% of the population is homozygous for a nonfunctional form of the TPMT enzyme, which metabolizes azathioprine.[111] These patients are at risk for life-threatening myelosuppression if given azathioprine. Heterozygotes may also be at an elevated risk of myelosuppression. These patients can be identified by genotyping or by testing enzyme activity levels prior to the initiation of azathioprine treatment.

Methotrexate. Methotrexate is a folate analogue used to treat some malignancies, rheumatoid arthritis, and other autoimmune conditions. It has been used for a number of years in MS, but it is not FDA approved for this diagnosis. The Avonex Combination Trial randomized patients with continued disease activity on Avonex to receive Avonex plus either methotrexate, pulse dose corticosteroids, or methotrexate and pulse dose corticosteroids. Although trends favored the combination group, there was not a statistically significant difference among the treatment groups.[112] The full results of this trial have not yet been published. In an open-label study of 15 patients, weekly oral methotrexate (20 mg) and interferon beta-1a were given to patients who had breakthrough disease on interferon beta.[113] MRI scans on the combination therapy showed 44% fewer gadolinium-enhancing lesions when compared to baseline scans in the same patients when they were on interferon beta monotherapy.

Adverse events associated with methotrexate include gastrointestinal toxicity, myelosuppression, hepatotoxicity, secondary lymphomas, infections, fetal death or congenital anomalies, lung disease, skin reactions, and encephalopathy. At baseline, patients should be screened with a complete blood count including platelet count, liver function tests, renal function tests, chest radiograph, and pregnancy test, as applicable. Hematologic monitoring is recommended at least monthly, and renal and liver function should be checked every 1 to 2 months. Patients should be counseled that pregnancy should be avoided if either partner is receiving methotrexate.

Mycophenolate Mofetil. Mycophenolate mofetil (Cellcept) blocks purine metabolism and is used for posttransplantation immunosuppression. Although not FDA approved for MS, several uncontrolled studies have reported benefits using this treatment.[114-116] Further studies are needed to better establish the utility of this treatment in MS. Potential adverse effects include infections, leukopenia, gastrointestinal bleeding, diarrhea, and secondary malignancies. Complete blood counts are needed weekly during the first month, twice monthly for the second and third months, and monthly through the first year. Women of childbearing age should be tested for pregnancy and advised that the use of mycophenolate during pregnancy increases the risk of fetal loss and congenital malformations.

Intravenous Immune Globulin. Intravenous immune globulin (IVIG) is used to treat a number of autoimmune neurologic diseases such as myasthenia gravis and acute inflammatory demyelinating polyneuropathy. Several trials have tested IVIG in MS. A randomized trial of monthly 0.15- to 0.2-g/kg IVIG or placebo found a 59% reduction of the annual relapse rate in the IVIG group relative to placebo.[117] A more recent placebo-controlled trial of two doses of IVIG did not find a difference in its primary outcome of the proportion of relapse-free patients, although the full results have not yet been published.[118] The role of IVIG in MS remains unclear. One interesting use of IVIG has been to reduce the risk of relapses in the postpartum period, but its role in this situation is unclear (see "Treatment Considerations Related to Pregnancy" section later). IVIG can cause allergic reactions, headache, fluid overload, aseptic meningitis, encephalopathy, renal failure, and thrombosis/hyperviscosity syndromes.

Therapeutic Approach

Several important issues regarding treatment of patients with MS remain unresolved. In some instances, high-quality evidence is available to guide our decisions, but in many instances these data are lacking and treatment decisions must be based on uncontrolled trials, expert opinion, or personal experience. Several key treatment issues and the available evidence are reviewed in this section.

Treatment with DMT: Patient Selection and Initiation

The initial trials of the first DMTs, interferon beta and glatiramer acetate, were on patients with clinically definite RRMS with relatively high relapse rates. All these agents were shown to reduce relapse rate in RRMS. For interferons, the rate of relapse reductions ranged from 18% to 32% depending on the study.[44,119,120] The reduction in relapse

rate was 29% in the pivotal study of glatiramer acetate.[121] All interferon formulations and glatiramer have also shown a beneficial effect on MRI measures of disease activity. Based upon these data, the FDA has approved glatiramer acetate and three formulations of interferon beta for use in relapsing forms of MS. Demonstration of an effect on disability was more variable in these trials.

After interferon beta was proven to benefit RRMS patients, questions arose about whether it might also help patients who have had a single clinical episode of CNS inflammation and are deemed to be at high risk of developing MS. Diagnostic criteria for MS require two episodes of CNS inflammation that are disseminated in time and space. Patients who have had a single attack are referred to as having a "clinically isolated syndrome" (CIS). Criteria for MS can be fulfilled by waiting for a second attack or, in some cases, by using paraclinical evidence of MS such as the development of new lesions on an MRI. When evaluating patients with CIS, it is important to consider their risk of having further events that would qualify them for the diagnosis of MS. The best tool to stratify risk of developing MS is brain MRI. The Optic Neuritis Treatment Trial enrolled patients with new optic neuritis and followed them prospectively. It found that patients with one or more lesions typical of MS on brain MRI had a 56% chance of developing MS (defined as a second clinical attack) after 10 years versus a 22% risk for those with a normal brain MRI.[122] Therefore, a study was undertaken in which patients with an initial clinical demyelinating event and subclinical demyelination on MRI were randomized to weekly intramuscular interferon beta-1a or placebo.[123] Patients receiving interferon beta-1a had a 44% lower chance of progressing to clinically definite MS during the follow-up period, and there were fewer new lesions on MRI. Similar findings were seen in studies using the other formulations of interferon beta.[124,125] A trial using glatiramer acetate in CIS showed that this drug reduced the risk of developing MS and delayed the development of MS in individuals with CIS.[126]

The American Academy of Neurology (AAN) published guidelines on the treatment of MS in 2002 (reaffirmed in 2003).[127] The guidelines concluded that, on the basis of several class I studies (see Table 46-2 for a summary of levels of evidence), interferon beta and glatiramer acetate have been demonstrated to reduce the attack rate in patients with MS (level A recommendation). Interferon beta also reduces the attack rate in patients with CIS who are at high risk for developing MS (level A). Consequently, the guidelines concluded that it is appropriate to consider interferon beta treatment for any patient who is at high risk for developing MS or who already has RRMS or SPMS and is still experiencing relapses (level A). Glatiramer acetate is appropriate to consider for treatment of any patient with RRMS (level A). It was concluded that there were insufficient data to recommend interferon beta or glatiramer for SPMS without relapses (level U recommendation). They also thought that there was insufficient evidence to determine whether certain populations of MS patients (e.g., those with more attacks or at earlier disease stages) are better candidates for therapy than others (level U recommendation). Most MS experts believe that early treatment of MS with a DMT offers patients the best chance of minimizing relapses and preventing or delaying disability.

First-Line Treatment for RRMS

Opinions differ regarding what is the optimal first-line RRMS therapy. Since the three interferon beta formulations and glatiramer acetate all have similar efficacy in reducing relapse rates, the choice of therapy is often best guided by the characteristics and preferences of the individual patient. These treatments do differ in the type of injection, frequency of injection, side effects, and frequency and significance of neutralizing antibody formation.

The three formulations of interferon beta have several differences. Betaseron (or Betaferon in Europe) is subcutaneous interferon beta-1b 250 mcg every other day, Avonex is intramuscular interferon beta-1a 30 mcg weekly, and Rebif is subcutaneous interferon beta-1a 44 mcg three times per week. Avonex is considered to be a "low-dose" interferon, while Rebif and Betaseron are considered "high-dose." The AAN treatment guidelines note that evidence indicates that it is "probable that there is a dose-response curve associated with the use of interferon beta" (level B recommendation); that is, a higher dose or higher frequency of administration probably improves efficacy.[127]

Avonex has the lowest frequency of shots (once per week), while the others are about three times per week and glatiramer acetate is daily. This makes Avonex advantageous for patients who are particularly averse to injections. However, Avonex requires a deeper, intramuscular

TABLE 46-2 SUMMARY OF EVIDENCE GRADES

Rating of Recommendation	Translation of Evidence to Recommendations	Rating of Therapeutic Articles
A = Established as effective, ineffective, or harmful for the given condition in the specified population	Level A rating requires at least one convincing class I study or at least two consistent convincing class II studies	**Class I:** Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) is/are clearly defined b) exclusion/inclusion criteria are clearly defined c) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
B = Probably effective, ineffective, or harmful for the given condition in the specified population	Level B rating requires at least one convincing class II study or at least three consistent class III studies	**Class II:** Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above *or* an RCT in a representative population that lacks one of criteria a–d
C = Possibly effective, ineffective, or harmful in the specified population	Level C rating requires at least two convincing and consistent class III studies	**Class III:** All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
U = Data inadequate or conflicting. Given current knowledge, treatment is unproven.		**Class IV:** Evidence from uncontrolled studies, case series, case reports, or expert opinion

injection with a needle that is larger than what is used for the subcutaneous injections for the other medications.

The interferon beta preparations also differ in their frequency of inducing neutralizing antibodies (NAbs). NAbs are antibodies that bind to the interferon molecule and potentially can decrease its clinical efficacy. Estimates of the frequency of NAbs have differed significantly depending on the type of study and the definition of NAb positivity. Betaseron is associated with the highest rate of NAb formation, which was 38% in the Phase III study.[44] For Rebif, NAb positivity was seen in 14% of patients in the Phase III study.[120] The manufacturers of Rebif are testing a new formulation that may decrease the development of NAbs. The Phase III trial of Avonex had a 22% rate of NAb positivity[119]; however, using a newly formulated product, most studies have found NAb formation to be less than 7%.[128] Therefore, Avonex appears to have the lowest rate of NAb formation, while Betaseron has the highest. The clinical significance of NAbs has been debated. To address this question, the AAN published a practice guideline on NAbs in 2007.[129] The authors concluded that "it is probable that the presence of NAbs, especially in persistently high titers, is associated with a reduction in the radiographic and clinical effectiveness of interferon beta treatment (level B recommendation)."[128] They also concluded that the rate of NAb formation is probably less with interferon beta-1a compared to interferon beta-1b (level B) and the rate of NAb formation probably depends on the formulation, dose, route of administration, or frequency of administration (level B). NAbs to glatiramer acetate have not been found.[129]

The side effect profile differs significantly between interferon beta and glatiramer acetate. Interferon beta causes flulike symptoms, including fever, myalgia, headache, and fatigue, in up to 75% of patients at initiation of therapy.[130] Interferon beta can cause a transient worsening of preexisting MS symptoms, especially spasticity.[131,132] This often accompanies flulike symptoms in the first 12 weeks. These effects resemble the worsening seen in MS patients with stress, heat, or inflammation. Interferon beta treatment requires blood monitoring for leukopenia or elevated transaminases; glatiramer acetate does not require any blood monitoring. Depression is a common comorbidity in MS. Data have been conflicting on the role of interferon beta in exacerbating depression; however, it appears that this treatment can induce or exacerbate depression in some patients. Other side effects of interferon beta include menstrual disorders and exacerbation of migraine headaches. Glatiramer acetate is associated with a rare immediate postinjection reaction. This reaction is benign but can be frightening for the patient. The reaction occurs within minutes of the injection and can include flushing, chest tightness or pain, dyspnea, palpitations, and anxiety that can last from seconds up to 30 minutes. This reaction is considered benign and not associated with cardiac dysfunction. It is relatively uncommon, occurring from one to seven times during the 30-month Phase III trial in 15% of patients.[121] Anaphylaxis has been reported as a rare event with both glatiramer and interferon beta.[133,134]

Some direct comparisons have been made between different interferon beta formulations. The EVIDENCE trial randomized patients with RRMS to receive either Rebif or Avonex.[135] Due to different routes and frequencies of administration, the patients and treating physicians were not blinded, but relapses and disability were evaluated by a second physician who was blinded. The study found a 17% reduction in annualized relapse rate in the Rebif group compared to the Avonex group. The number of patients needed to treat with Rebif compared to Avonex for one additional patient to remain relapse-free is 12. The INCOMIN study randomized patients with RRMS to Betaseron or Avonex and followed them for 2 years.[136] Patients and physicians were unblinded in this study, but the MRI assessments were blinded. They found a 31% relative risk reduction of annualized relapse rate in the Betaseron group relative to the Avonex group. The Betaseron group also had a higher proportion of patients remaining relapse-free, and MRI measures favored Betaseron. However, interpretation of the results must take into account the lack of blinding regarding clinical outcomes.

Randomized trials comparing interferon beta and glatiramer acetate have also been performed. The REGARD trial randomized patients with RRMS to Rebif or glatiramer acetate.[137] There was no significant difference in the primary end point of time to first relapse. In a prespecified subgroup analysis, the subgroup of patients with lower baseline disability had a greater time to first relapse in the Rebif group relative to the glatiramer group. The authors noted that patients in this trial had much lower relapse rates than had been predicted based on prior studies. The BECOME trial is an MRI study that randomized patients to glatiramer or Betaseron and followed them for up to 2 years with monthly MRI scans.[138] The primary outcome of the number of new MRI lesions was not significantly different in the two treatment groups. Taken together, these two studies support the conclusion that the efficacy of glatiramer and high-dose interferon are similar.

Based on the data discussed here, a few suggestions can be made regarding initial choice of therapy in RRMS. Glatiramer acetate has the best side effect profile and is a good choice for patients who want to avoid flulike symptoms and do not mind daily injections. Patients who are very averse to injections may prefer the weekly injection of Avonex. For patients with particularly active disease, the additional efficacy of high-dose interferon (Rebif or Betaseron) may be preferred over a low-dose interferon. The lower risk of NAb formation with Avonex may be an advantage over high-dose formulations for some patients. Also, between high-dose formulations, the lower frequency of NAb formation in Rebif may make it preferable to Betaseron. The presence of a history of depression or migraine headache favors use of glatiramer over interferon beta.

Treatments Helpful in SPMS

The results of treatment trials in SPMS have been mixed, and this stage of the disease is more difficult to treat than RRMS. Mitoxantrone is the only FDA-approved treatment for SPMS. As discussed earlier, mitoxantrone was given to patients with worsening RRMS or SPMS who had experienced an increase in disability over the prior 18 months.[87] The effective dose used in this double-blind, randomized, placebo-controlled study was 12 mg/m^2 IV every 3 months for 2 years. Relapse rate and disability measures were better in the group receiving mitoxantrone.

Use of mitoxantrone is a reasonable strategy in patients with very active RRMS or rapidly progressive SPMS. For SPMS patients, it is probably most useful in patients who still have a significant inflammatory component to their disease, such as patients in a transitional phase between RRMS and SPMS. Patients with later stages of SPMS are less likely to benefit. The major limitation of this treatment strategy is the adverse effect profile of mitoxantrone. As discussed previously, mitoxantrone is associated with cardiomyopathy, myelosuppression, secondary leukemias, and other side effects. The AAN published guidelines on the use of mitoxantrone in MS in 2003.[139] The authors concluded that "it appears that mitoxantrone may have a beneficial effect on disease progression in patients with MS whose clinical condition is deteriorating" (level B recommendation). However, they cautioned that "this agent is of limited use and of potentially great toxicity. Therefore, it should be reserved for patients with rapidly advancing disease who have failed other therapies."

Although it is not FDA approved for this indication, several trials have shown positive results with cyclophosphamide in SPMS. A 1983 study randomized patients with severe, progressive MS to IV cyclophosphamide plus ACTH, ACTH alone, or plasma exchange with ACTH and oral cyclophosphamide.[101] Although the study was neither blinded nor placebo controlled, it found that 80% of patients treated with cyclophosphamide had stabilized at 1 year compared to 20% in the group treated with ACTH alone. Other studies of cyclophosphamide in progressive MS have been negative.[103,104] Post-hoc analyses of these studies have identified subgroups that are most likely to respond to cyclophosphamide—specifically, younger patients with a shorter duration of progressive disease with an inflammatory component to their disease as evidenced by MRI or clinical activity.[105] Based on this evidence, the AAN treatment guidelines concluded that pulse cyclophosphamide treatment does not seem to alter the course of progressive MS (level B recommendation), but that it is possible that younger patients with progressive MS might derive some benefit from pulse plus booster cyclophosphamide treatment (level U recommendation).[127]

The utility of interferons in SPMS has been an area of controversy. A European study randomized SPMS patients to subcutaneous interferon beta-1b or placebo.[140] SPMS was defined as a period of deterioration independent of relapses sustained for 6 months, and patients needed to have a history of two or more relapses or an increase in disability in the prior 2 years. This study was terminated early due to a benefit in the interferon beta-1b group for the primary outcome of time to confirmed disability progression. Based on these data, the European Union approved interferon beta-1b for use in SPMS. In contrast, a North American study of interferon beta-1b in SPMS had completely different results.[141] This study enrolled patients with MS for at least 2 years who had had at least one relapse and a progressive course for at least 6 months. Patients also had to have an increase in disability in the preceding 2 years. This study found no benefit of interferon beta for the primary outcome of time to progression. In fact, the study was stopped early due to futility. However, the interferon beta group did show benefit on some secondary outcome measures, including a reduction in relapse rate and number of new MRI lesions. A post-hoc combined analysis of the two trials was performed.[142] The patients in the European study were more likely to be at an earlier phase of SPMS and had more inflammatory activity as evidenced by relapse rate and MRI activity. The authors concluded that SPMS patients with pronounced disability progression and continuing relapse activity are more likely to respond to interferon beta. AAN treatment guidelines state that it is appropriate to consider interferon beta for treatment of SPMS patients who are still experiencing relapses (level A recommendation); however, the effectiveness of interferon beta in patients with SPMS without relapses is uncertain (level U recommendation).[127]

Treatments Helpful in PPMS

Unlike RRMS, attempts to find treatments for PPMS have been disappointing. There are currently no FDA-approved treatments for PPMS; this is a major unmet medical need. With the exception of natalizumab, the approved therapies for RRMS have been tested in PPMS. The PROMiSe trial randomized PPMS patients to receive glatiramer acetate or placebo and followed them for 3 years.[88] The primary end point was time to sustained progression of disability. The study found no significant treatment effect. Interferon beta-1b has been tested in a randomized, placebo-controlled trial of patients with PPMS or transitional MS, defined as progressive disease with a history of a single relapse prior to, at the onset of, or during the progressive phase.[143] Preliminary results were reported, but the full results have not yet been published. There was no difference in the groups with respect to the outcome of confirmed 6-month progression. However, the interferon group had better Multiple Sclerosis Functional Composite scores and better results on some MRI measures. A double-blind, placebo-controlled trial of mitoxantrone in PPMS has been completed. The preliminary analysis indicated that there was no benefit on clinical outcomes, but the results have not yet been published.[144] A trial of rituximab in PPMS was reported to be negative in a company press release.

Definition of Treatment Failure

Many physicians struggle with how to define treatment failure in MS. Although no universal definition of treatment failure exists, most people would agree that more than two relapses per year, an evolving MRI, or development of new disability should prompt consideration of a change in therapy. However, we know from clinical trials that first-line therapies such as interferon beta and glatiramer acetate only decrease the relapse rate by about one third. Consequently, it may be unrealistic to expect complete quiescence with these medications. If one knows the pretreatment relapse rate or the frequency at which new MRI lesion developed, then this can be used as a comparison. Unfortunately, decisions must usually be made without these data.

The most challenging situation is the patient with about one relapse per year or no relapses but continued development of new MRI lesions. The management of this patient often depends on several questions: Are they true relapses (as opposed to heat- or infection-related "pseudorelapses")? How severe are they? How well does the patient recover? Are there prognostic factors that portend a worse disease course? Does the patient want to change treatments? What other treatments are available, and what are their risk:benefit ratios? An important consideration when faced with breakthrough disease activity is the patient's compliance. As with any disease, a treatment only works if a patient takes it. Another consideration in patients on interferon beta is the possible presence of NAbs. Although the clinical importance of NAbs remains controversial, an AAN guideline concluded that it is probable that the presence of NAbs, especially in persistently high titers, is associated with a reduction in the radiographic and clinical effectiveness of interferon beta treatment (level B recommendation).[128] The presence of high-titer NAbs in the context of breakthrough disease activity should prompt consideration of changing to a non-interferon treatment. Antibodies to natalizumab have also been observed.[76] Persistent antibodies were seen in 6% of trial patients and were associated with decreased efficacy of the drug. Testing for antibodies to interferon beta and natalizumab is commercially available. The presence of other non-MS pathologies should also be a consideration in breakthrough disease (e.g., PML in a patient receiving natalizumab).

Management of Breakthrough Disease Activity

Breakthrough disease activity remains a common problem with our current armamentarium of treatments. As discussed previously, assessment of treatment compliance and consideration of the presence of NAbs to interferon beta or natalizumab should be considered. If it is decided that the degree of disease activity is not acceptable, then several strategies are available. Opinions on how to manage ongoing disease activity differ significantly, and there are limited data to guide decision making. Some clinicians will change a patient from a low-dose to high-dose interferon, although there are no data to support this. Switching from interferon beta to glatiramer acetate or vice versa is another strategy. The combination of interferon beta and glatiramer was found to be safe in a pilot trial,[145] and a large National Institutes of Health–sponsored trial is underway to test the effectiveness of this regimen.[69]

Another approach for managing breakthrough disease activity is to switch to a more potent agent. Two FDA-approved treatments that can be used in this circumstance are natalizumab and mitoxantrone. Clinical trials with natalizumab showed robust effects on relapse rate and MRI measures in relapsing MS. However, due to the risk of PML, a potentially fatal viral infection of the brain, natalizumab should only be used as monotherapy in patients with relapsing forms of MS who have had an inadequate response to alternate MS therapies. As described earlier, mitoxantrone is indicated for treatment of SPMS or worsening RRMS. Although not FDA approved for this indication, IV cyclophosphamide has often been used for MS patients with relatively aggressive disease. One trial randomized RRMS patients who continued to have very active disease on interferon beta to receive 6 months of pulse corticosteroids or pulse corticosteroids plus IV cyclophosphamide (800 mg/m^2) in addition to interferon beta.[107] In the 18-month follow-up, there were a lower relapse rate and fewer new gadolinium-enhancing lesions in the group receiving IV cyclophosphamide, pulse corticosteroids, and interferon beta.

Other non–FDA-approved therapies are commonly used in breakthrough MS. Some clinicians will add pulse dose corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, cladribine, cyclosporine, or IVIG to the patient's regimen. The data for use of these agents are often limited. The AAN treatment guidelines concluded that regular pulse corticosteroids may be useful in the long-term management of RRMS (level C recommendation),[127] azathioprine may reduce relapse rate in MS (level C), cladribine does not appear to favorably affect the disease course (level C), cyclosporine may possibly have some benefit in MS (level C), and IVIG could possibly affect relapse rate (level C).

Management of Acute Relapses

The treatment of an acute MS relapse largely depends on its severity. Early in the disease, most relapses are followed by significant recovery

even in the absence of treatment. Studies have shown that high-dose IV corticosteroids can speed up the recovery from a relapse (level A recommendation).[127] However, there does not appear to be any long-term benefit to a brief use of corticosteroids in an acute relapse (level B recommendation). Therefore, many clinicians will use high-dose IV steroids for any relapse that causes functional impairment (e.g., weakness, notable visual impairment). For milder symptoms not causing functional impairment (e.g., a mild sensory disturbance), corticosteroids are often withheld. A typical regimen is methylprednisolone 1000 mg IV daily for 3 to 7 days. Some clinicians will follow this with a 10- to 14-day oral prednisone taper, although many do not. The Optic Neuritis Treatment Trial found that optic neuritis patients treated with a moderate dose of oral corticosteroids (prednisone 1 mg/kg) had a higher risk of developing a new optic neuritis than the groups treated with placebo or high-dose IV methylprednisolone.[99] Therefore, moderate-dose oral corticosteroids are not recommended. High-dose oral and IV corticosteroid regimens have been compared in small randomized trials.[146,147] They have found no difference in efficacy, suggesting that high-dose oral regimens may be a more convenient and less expensive option to IV methylprednisolone. The AAN treatment guidelines found that there is no compelling evidence to indicate that the route, type, or dosage of corticosteroid affects the clinical benefit that is observed, at least at the dosages that have been studied (level C recommendation).

For patients with a severe relapse that does not respond to high-dose corticosteroids, one option is plasma exchange. In one trial patients with severe deficits that did not respond to high-dose corticosteroids were randomized to seven courses of plasma exchange or sham treatment.[148] The group receiving plasma exchange was significantly more likely to experience at least moderate neurologic recovery. This treatment was given a level C recommendation in the AAN treatment guidelines.[127]

Treatments Helpful for Common MS-Related Symptoms

Besides disease-modifying agents, physicians will often need to prescribe medication for symptomatic therapy. Patients with MS suffer from a variety of secondary symptoms including spasticity, incontinence, fatigue, pain, and depression. Successful management of those symptoms is a significant part of improving patients' quality of life. Table 46-3 lists various therapeutic options for common secondary symptoms and their potential side effects. At times, a side effect profile can be used to the patient's advantage. For example, if a patient presents with insomnia, depression, neuropathic pain, and incontinence, he or she may not need four prescriptions. Using amitriptyline as an antidepressant may treat all four symptoms based on its anticholinergic properties (causing drowsiness in the evenings and decreased urination) as well as its ability to treat neuropathic pain.[149-151] It is critical to determine the root cause of various symptoms before prescribing a medication. An MS patient with fatigue may be suffering from sleep apnea rather than MS-related fatigue. Successful treatment of these symptoms will only occur if all potential causes have been considered.

Spasticity is a velocity-dependent increase in muscle tone that results from lesions of the descending corticospinal tract. Commonly, patients will complain of stiffness of gait, loss of dexterity, or painful muscle spasms. Physical therapy can be helpful in improving spasticity and preventing contractures. Baclofen (Lioresal) is a γ-aminobutyric acid B receptor agonist that is used to treat spasticity. Patients should begin at a dose of 5 mg three times per day and be titrated up as tolerated. The dose-limiting side effect is usually sedation. In addition, decreased muscle tone can sometimes make it more difficult for patients to walk. Patients should be cautioned not to stop the medicine abruptly due to risk of withdrawal seizures. Tizanidine (Zanaflex) is another centrally acting antispasmodic agent. It is an agonist of α_2-adrenergic receptors. Sedation is the most common side effect encountered with tizanidine. Botulinum toxin injections can be used to relieve localized adductor spasms. However, these large muscles often require a high dose to be effective. Other treatments used to relieve spasticity include benzodiazepines, dantrolene, dronabinol, and an intrathecal baclofen pump.

TABLE 46-3 COMMONLY USED SYMPTOMATIC THERAPIES

	Potential Side Effects
SPASTICITY	
Baclofen	Drowsiness, headache, insomnia, nausea, confusion, seizures
Dantrolene	Drowsiness, dizziness, diarrhea, constipation, headache, palpitations, hepatotoxicity
Diazepam	Drowsiness, dizziness, fatigue, constipation, headache, blurred vision, confusion, ataxia
Dronabinol	Dizziness, insomnia, mood changes, ataxia, anxiety, paranoia, unusual thoughts, increased appetite
Tizanidine	Drowsiness, fatigue, dry mouth, dizziness
NEUROPATHIC PAIN	
Amitriptyline	Drowsiness, dizziness, dry mouth, headache, urinary retention, weight gain
Carbamazepine	Ataxia, clumsiness, dizziness, drowsiness, nausea
Gabapentin	Drowsiness, dizziness, fatigue, irregular eye movements
Lamotrigine	Rash, headache, fatigue, dizziness, blurred vision, ataxia
Paroxetine	Drowsiness, nausea, diarrhea, insomnia, dry mouth, tremor, decreased libido, sexual dysfunction
Topiramate	Paresthesias, weight loss, dizziness, cognitive difficulties, ataxia, somnolence
Tramadol	Nausea, constipation, dizziness, lowered seizure threshold
FATIGUE	
Amantadine	Nausea, drowsiness, headache, constipation, rash
Modafinil	Headache, anxiety, insomnia

Bladder dysfunction is a very common complaint among MS patients. Furthermore, bladder and kidney stones, renal dysfunction, and urosepsis can be major sources of morbidity in MS. When patients present with a new urinary complaint, it is important to perform a urine culture to evaluate for an infection. There are three general types of urinary problems in MS. It is often difficult to distinguish them based on history, and urodynamic studies can be helpful in some cases. First is the atonic bladder, which presents with difficulty voiding and overflow incontinence. Urinary tract infections are common. Cholinergic medications such as bethanecol can sometimes assist with bladder emptying. However, many patients will need to perform clean intermittent bladder catheterization. Patients with frequent urinary tract infections may benefit from the use of urine acidifiers such as cranberry juice or vitamin C. The second type of bladder problem is the spastic bladder. Patients are unable to store urine well, resulting in urinary urgency and incontinence. Anticholinergics such as oxybutynin (Ditropan) and tolterodine (Detrol) can alleviate some of these symptoms. The third bladder problem is detrusor-sphincter dyssynergia. This occurs when the detrusor muscle and external urinary sphincter contract simultaneously, leading to high pressures in the bladder. This is also best treated with clean intermittent catheterization, but α-blockers such as terazosin (Hytrin) can be helpful. Constipation can be treated with dietary changes and stool softeners. Bowel incontinence is less common, but more distressing. Use of a bulk fiber agent such as psyllium (Metamucil) can be suggested.

Fatigue is the most commonly reported symptom of MS, with an estimated frequency between 76% and 92%.[152] The first step in

managing fatigue is to evaluate for a cause other than MS. Hypothyroidism, anemia, depression, sleep apnea, or medication effects all can contribute to fatigue. The patient's sleep habits should be explored, including the frequency of awakenings due to nocturia. Regular exercise can improve endurance and should be recommended. If this is insufficient, several pharmacologic interventions can be tried. About 30% of patients will respond well to amantadine (Symmetrel) 100 mg in the morning and 100 mg in the early afternoon. Patients may experience livedo reticularis or anticholinergic effects with this treatment. Modafinil (Provigil) is a medication that promotes wakefulness and is used in narcolepsy. The evidence for its utility in MS fatigue is mixed. Although benefits were seen in an open-label study of MS fatigue, a randomized, double-blind, placebo-controlled trial failed to show a benefit.[153] Nonetheless, many experts believe that a subset of patients will respond favorably to Modafinil. CNS stimulants such as methylphenidate (Ritalin) are an option for patients with severe fatigue that has not responded to other treatments. One double-blind, placebo-controlled, crossover study of aspirin 1300 mg daily showed a benefit on fatigue scores in MS.[154] Although not FDA approved in the United States, 4-aminopyridine has been used for many years for management of MS symptoms. It is thought that it may improve conduction in demyelinated nerves through blocking currents in the $K_v1.4$ potassium channels on axons. Its use has been limited by an increased seizure risk, but a longer acting formulation (fampridine) is being tested in clinical trials.

MS patients can experience both musculoskeletal pain and centrally mediated dysesthesias. For neuropathic pain, commonly used treatments include gabapentin (Neurontin), tricyclic antidepressants such as amitriptyline or nortriptyline, tramadol (Ultram), pregabalin (Lyrica), duloxetine (Cymbalta), topiramate (Topamax), baclofen (Lioresal), carbamazepine (Tegretol), and lamotrigine (Lamictal). In MS, trigeminal neuralgia can result from a demyelinating plaque at the dorsal root entry zone of the trigeminal nerve. Carbamazepine, gabapentin, and phenytoin (Dilantin) are frequently used for this condition, although some patients may require gamma knife or neurosurgical intervention. Musculoskeletal pain can be treated with nonsteroidal anti-inflammatory medications.

Several other symptoms are commonly encountered in MS patients. Patients can experience cognitive dysfunction, particularly with regard to sustained attention, working memory, and speed of information processing. It is hoped that use of DMTs will decrease the development of cognitive impairment. Studies of acetylcholinesterase inhibitors for cognitive impairment in MS have generally been negative, although subsets of patients may benefit from this approach.[155] Cognitive rehabilitation can be tried. Depression and bipolar disorder are seen at a higher frequency in MS patients. Treatment of these conditions is the same as for non-MS patients with these conditions. Sexual dysfunction is also identified commonly in MS patients. Since many patients will not spontaneously report this problem, it is often useful to question patients about it. As with other symptoms, a contribution of depression, other medical conditions, or medication effects should be ruled out. Men may experience erectile dysfunction, which can be treated with phosphodiesterase-5 inhibitors such as sildenafil (Viagra). Women may report decreased libido, decreased vaginal lubrication, or decreased perineal sensation. Water-soluble lubricants can assist with vaginal dryness, but pharmacologic options are not available for other causes of sexual dysfunction.

Treatment Considerations Related to Pregnancy

Given that MS is most commonly diagnosed in women between 20 and 40, clinicians are frequently faced with questions relating to pregnancy. Many women with MS have successful deliveries, and there is no evidence that MS has any adverse effects on the health of the baby. Epidemiologic studies of pregnant patients have found that the MS relapse rate is lower during pregnancy, especially during the third trimester.[156] However, the risk of relapses is increased in the 3-month period following delivery. After that 3-month period, the relapse rate returns to the prepregnancy level, indicating that pregnancy does not accelerate the disease process. Taken together, the relapse rate for the 1-year period including the pregnancy is the same as the rate in nonpregnant patients. In addition, neither epidural analgesia nor breast-feeding is associated with an increased relapse rate or disease progression.[156]

None of the DMTs has been proven to be safe in pregnancy or breast-feeding. Glatiramer acetate is in FDA Pregnancy Category B (animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect [other than a decrease in fertility] that was not confirmed in controlled studies in women in the first trimester [and there is no evidence of a risk in later trimesters]). Interferon beta and natalizumab are Category C (either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women, or studies in women and animals are not available). Mitoxantrone is Category D (there is positive evidence of human fetal risk, but the benefits from its use in pregnant women may be acceptable despite the risk). For women who want to get pregnant, the first step is to discuss what is known about pregnancy and MS. For women on interferon, it should be discontinued 1 to 2 months before the woman wants to start trying to get pregnant because of the known abortifacient potential of this class. As for any woman, the use of prenatal vitamins and folic acid supplementation is recommended prior to and during pregnancy. If a pregnancy is discovered while the woman is on a DMT, the treatment should be stopped immediately. The potential effects of using these therapies while breast-feeding are unknown. Consequently, it should be recommended that they not be used while breast-feeding.

Management of the postpartum patient can be challenging. However, 72% of women will not have a relapse in the 3 months after pregnancy.[157] In the Pregnancy in Multiple Sclerosis study, the best predictors of which patients were most likely to experience a postpartum relapse were the prepregnancy relapse rate, relapse rate during pregnancy, and a higher disability score.[157] In other words, those with active disease before and during pregnancy were most likely to have a postpartum relapse. The decision about whether to forego breast-feeding in order to resume a DMT after delivery should depend on the clinician's estimate of the likelihood of a postpartum relapse, the severity of prior relapses, and the patient's preferences.

One strategy that has been employed to try to decrease postpartum relapses is the use of IVIG. In a retrospective analysis of patients treated with different IVIG regimens during and/or after pregnancy, one group found a lower relapse rate compared to untreated patients.[158] A prospective randomized trial of postpartum IVIG was performed for the purpose of identifying an optimal dose.[159] The first group received one dose of 150 mg/kg IVIG and the second group received 450, 300, and 150 mg/kg on days 1, 2, and 3 after delivery, respectively. Both groups then received 150 mg/kg of IVIG every 4 weeks for five treatments. The treatment regimens did not differ with respect to the outcome of the number of patients remaining relapse-free in the first 3 months postpartum. The postpartum relapse rate was not significantly higher than the relapse rate before pregnancy, leading the authors to conclude that IVIG appears to decrease the postpartum relapse rate.

Treating the Pediatric MS Patient

Although MS classically has its onset in early adulthood, approximately 3% to 10% of cases will have onset before age 18.[160] In some instances it can initially be difficult to differentiate pediatric MS from conditions such as acute disseminated encephalomyelitis (ADEM). To assist with this, Krupp et al. have published proposed diagnostic criteria for pediatric MS and related conditions.[161] None of the therapies used in MS are FDA approved for use in children. However, based on the same rationale for use in adults, glatiramer acetate and all three forms of interferon beta have been assessed in clinical trials in children.[160] These studies have generally found that the side effect profile in children is similar to that of adults,[162] although children under 10 may be more likely to develop abnormal liver function tests with interferon beta.[162,163] Although these smaller studies were not generally designed to look for treatment effects, most studies have found a lower relapse rate in

the treated group.[162] Data on long-term safety and efficacy are not available.

A recent review by the International Pediatric MS Study Group recommended that immunomodulatory therapy should be started in children with active relapsing-remitting disease.[162] The authors defined this as more than one exacerbation in a period of 1 to 2 years and new T2-hyperintense lesions or gadolinium-enhancing lesions on repeat brain MRI scans over the same time frame. They cautioned that, in patients whose initial episode includes encephalopathy, the use of DMTs should be delayed until a second or third attack with more typical MS features has occurred to avoid giving inappropriate treatment to a child with ADEM. Interferon beta or glatiramer acetate is an appropriate first-line therapy. The choice should be made based on a discussion with the child and parents. IVIG can be considered as an alternative, especially for children under 6 years, in whom there is limited knowledge about the tolerability of these medications.[162] Azathioprine is an option for patients who cannot tolerate injections.[162] Dose adjustment for interferon beta may be necessary for children younger than 10 years or those with a low body weight, especially at the initiation of therapy.[162]

Emerging Targets and Therapeutics

As the pathogenesis of MS has been further elucidated, a variety of novel therapeutic targets have been identified. There are currently over a dozen clinical trials of new therapies and new combinations of therapies for MS. Some treatments aim to modify or suppress the immune system. Other drugs are being tested as putative neuroprotectants. These agents are meant to protect neurons from damage regardless of inflammation-mediated demyelination. Beyond the mechanisms of action, the other area of change is in the route of administration—the newer agents include a number of oral and infusible drugs.

FTY720 (fingolimod) is an agonist to sphingosine-1 phosphate (S1P) receptors on the surface of lymphocytes (specifically the S1P1 receptor). Binding of this receptor results in its internalization, which then prevents normal lymphocyte egress from the secondary lymph organs. This reduces the number of circulating lymphocytes available to mount an autoimmune attack in the CNS. This agent, derived from the fungus *Isaria sinclairii,* has been studied in MS and kidney transplantation patients.[164,165] A Phase II double-blind, placebo-controlled trial randomized 281 patients with RRMS to 1.25 mg or 5 mg of FTY720 or placebo. Patients were followed for 6 months, after which most patients participated in an extension study.[166] There was a significant reduction in relapses and new MRI lesions. Side effects included an increased risk of nasopharyngitis, influenza, headache, and diarrhea. Two Phase III trials are underway.

BG-12 is an oral fumarate that is currently in Phase III clinical trials for RRMS. While the exact mechanism of action is unknown, there is some evidence for an anti-inflammatory effect that ameliorates immune-mediated CNS damage.[167] A promising Phase II trial analyzed three doses of BG-12 (120, 360, and 720 mg) versus placebo and reported a reduction in relapse rate and MRI benefits. The most common adverse events were flushing, gastrointestinal disorders, headache, and nasopharyngitis.

Laquinimod is a synthetic compound with excellent oral bioavailability that is structurally related to linomide. In Phase II and III studies, linomide was effective at preventing new lesions on MRI, but was discontinued due to side effects including myocardial infarction and serositis.[168] A Phase II double-blind, placebo-controlled trial of laquinimod (0.1 and 0.3 mg/day) versus placebo reported a reduction in the appearance of new MRI lesions.[169] Phase III trials will be conducted in order to confirm these results and further evaluate the safety profile in a larger cohort of patients.

Teriflunomide is another oral immunomodulatory agent that inhibits pyrimidine synthesis in T cells.[170,171] After showing promising results in animal models of MS, Phase I and II studies were conducted.[172] A 36-week, double-blind, placebo-controlled trial compared two doses of teriflunomide (7 and 14 mg/day) to placebo. Patients receiving the higher dose of teriflunomide had fewer relapses, fewer new MRI lesions, and less accrual of disability (albeit over a short period).[172] A Phase III trial is currently underway.

Cladribine (Leustatin) is an immunosuppressant that is cytotoxic for resting and proliferating lymphocytes. T lymphocytes are preferentially depleted compared to B cells.[173] Injectable versions of this drug have shown efficacy in RRMS.[174,175] Studies attempting to identify a beneficial effect on progressive forms of MS failed to achieve clinically significant outcomes.[176,177] The major toxicity of this agent has been myelosuppression.[178] Currently, a Phase III trial of oral cladribine in RRMS is underway.

In addition to oral agents, a variety of monoclonal antibodies have shown significant potential in MS. Rituximab (Rituxan) is a chimeric monoclonal antibody that binds to CD20, a molecule on the surface of all B cells except plasma cells. Originally used to treat B-cell lymphoma, this agent has become an attractive therapy for several autoimmune disorders. Indeed, rituximab has been FDA approved for use in certain regimens for rheumatoid arthritis.[179] This treatment causes death of B cells via complement-mediated cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and apoptosis.[180] Given that B cells are a source of IL-6 and TNF-α, depleting the B-cell population with rituximab would also reduce these proinflammatory cytokines. When patients with MS were treated with rituximab, CSF analysis revealed a decrease in the number of B and T cells.[181] Small Phase I and II trials have found a reduction in relapses and new MRI lesion formation.[182,183] Whether this clinical outcome implicates antibodies in the pathogenesis of MS or indicates the importance of B cells as antigen-presenting cells is unclear.

Daclizumab (Zenapax) is a humanized monoclonal antibody that recognizes CD25, the alpha subunit of the IL-2 receptor on T cells. This antibody interferes with IL-2 signaling pathways in T cells, but does not cause apoptosis or cell death.[184] While T-cell function is altered with daclizumab, the number of $CD56^+$ natural killer cells increases. The effect of this cell population on the pathogenesis of MS is unknown, but they may have protective capabilities.[185] Two small open-label studies of daclizumab for patients with RRMS have indicated that the drug is well tolerated and there is a significant improvement in both MRI and clinical end points.[186,187]

Alemtuzumab (Campath) is a monoclonal antibody that recognizes CD52, a molecule found on mature lymphocytes. While the mechanism of action has not been elucidated in vivo, some studies have shown that alemtuzumab can induce apoptosis in lymphocytes.[188,189] It has been approved by the FDA for treatment-refractory chronic lymphocytic leukemia.[190] Multiple open-label studies of alemtuzumab in RRMS and SPMS have shown promising clinical results.[19,21,191] While larger studies are currently underway, some concerning side effects have been identified. Specifically, many patients develop autoimmune hyperthyroidism and infusion reactions.[192,193] Also, there is an increased risk of opportunistic infections with agents such as cytomegalovirus. In data presented at the 59th AAN meeting, the CAMMS223 study comparing alemtuzumab to interferon beta showed a significant reduction in relapses and progression to disability. Adverse events included a significant increase in autoimmune thyroid disease and several unexpected cases of idiopathic thrombocytopenic purpura (ITP).[193,194] Unfortunately, one case of ITP resulted in a fatal intracerebral hemorrhage. The side effect profile may significantly limit this drug's clinical utility.

Various drugs that are currently indicated for the treatment of other conditions have shown promise in MS. In animal studies and small human trials, drugs such as minocycline, statins, and estriol have shown promise as MS therapies.[195-201] Experimental data suggest that minocycline could function as an MMP inhibitor, thereby reducing the migration of lymphocytes into the parenchyma.[202] Statins are thought to have both neuroprotective effects and a capability to alter the permeability of the BBB.[203-205] The sex hormone estriol has been shown to alter chemokine expression and T-cell migration.[206,207] Thus, each of these drugs, as well as many others, is being investigated in clinical trials.

While the majority of therapeutics studied to date suppress or modulate the immune system, more recent strategies have targeted

neuroprotection. Multiple studies have identified axonal loss early in the course of MS, and axonal loss is predictive of the development of disability.[4,208-210] Moreover, in progressive forms of MS, axonal damage appears to be at least partly independent of inflammation, and immunosuppression is usually ineffective. Therapeutically, it would be advantageous to have neuroprotective therapies that could lessen or prevent axonal damage and disability accrual. Several agents have shown promise in early clinical trials. One theory of the cause of neuronal damage is glutamate-mediated excitotoxicity. Riluzole (Rilutek), a glutamate/N-methyl-D-aspartate pathway blocker, was tested in a small group of patients with PPMS. Results suggested a slowing of neuronal loss.[211,212] Use of erythropoietin (Epogen, Procrit) is another potential neuroprotective strategy. When examined in preclinical studies, results suggested that erythropoietin may help maintain neuronal integrity despite intense inflammation.[213] A third neuroprotective strategy is based on the observation that certain sodium channels are implicated in axonal damage.[214] Agents that block sodium channels have shown a benefit in animal models of MS and are progressing to clinical trials.[215-217] These are just a few of the potential strategies that are being investigated from a neuroprotection perspective.

Both immunomodulatory and neuroprotective strategies, however, achieve clinical efficacy by preventing future damage in patients with MS. There are no approved therapies that are targeted at promoting or inducing repair of the damaged nervous system. Restorative therapies currently under investigation include drugs that will promote remyelination and cell-based therapies (e.g., stem cells) that are meant to re-create normal CNS circuitry. There are natural inhibitors of axonal regeneration, such as the Nogo pathway. The Nogo receptor utilizes a series of proteins, such as LINGO-1, to transduce its signal.[218] Strategies that interfere with this signaling pathway may promote regeneration within the CNS after inflammation. Likewise, a multitude of researchers are pursuing cell-based therapies as a way to induce repair within a damaged CNS. Glial-restricted precursor cells have the potential to repair CNS damage from inflammatory processes.[219] These approaches require significant preclinical data before human trials will commence.

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