REVIEW

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CME CREDIT

Multiple sclerosis: Advances in understanding, diagnosing, and treating the underlying disease

ABSTRACT

Recent advances in our understanding of the diagnosis, imaging, pathology, and clinical monitoring of multiple sclerosis (MS) have significantly increased our ability to successfully treat this often perplexing neurologic disorder. Magnetic resonance imaging (MRI) is now integral to the diagnostic process. Treatment of MS can be considered as three parallel pathways: treatment of relapses, symptom management, and long-term prevention of tissue injury.

KEY POINTS

Although MS often has a benign initial clinical course, pathological studies have found significant axonal injury and tissue loss early in the disease.

Symptoms of MS can be subtle and are sometimes confused with those of other disorders or are simply attributed to emotional distress.

MRI has aided the diagnosis and management of MS and is a key outcome measure in early-phase clinical trials in MS.

Although corticosteroids are most effective immediately after the onset of symptoms, we have often found them to be at least partially effective when given several weeks—or even months—after the onset of clinical symptoms.

The choice of disease-modifying therapies remains a clinical judgment that involves consideration of patient preference and concurrent symptomatic issues, including spasticity, depression, or headaches.

Editor's note: This review covers advances in the pathophysiology, diagnosis, imaging, and treatment of the underlying disorder. In a separate article next month, the same authors will address in greater detail the management of the symptoms of multiple sclerosis.

ADVANCES in diagnosis, imaging, pathology, and clinical monitoring have significantly improved our understanding of multiple sclerosis (MS). These advances have supported the development of many effective therapies for MS that appear to slow the disease course.

Although there have been setbacks in the development of therapies for relapsing-remitting MS and although there remains a paucity of treatments for progressive forms of MS, the future promises new hope for patients and clinicians struggling with this disease.

A DISEASE OF YOUNG ADULTS

MS, a chronic disorder affecting the brain, spinal cord, and optic nerve, is the leading cause of nontraumatic disability among young adults. About 300,000 to 350,000 people are

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estimated to have MS in the United States, incurring a cost of about $10 billion per year.[1] Up to 2 million people are affected worldwide. Women with MS outnumber men by 2 to 1. Symptoms typically first develop in the third or fourth decade, but progressive myelopathy due to previously unrecognized MS may not manifest until the seventh or eighth decade.

SYMPTOMS VARY

MS inflammation can occur anywhere in the brain, spinal cord, or optic nerve, and the resulting symptoms can involve a single neurologic function or a combination of them.

Sensory symptoms are among the most common presenting symptoms of MS.[2] Sensory symptoms can consist of an absence of sensation (frank numbness) or can involve positive, uncomfortable sensations, including pain or tingling (paresthesias). Numbness is usually vague and difficult for patients to describe, occasionally being severe enough to impair functional use of an arm or leg despite excellent strength and coordination. Sensory examination is often normal, which contributes to the frequent misattribution of these symptoms to emotional distress.

Up to 90% of MS patients report having fatigue

Motor symptoms in MS typically involve weakness and spasticity. Weakness is usually accompanied by numbness, and spasticity often manifests during the recovery period following an exacerbation. Spasticity can also develop without a previously recognized episode of weakness, particularly in the legs.

Coordination abnormalities can include difficulties in hand dexterity or gait. Gait difficulties can develop from weakness, dyscoordination, spasticity, sensory loss, or a combination of any of these symptoms.

Visual difficulties are another common presentation of MS. Optic neuritis arises from inflammation of the optic nerve, and visual deficits can vary from subtle visual distortion to complete visual loss. Retro-orbital pain or soreness with eye movement is common. Ocular dyscoordination from focal brainstem inflammation (most typically an internuclear ophthalmoplegia) causes diplopia that resolves when either eye is covered.

Bladder dysfunction. MS plaques in the spinal cord commonly cause bladder overactivity, which can manifest as frequency or urgency. Bladder function can also be underactive, with failure to properly store and empty.

Bowel symptoms of urgency and constipation are also common.

Sexual dysfunction can include erectile dysfunction in men and altered libido and genital sensation in both men and women.

Cognitive dysfunction can occur throughout the disease course and often involves problems with concentration, processing speed, executive function (eg, planning), and visuospatial abilities. Formal neuropsychological testing can help identify specific deficits and is helpful to clarify a patient's self-report of cognitive symptoms or to document impairment. Depression is common and can present with primarily cognitive symptoms.

Fatigue is reported by up to 90% of MS patients and is very common at the time of diagnosis. Fatigue may refer to early muscle fatigue with exertion or generalized lassitude independent of exertion. Paradoxically, symptoms of fatigue are inversely proportional to the degree of clinical disability and the amount of brain injury measured on magnetic resonance imaging (MRI).[3]

DISEASE CLASSIFICATIONS

MS is classified on the basis of both the initial and the current clinical disease course. These classifications do not represent separate and distinct disease pathophysiologies, but rather provide a framework for organizing an approach to diagnosis and long-term management. The disease course and tempo vary tremendously among patients.

Relapsing-remitting MS

About 85% of MS patients experience relapsing neurologic symptoms during their initial disease course, and this form is called relapsing-remitting MS.[4] During episodes of inflammation, acute symptoms typically develop over several days, become maximal after 1 to 2 weeks, and gradually resolve over several weeks or months. Residual symptoms may persist indefinitely, especially sensory symptoms. Patients presenting with only a single isolated

episode of inflammation are classified as having a clinically isolated syndrome.

Secondary progressive MS

After 10 to 20 years of relapsing-remitting MS, intermittent relapses typically become infrequent and are usually replaced by gradual worsening of neurologic symptoms over months to years.[5] This stage, called secondary progressive MS, probably represents a neurodegenerative process initiated by earlier episodes of tissue injury (FIGURE 1). Clinical relapses can still occur during secondary progressive MS, particularly during the early transition from relapsing-remitting to secondary progressive MS.

Primary progressive MS

About 15% of MS patients present with gradually progressive neurologic symptoms from the onset, called primary progressive MS. This group is probably a mixture of patients with secondary progressive MS in whom previous foci of inflammation did not affect white matter areas that would cause symptoms if affected or in whom clinical relapses were not recognized or remembered. Other patients with primary progressive MS probably have a primary neurodegenerative process with secondary inflammation.

Devic disease

Inflammation restricted to the optic nerve and spinal cord and sparing the brain is called neuromyelitis optica, or Devic disease. It remains debated whether Devic disease is a separate entity from MS or simply an MS variant.

Recent studies have identified an antibody that binds brain microvessels and meninges, called NMO-IgG, and this antibody appears to be a sensitive and specific indicator of Devic disease.[6] Identification of this specific antibody implicates a primary humoral immune mechanism in Devic disease.

DIAGNOSIS BASED ON MULTIPLE EPISODES

Although several diagnostic criteria for MS have been used over the last several decades, they are all unified by the underlying concept of multiple episodes of inflammation disseminated in time and space.

Natural history of multiple sclerosis

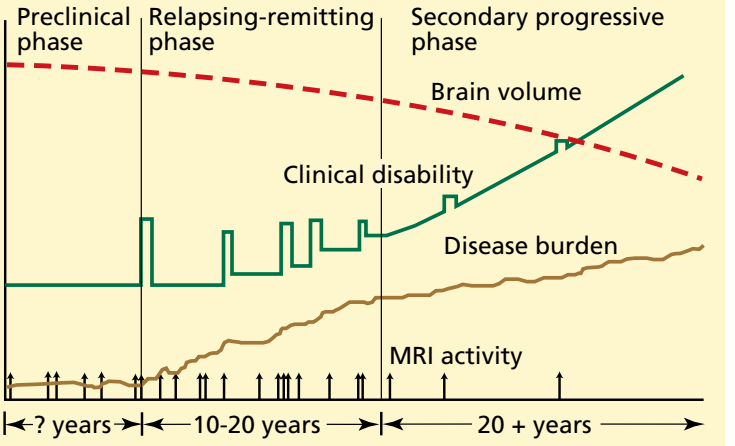

FIGURE 1. Typical clinical and magnetic resonance imaging (MRI) course of multiple sclerosis. MRI activity (vertical arrows) indicates an inflammatory lesion measured on brain MRI. MRI activity typically is more frequent than clinical relapses (spikes in clinical disability). Loss of brain volume, or atrophy, is measured on MRI and indicates permanent tissue damage. Atrophy is observed early in the disease and continues to progress after inflammatory activity has become quiescent. The early inflammatory activity is thought to be replaced later by a neurodegenerative process.

ADAPTED FROM FOX RJ, COHEN JA. MULTIPLE SCLEROSIS: THE IMPORTANCE OF EARLY RECOGNITION AND TREATMENT. CLEVE CLIN J MED 2001; 68:157–170.

The diagnostic criteria for MS were updated recently and now incorporate MRI of the brain and spine and other paraclinical testing to fulfill the "dissemination in time and space" criteria for definite MS (TABLE 1).[7] Specifically, after a single clinical episode of inflammation such as optic neuritis, a new MRI lesion 3 months or more after the first MRI fulfills the requirement for dissemination in time. Although somewhat complicated, these updated criteria have increased sensitivity in diagnosing MS at an early stage.

MRI is an important tool

MRI is an important tool in evaluating MS patients. Affected patients typically have multiple hyperintense lesions in the cerebral white matter on T2-weighted images.

However, T2 lesions in the deep cerebral white matter and anterior and posterior to the

TABLE 1

International Panel criteria for the diagnosis of multiple sclerosis

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED FOR MS DIAGNOSIS
Two or more attacks; objective clinical evidence of 2 or more lesions	None
Two or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: MRI,* or 2 or more MRI lesions plus positive CSF, or Another clinical attack
One attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by: New MRI lesion, or Second clinical attack
One attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space, demonstrated by: MRI,* or Two or more MRI lesions plus positive CSF; And dissemination in time, demonstrated by: New MRI lesion, or Second clinical attack
Insidious neurologic progression suggestive of MS (ie, primary progressive MS)	Positive CSF, and dissemination in space, demonstrated by: ≥ 9 brain lesions, or ≥ 2 spinal cord lesions, or 4–8 brain lesions and 1 spinal cord lesion; or Abnormal visual evoked potentials, and 4–8 brain lesions; or > 4 brain lesions plus 1 spinal cord lesion; or Dissemination in time, demonstrated by MRI; or Continued progression for 1 year

MRI = magnetic resonance imaging, CSF = cerebrospinal fluid

*MRI criterion for dissemination in space is a single gadolinium-enhancing lesion or nine T2 lesions, in appropriate locations

FROM MCDONALD WI, COMPSTON A, EDAN G, ET AL. RECOMMENDED DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS: GUIDELINES FROM THE INTERNATIONAL PANEL ON THE DIAGNOSIS OF MULTIPLE SCLEROSIS. ANN NEUROL 2001; 50:121–127.

The updated criteria have increased sensitivity in diagnosing MS at an early stage

lateral ventricles are not specific for MS and are often seen in many other conditions, including vascular disease (hypertension, diabetes), migraine, and aging. Lesions are more specific for MS if they are in the corpus callosum, juxtacortical area, brainstem, or adjacent to the body of the lateral ventricles.

Lesions are often round or ovoid, oriented perpendicularly to the lateral ventricle (**FIGURE 2**) and are also referred to as "Dawson fingers." Active inflammatory lesions demonstrate gadolinium enhancement, which indicates breakdown of the blood-brain barrier. Cumulative inflammatory tissue injury leads to tissue destruction, which can be appreciated on imaging as spinal cord and brain atrophy.

Atypical presentations

Some patients present without specific symptoms of an MS relapse but have classic MRI findings of MS. Cerebrospinal fluid studies

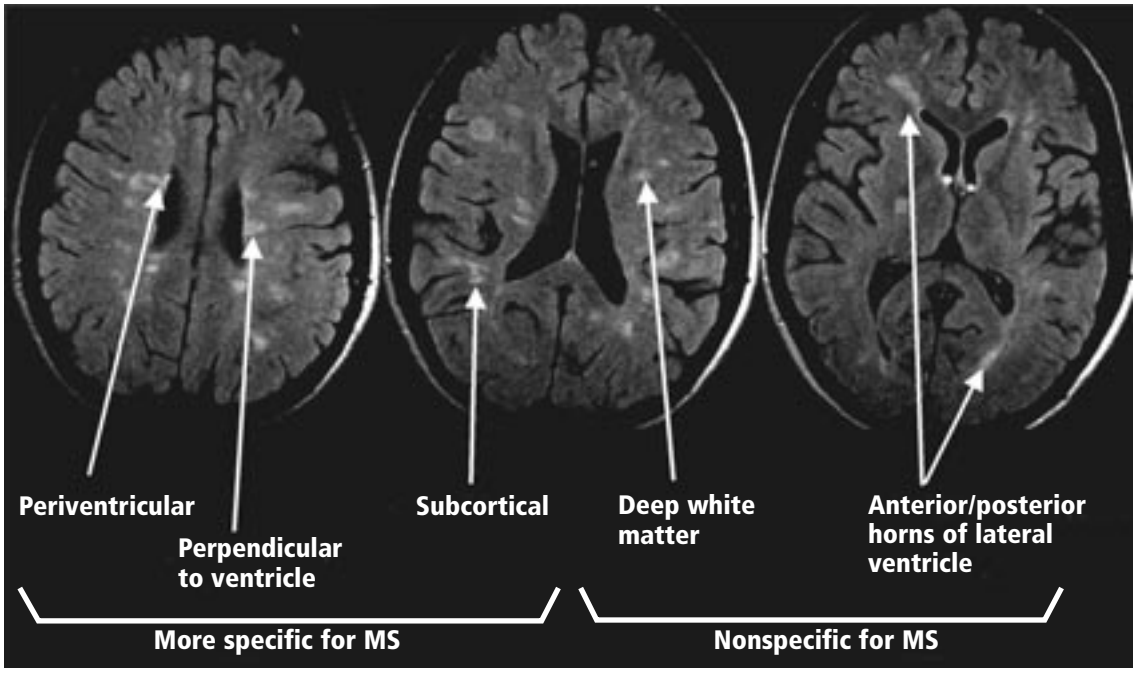

FIGURE 2. Typical T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI images from an MS patient, illustrating different types of cerebral lesions.

and visual evoked potentials can further support the diagnosis of MS in these patients.

Diagnostic criteria continue to require that alternative diagnoses are excluded. Therefore, the diagnosis of MS is ultimately a clinical decision that involves weighing factors that support it *and* those that fail to support it or point to the possibility of an alternative diagnosis.

A limitation in even the most recent diagnostic criteria is that patients with a clinical isolated syndrome with multiple lesions on a single brain MRI do not fulfill the dissemination-in-time criteria. However, several clinical trials have demonstrated that these patients may benefit from MS therapies,[8,9] and so clinical judgment is particularly important when evaluating and treating patients at this very early stage of disease.

Excluding other diagnoses

There is little consensus about which additional studies, particularly blood tests, should be obtained to exclude other diagnoses. The differential diagnosis for a patient with symptoms suggestive of MS is extensive, but most can be excluded on the basis of clinical and radiologic assessments.

Routine laboratory studies could include measuring vitamin B_{12} and thyroid-stimulating hormone levels, serologic testing for syphilis, and a complete blood cell count. The antinuclear antibody (ANA) titer and erythrocyte sedimentation rate are useful to screen for connective tissue disorders, although a low-positive ANA titer can be seen in approximately 25% of MS patients and appears to have no impact on the long-term disease course.[10] Lyme disease titers can be useful in the appropriate geographic setting.

Laboratory studies for suspected MS could include vitamin B_{12}, TSH, syphillis serology, CBC, ANA, and ESR

PATHOPHYSIOLOGY: INJURY OCCURS EARLY

Most clinical relapses are followed by a full or nearly full recovery over the ensuing weeks or months, particularly early in the disease. Previously, this clinical improvement was thought to reflect remyelination, and not until the secondary progressive MS stage was this cycle of inflammation and recovery thought to break down. In the past decade, however, pathologic studies have revealed significant permanent tissue injury during the initial stages of inflammation.

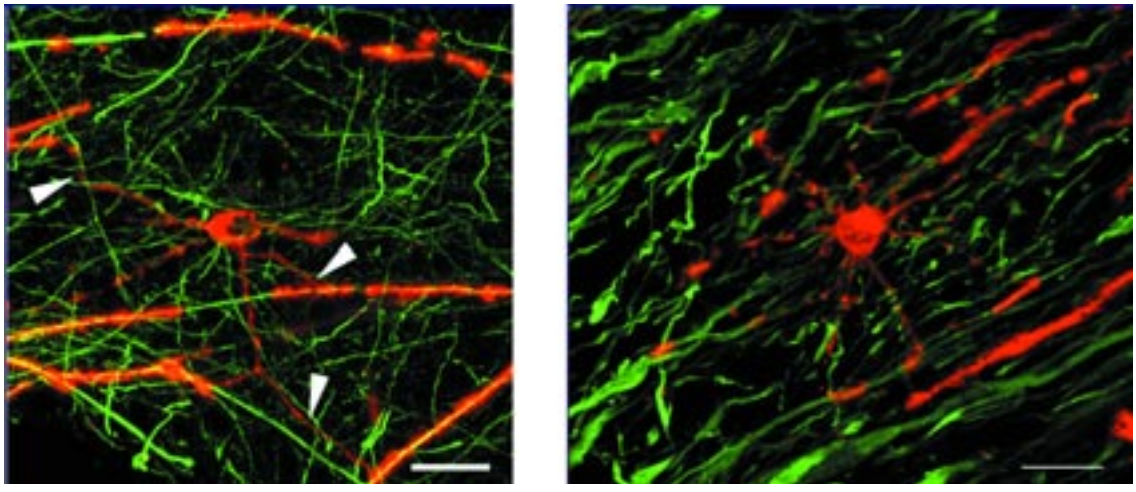

FIGURE 3. A premyelinating oligodendrocyte (red) showing effective myelination (arrows, left), and another showing ineffective remyelination despite appropriate axial extensions. Scale bar represents 20 µm.

FROM CHANG A, TOURTELLOTTE WW, RUDICK R, TRAPP BD. PREMYELINATING OLIGODENDROCYTES IN CHRONIC LESIONS OF MULTIPLE SCLEROSIS. N ENGL J MED 2002; 346:165–173.

Different MS patients have different immunopathologic processes

In acute inflammatory lesions, there is an average of 11,000 transected axons per mm^3, compared with an average of 1 transected axon per mm^3 in unaffected controls.[11] Most tissue injury occurs early in the disease course and can involve the spinal cord and cerebral gray matter.[12,13] Gray matter involvement broadens the previous concept of MS as a "white matter disease."

Functional MRI studies have revealed increased cortical recruitment during simple motor tasks in MS patients. Even in patients with only a single episode of transverse myelitis and minimal brain lesions, there can be significant functional reorganization of the cerebral cortex.[14] These functional MRI studies suggest that recovery from a clinical relapse may involve more than just remyelination. Accordingly, secondary progressive MS may develop when multifocal tissue injury outstrips this compensatory adaptation.

Pathologic studies have also helped us to understand secondary progressive MS. The myelin sheath is an extension of oligodendrocytes, and axons denuded of their myelin sheath probably have impaired survival. Oligodendrocyte progenitor cells are located in the periventricular regions and can migrate into areas of tissue injury and replace injured myelin sheath. In some patients, these cells can successfully remyelinate, while in others these cells extend processes to the axons but are unable to properly remyelinate (FIGURE 3). Importantly, these cells can be observed after decades of disease, so improving their ability to remyelinate is a potential therapeutic target in secondary progressive MS.

Previous models of MS implicated a T-cell pathogenesis, but there is growing recognition of monocyte, macrophage, and humoral mechanisms. Other pathologic studies have described specific, stereotyped immunopathologies within inflammatory lesions of MS patients that utilize various components of the immune system.[15] Despite pathologic heterogeneity between patients, individual patients tend to demonstrate only one immunopathology within all of their lesions. These different immunopathologies may explain the differential response to MS treatments between patients, although methods to identify a patient's specific immunopathology short of brain biopsy have not yet been developed.

The immune targets in MS have remained elusive. Cross-reactivity between an infectious agent and endogenous central nervous system protein is suspected, but no single agent has been conclusively demonstrated.[16]

TABLE 2

Common side effects of high-dose corticosteroids

Metallic taste—candy may help

Insomnia—over-the-counter sleep aids and short-acting benzodiazepines can be helpful

Altered mood—nervousness, restlessness, irritability; rarely, mania

Indigestion/heartburn—minimize aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), caffeine

Fluid retention—minimize salt intake

Potassium depletion (muscle weakness, fatigue)—increase dietary potassium if necessary (eg, bananas, orange juice)

Flushing in face, neck, or chest

Tachycardia

Headaches—use acetaminophen; avoid aspirin and NSAIDs because of possible gastritis

Acute adrenal insufficiency—very rare, but may be prevented by oral prednisone taper

Avascular necrosis—very rare

CLINICAL MONITORING

MS Functional Composite score

Clinical monitoring is an ongoing challenge in the management of MS patients. Since MS affects almost all neurologic functions, it is very difficult to quantify clinical impairment and monitor therapeutic efficacy.

A task force of the National Multiple Sclerosis Society developed a new clinical measure called the MS Functional Composite (MSFC),[17] composed of measures of ambulation, arm and hand function, and cognition. Results from the three individual measures are combined into a single composite score. Studies have found that the MSFC has greater reliability, sensitivity, and statistical validity than the traditional Kurtzke Expanded Disability Status Scale (EDSS), and the MSFC has been used successfully in several large clinical trials to measure disability.[18] The qualitative tests that make up the MSFC also can be useful for following individual patients in clinical practice.

The MSFC score combines measures of ambulation, arm and hand function, and cognition

MRI for monitoring disease activity

MRI is a useful tool to monitor ongoing disease activity in MS patients and has been integrated into general clinical practice. Gadolinium-enhancing lesions and new T2 lesions are typical primary outcomes of phase II clinical trials in relapsing-remitting MS. In clinical practice, MRI can confirm disease activity in patients for whom disease activity is unclear, and persistent MRI activity after starting MS medications can predict long-term clinical activity.[19]

Advanced methods of MRI, ie, diffusion tensor imaging, magnetization transfer imaging, and spectroscopy, hold promise in assessing tissue injury more accurately and in characterizing its recovery following treatment.

TREATING RELAPSES AND SYMPTOMS AND PREVENTING TISSUE INJURY

Treatment of MS can be considered as three parallel pathways: treatment of relapses, symptom management, and long-term prevention of tissue injury. Effective management of MS should include consideration of each of these three areas. We will discuss symptom management in detail in a separate article in this journal.[20]

Treatment of MS relapses

The neuronal injury in acute MS lesions was not previously appreciated because most relapses are followed by complete clinical recovery, even without treatment with acute

TABLE 3

Brief description of MS therapies approved by the US Food and Drug Administration

INTERFERON BETA-1 (Avonex, Betaseron, Rebif)
Identical or nearly identical to human interferon beta-1
Alters inflammatory response through specific receptors
Injection:
- Avonex (intramuscular injection once a week)
- Betaseron (subcutaneous injection every other day)
- Rebif (subcutaneous injection three times a week)

Common adverse effects
- Flu symptoms—myalgia, fever, fatigue, chills
- Skin reaction (subcutaneous preparations only)
- Antibodies (with subcutaneous more than intramuscular preparations)

Uncommon adverse effects
- Aminotransferase elevations
- Anemia
- Depression

Pregnancy category C

GLATIRAMER ACETATE (Copaxone)
Complex random mixture of four polypeptides: ala, glu, lys, tyr
Potential immunochemical mimic of myelin proteins
Alters antigen-specific immune response
Injection: subcutaneous daily
Common adverse effects
- Skin reactions

Uncommon adverse effects
- Systemic reaction (chest pain, shortness of breath, palpitations, vasodilation)
- Anaphylaxis

Pregnancy category B

MITOXANTRONE (Novantrone)
Synthetic anthracenedione
Inhibits DNA replication, which reduces immune cell proliferation
Infusion: once every 3 months to maximum dose of 100–120 mg/m^2
Common adverse effects
- Blue sclera, urine
- Alopecia (usually mild)
- Nausea
- Leukopenia

Uncommon adverse effects
- Decreased cardiac function
- Menstrual irregularities
- Vomiting
- Very rarely: leukemia

Pregnancy category D

NATALIZUMAB (Tysabri)
Monoclonal antibody that inhibits cell trafficking from circulation into central nervous system
Infusion: monthly
Common adverse effects
- Headache
- Fatigue
- Arthralgia

Uncommon adverse effects
- Depression
- Allergic reactions
- Cholelithiasis
- Progressive multifocal leukoencephalopathy

Pregnancy category C

anti-inflammatory therapy. Controlled trials have found that corticosteroid treatment hastens recovery, and that high-dose corticosteroids are more effective than moderate-dose regimens.[21,22]

Although corticosteroids are most effective immediately after the onset of symptoms, we have often found them to be at least partially effective when given several weeks—or even months—after the onset of clinical symptoms. The risks from a short exposure to corticosteroids appear to be reasonable relative to the benefits, although side effects from corticosteroids are common (TABLE 2).

Infections can precipitate relapses and blunt the effectiveness of corticosteroids. Bladder infections are particularly common. Physical therapy can also be beneficial during recovery from a clinical relapse.

Corticosteroid dose. The optimal dose of corticosteroids is unknown, but our typical practice is to give a 3-day course of methylprednisolone 1,000 mg intravenously daily, followed by a 12-day prednisone taper. Extending the methylprednisolone course can be considered, particularly if there is a poor response to the initial 3-day course or if prolonged treatment was necessary previously. There is evidence that equivalent doses of oral corticosteroids have acceptable pharmacokinetics and tolerability, but definitive studies of this route of administration are lacking.[23]

Similarly, the need for prednisone taper remains unknown.

Mild relapses. Some relapses involve only mild sensory symptoms, which are not troublesome to the patient. Given the known tissue damage from MS inflammation, treatment of these mild relapses could be considered, especially if there are new or enhancing lesions on MRI of the brain or spine.

Long-term MS therapies

Four medications approved by the US Food and Drug Administration (FDA) are currently available as first-line therapy for relapsing remitting MS (TABLE 3):

- Interferon beta-1a (two preparations: Avonex 30 µg intramuscularly once a week, and Rebif 44 µg subcutaneously three times a week)
- Interferon beta-1b (Betaseron 250 µg subcutaneously every other day)
- Glatiramer acetate (Copaxone 20 mg subcutaneously daily).[24–27]

Mechanism of action. The precise mechanism of action for each therapy is unknown. The interferon therapies may work by modulating T cells and B cells and altering expression of any of a number of cytokines. Glatiramer acetate is a random polypeptide based on the amino acid structure of a myelin protein and is hypothesized to alter autoreactive regulatory T cells, thereby suppressing immune responses to myelin and other brain antigens.[28]

All four treatments are reasonable options for initial treatment of relapsing-remitting MS. In phase III clinical trials, all of these medications decreased clinical relapses over 2 years by about 30% and reduced the development of new brain lesions on MRI. Several trials were large enough to demonstrate a reduction in progression of disability as measured by the EDSS, and several therapies have been shown to slow the progression of brain atrophy.

Interferon dose. Some studies have suggested that high-dose, high-frequency interferon preparations (ie, Rebif, Betaseron) are more effective than the low-dose, low-frequency preparation (Avonex), but this advantage appears to be limited to the first 6 months of treatment and disappears thereafter.[29,30] High-dose, high-frequency interferon preparations are associated with a higher incidence of skin reactions (redness, swelling, pain), aminotransferase elevations, anemia, and neutralizing antibodies. Therefore, the increased initial efficacy of these preparations needs to be weighed against their tolerability and side effects as well as their similar long-term efficacy compared with the low-dose, low-frequency preparation. Accordingly, the optimal interferon dose for long-term management of relapsing remitting MS remains unclear. All interferon preparations can worsen spasticity, depression, and headaches.

Glatiramer acetate appears to modulate the immune response more than it decreases inflammation. Accordingly, it has a less robust effect than interferons on imaging measures of active inflammation, despite a comparable reduction in clinical relapses. Glatiramer acetate is not associated with aminotransferase elevations, anemia, depression, neutralizing antibodies, or worsening spasticity. Randomized, controlled trials comparing glatiramer acetate to interferons are under way.

The choice of disease-modifying therapies remains a clinical judgment that involves consideration of patient preference and concurrent symptomatic issues, including spasticity, depression, or headaches.

Interferon beta and glatiramer acetate reduced clinical relapses over 2 years by about 30%

Chemotherapy

Mitoxantrone (Novantrone) is a synthetic anthracenedione with demonstrated efficacy in several cancers. It arrests the cell cycle and interferes with DNA repair and RNA synthesis.

Mitoxantrone is effective in reducing clinical relapses and progression of disability in patients with worsening relapsing-remitting MS and secondary progressive MS.[31] Because there is little inflammation in the later stages of secondary progressive MS, the use of mitoxantrone in secondary progressive MS is generally targeted to patients in its early stages who have ongoing inflammation (ie, clinical relapses or gadolinium-enhancing lesions on brain MRI). Mitoxantrone is labeled for intravenous infusion every 3 months, although monthly induction for 3 months is sometimes used in very active disease.

Mitoxantrone-associated cardiotoxicity includes decreased ejection fraction and con-

gestive heart failure. The risk of cardiotoxicity appears proportional to the total lifetime, cumulative dose of the medication, but can occur at any time during mitoxantrone treatment.[32] Multiple gated acquisition scanning (MUGA) or echocardiography should be performed prior to each infusion of mitoxantrone to monitor ejection fraction. Mitoxantrone should not be given if there is a decrease in the ejection fraction to below 50% or a 5% or more decline from baseline measures, except in consultation with a cardiologist.

Blood cancers, particularly secondary acute myelogenous leukemia, have been rarely associated with mitoxantrone.

Because of these adverse effects, mitoxantrone is usually reserved for patients who have not responded sufficiently to or could not tolerate interferon beta-1 and glatiramer acetate treatments.

Cyclophosphamide (Cytoxan) is an alkylating agent related to nitrogen mustards and has been used extensively in various autoimmune disorders, including MS.[33] A recent placebo-controlled trial combining monthly cyclophosphamide and corticosteroids with interferons has confirmed its efficacy in reducing clinical relapses and MRI lesions.[34] Common side effects include mild to moderate alopecia, infertility, nausea, and infections. Uncommon complications include hemorrhagic cystitis, bladder cancer, and possibly other cancers. Aggressive hydration can minimize cystitis, and bladder cancer screening should be considered with chronic use.

Oral chemotherapies. Methotrexate (Rheumatrex) and azathioprine (Imuran) are sometimes used when standard therapies are ineffective, although data from controlled clinical trials are scant. The preferential effect of azathioprine on the humoral immune system has led to its frequent use in Devic disease. Mycophenolate mofetil (Cellcept), another oral agent, has shown reasonable efficacy and tolerability in preliminary studies.[35]

MUGA or echo should be done before each mitoxantrone infusion to monitor ejection fraction

Treating breakthrough disease activity

Although there is general consensus that patients with relapsing MS should consider treatment with one of the four injectable immunomodulating medications,[36,37] there is little consensus on the appropriate treatment for patients who demonstrate breakthrough disease activity on a standard MS therapy. Even the definition of breakthrough disease activity is not clear, although most clinicians integrate clinical relapse rate, recovery from relapses, and MRI measures of ongoing inflammation (gadolinium-enhancing lesions or new T2 lesions) into this judgment.

Treatment options for patients with breakthrough disease activity include switching from one injectable therapy to another and adding medications with or without an injectable therapy (ie, bimonthly pulse intravenous methylprednisolone, oral methotrexate, mycophenolate mofetil, or azathioprine). Several large clinical trials are evaluating these combination therapy approaches. Treatment with intravenous chemotherapy such as mitoxantrone or cyclophosphamide can also be considered.

Natalizumab

Natalizumab (Tysabri) is a monoclonal antibody that blocks very late antigen-4 (VLA-4), which is a cell-trafficking adhesion molecule on the surface of circulating leukocytes. Two large clinical trials found that natalizumab reduced the clinical relapse rate by 53% to 68% over 2 years, and also reduced the progression of clinical disability and development of new brain lesions on MRI.[38–40]

Safety. Initial safety reports indicated that natalizumab was generally well tolerated. Allergic hypersensitivity (ie, generalized urticaria) was occasionally observed (in 1.7% to 4.0%), with about half of the reactions developing after the second infusion. However, natalizumab was withdrawn from clinical use 3 months after its initial FDA approval because of two cases of progressive multifocal leukoencephalopathy (PML) during the patients' 3rd year of natalizumab therapy.[41,42] A third case of PML was identified in a patient treated in a clinical trial for Crohn disease.[43]

PML is a demyelinating brain disorder caused by the ubiquitous JC virus. In the setting of immune compromise (ie, solid-organ transplantation, late-stage acquired immune deficiency syndrome), the JC virus infects the brain and causes widespread demyelination and tissue destruction. In most cases, PML is

fatal, although correcting the immunosuppressed state has stabilized some patients with PML. The magnitude of PML risk, treatment options, and long-term prognosis for MS patients developing PML in association with natalizumab remain unclear.

Natalizumab is significantly more effective than the interferon or glatiramer acetate therapies, but also has potentially fatal complications. The experience with natalizumab highlights the potential risks for rare and unanticipated serious complications from novel, potent therapies. Natalizumab was approved by the FDA under both expedited review and accelerated approval processes, leading to discussion of whether these review mechanisms are appropriate for novel treatments. However, PML was not detected during several large-scale pivotal trials but only during the open-label safety extension study. Therefore, we feel this experience probably attests more to the importance of detailed, long-term safety follow-up studies and the need for a more comprehensive post-marketing surveillance system than to the perils of accelerated FDA review.

Treatment of progressive MS

Treating progressive forms of MS, including secondary progressive MS and primary progressive MS, has remained a challenge. Clinical trials of interferon beta-1 therapies have produced mixed results depending on the stage of secondary progressive MS: the earlier stage of secondary progressive MS appears to respond better, while the middle and later stages responsed only minimally. These results conform to the emerging degenerative pathogenesis concepts of secondary progressive MS.

Clinical trials of anti-inflammatory therapies in primary progressive MS have been similarly disappointing. Intermittent pulses of high-dose corticosteroids or weekly oral methotrexate are sometimes effective in slowing the course of progressive disease, and several randomized clinical trials support their use in this setting.[44–46]

Future therapies in MS

Advances in our understanding of the immunopathogenic mechanism of MS have spurred the development of many novel approaches to treating MS.[47] General immunosuppressants are associated with widespread immunosuppression and generally unfavorable safety profiles. Inhibiting antigen-specific immune activation requires knowledge of the driving antigenic determinant, which remains unclear in MS and likely varies from patient to patient.

Despite the PML complication seen with natalizumab, there remains great interest in cell-trafficking approaches, including inhibition of chemokine receptors such as CCR2, as well as the lymphocyte receptor for sphingosine-1-phosphate. Previous attempts to neutralize immune effector mechanisms in MS such as TNF-alpha have been unsuccessful, but approaches targeting cytokine receptors for interleukin (IL)-1, IL-2, IL-12/23 appear promising.

Identification of the NMO antibody has fueled interest in humoral immune therapies, including the B-cell depletion therapy rituximab.[48] Transplantation of hematopoietic stem cells constitutes an attempt to reset an aberrant immune system, but significant toxicities will limit this approach to only the most severe MS cases.

Oral therapies for long-term MS treatment remain elusive, but several potential approaches have emerged. Statin medications affect immune cell signaling pathways, and if found to be effective, could rapidly be integrated into current treatment.

Treatment of progressive MS will likely require neuroprotective approaches, and these may be beneficial in early disease, too. Neurotrophic cytokines, erythropoietin, and corticosteroids all show potential efficacy as neuroprotective therapies. However, clinical trial methodology to screen candidate therapies and eventually provide convincing evidence for efficacy has not been established.

Natalizumab is more effective than interferon or glatiramer acetate but has potentially fatal complications

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