Highly Aggressive Multiple Sclerosis

By James D. Bowen, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

CITE AS:
CONTINUUM (MINNEAP MINN) 2019;25(3, MULTIPLE SCLEROSIS AND OTHER CNS INFLAMMATORY DISEASES): 689–714.

Address correspondence to Dr James D. Bowen, Multiple Sclerosis Center, Swedish Neuroscience Institute, 1600 E Jefferson St, Ste A, Seattle, WA 98122, *james.bowen@swedish.org*.

RELATIONSHIP DISCLOSURE:
Dr Bowen has served as a consultant for Biogen; Celgene Corporation; EMD Serono, Inc; Genentech, Inc; and Novartis AG and has received personal compensation for speaking engagements from Biogen; EMD Serono, Inc; Genentech, Inc; and Novartis AG. Dr Bowen receives research/grant support from Alexion; Alkermes; Biogen; Celgene Corporation; Genentech, Inc; the National Institute of Allergy and Infectious Diseases (UM1AI110557); the National Institutes of Health/National Institute on Aging (U01AG006781); the National Institutes of Health/National Institute of Allergy and Infectious Diseases (N01AI15416); the National Institute of Neurological Disorders and Stroke (U10NS077309); and Sanofi Genzyme.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Bowen discusses the unlabeled/investigational use of cyclophosphamide, high-dose immunosuppressive therapy with stem cell transplantation, and rituximab for the treatment of highly aggressive multiple sclerosis.

ABSTRACT

PURPOSE OF REVIEW: **Newly introduced disease-modifying therapies offer greater efficacy than previous therapies but also have serious side effects. This article reviews factors useful in identifying those at risk of developing aggressive relapsing multiple sclerosis (MS) and therapies available for treatment.**

RECENT FINDINGS: **Several factors predict aggressive MS, including demographic factors, relapses, symptom characteristics, MRI activity, and other biomarkers. These can be used to select patients for more aggressive therapies, including natalizumab, alemtuzumab, fingolimod, and ocrelizumab. Additional off-label treatments are available for patients with severe disease. The benefits and side effects of these treatments must be considered when making therapeutic decisions.**

SUMMARY: **Selecting patients who are most appropriate for aggressive therapy involves considering risk factors for poor outcomes, early recognition of treatment failure, balancing treatment efficacy and side effects, and sharing the decision with patients to assist them in making optimal treatment choices. Vigilance for signs of treatment failure and early switching to more aggressive therapy are important components in optimal care.**

INTRODUCTION

Treatment options for multiple sclerosis (MS) have expanded remarkably since the introduction of the first disease-modifying therapy in 1993. Newer disease-modifying therapies offer greater efficacy and convenience, but they also have serious side effects. One of the great challenges of treating MS is determining which patients will benefit the most from higher-efficacy, higher-risk treatments. This article discusses risk factors for aggressive MS and reviews higher-efficacy disease-modifying therapies.

RISK FACTORS FOR AGGRESSIVE MULTIPLE SCLEROSIS

Prospectively identifying aggressive MS would allow more appropriate targeting of higher-efficacy, higher-risk therapies. Unfortunately, the ability to predict future courses of individual patients is imprecise. Nevertheless, several risk factors have been recognized that identify patients at higher risk of aggressive disease (TABLE 6-1).

Demographic Factors

Demographic risk factors for MS include male sex, onset after 40 years of age, nonwhite race, and smoking.

MALE SEX. Men with MS reach disability milestones in two-thirds to three-fourths of the time required for women with MS.[1–4] Also, the number of males reaching higher levels of disability is greater than the number of females.[5,6] However, the effects of sex on MS outcomes is modest. Ten years after starting disease-modifying therapy, mean Expanded Disability Status Scale (EDSS)

TABLE 6-1 **Risk Factors for Aggressive Multiple Sclerosis**

Demographic Factors

- **Male**
- **Onset after age 40**
- **Nonwhite race**
- **Smoking**

Clinical

- **Relapse characteristics**
  - Number of relapses
  - Short interval between relapses
  - Incomplete recovery from relapse
  - Unfavorable neurologic symptoms (pyramidal, cerebellar, sphincter, cognitive)
  - Multifocal presentation
- **Disability**
  - Rapidly worsening disability
- **Phenotype of multiple sclerosis**
  - Progression from onset

MRI Characteristics

- **T2 lesion burden**
- **Gadolinium-enhancing lesions**
- **T1-hypointense lesions**
- **Brain atrophy**
- **Infratentorial lesions**
- **Spinal cord lesions**

CSF

- **Oligoclonal bands**

Biomarkers

- **Neurofilament light chain (not commercially available)**

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.

scores were slightly worse in males (0.26 points),[7] with the proportion of males reaching disability milestones 1.17 times higher than females.[8] The time from onset for a 30-year old to reach an EDSS score of 6.0 (needing a cane) was 9.7 years for females and 8.2 years for males.[9] Some studies found no significant association between sex and disability.[10]

AGE AT ONSET, ESPECIALLY IF AFTER AGE 40. Those presenting with MS after age 50 reach disability milestones at least twice as fast as those in their twenties.[1,2] Each decade of age at onset worsens disability on the EDSS by 0.43.[7] The EDSS is a 10-point scale ranging from no disability(0) to death (10).[7] The mean age of onset was 46.4 in those needing a cane by 5 years compared to 35.6 in those who did not.[6] However, a slowly progressive component of MS drives most correlations with age, whereas short-term aggressive inflammation can occur at any age.[11] Modest correlations between age and disability have been found in other studies.[5,8,9] The relationship between age and disability is weakened by confounding variables such as baseline disability or brain atrophy.[10]

NONWHITE RACE. African Americans reach higher levels of disability in about three-fourths of the time of whites.[12] African Americans represented 6.6% of those with nonbenign courses and 3.8% of those with benign courses.[5] The proportion of those with African ancestry requiring a cane was 2.2 to 2.8 times that of whites.[3,4]

SMOKING. Of those not needing a cane by 5 years, 44.5% were smokers; of those needing a cane by 5 years, 64.5% were smokers.[6] A meta-analysis found that smoking increased EDSS scores only slightly, by a mean of 0.15 points. However, the rate at which smokers and nonsmokers reached disability milestones was not statistically different.[13]

Clinical Characteristics

Clinical characteristics that predict the risk of aggressive MS include frequent relapses; shorter interattack intervals; incomplete recovery from attacks; pyramidal, cerebellar, sphincter, or cognitive symptoms; and multifocal onset.

FREQUENT RELAPSES. Relapses during the first year of treatment predict worsening disability or treatment failure in the subsequent 3 years. This risk is almost doubled for those having one attack and tripled for those with two or more attacks.[14] Attacks of MS during the first few years increase the risk of reaching various disability milestones, such as moderate disability in a single neurologic system, limited walking distance, or needing a cane.[1–4] Each attack during these early years further increases the risk of disability.[15] The number of attacks over time (annualized relapse rate) also correlates with poor outcomes.[10] After starting a disease-modifying therapy, continued attacks worsen the prognosis.[7]

SHORTER INTERATTACK INTERVALS. The time to develop difficulty walking was 6.6 years if the interval between the first and second attacks was less than 2 years, 9.6 years if the interval was 2 to 5 years, and 16.1 years if the interval was longer than 5 years (CASE 6-1).[1] Shorter times to reach other disability milestones, such as requiring a cane, are also seen with shorter interattack intervals.[15] Compared to people with longer intervals between attacks, those with less than 2 years

KEY POINTS

- Demographic factors that suggest a more aggressive multiple sclerosis course include male sex, onset after 40 years of age, nonwhite race, and smoking.
- Clinical characteristics that predict the risk of aggressive multiple sclerosis include frequent relapses; shorter interattack intervals; incomplete recovery from attacks; pyramidal, cerebellar, sphincter, or cognitive symptoms; and multifocal onset.

CASE 6-1

A 33-year-old woman developed optic neuritis. One year later, she had an episode of leg weakness. A diagnosis of multiple sclerosis (MS) was confirmed by brain MRI. She was treated with glatiramer acetate, but within 18 months, she had an attack with recurrence of left footdrop, which did not improve with corticosteroids. Three months later, she had another attack, with weakness in the right leg. An MRI showed 10 new lesions, six of which showed gadolinium enhancement (FIGURE 6-1). After a discussion of treatment options, she was switched to natalizumab following a negative JC virus antibody test. Additional JC virus antibody tests were performed every 6 months. Follow-up MRIs at 6 and 18 months were stable.

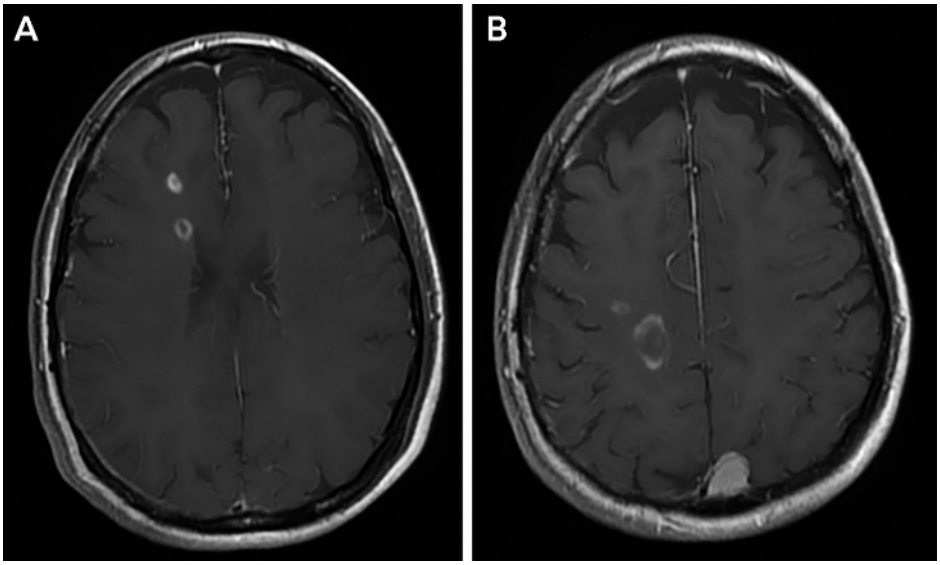

FIGURE 6-1
Axial postcontrast T1-weighted brain MRI demonstrates multiple enhancing lesions in the right frontal (*A*) and right parietal (*B*) regions. Unrelated to multiple sclerosis, an incidental meningioma is present in the left parasagittal parietal lobe.

COMMENT

This case illustrates a patient at high risk of having aggressive MS. Although her initial demographic factors (female with optic neuritis onset) were benign, her subsequent course with two attacks in 2 years was a sign of an aggressive course. Furthermore, she had many new T2 lesions and gadolinium-enhancing lesions. She also developed disability, with the failure of her footdrop to resolve. Her treatment was appropriately escalated to a more aggressive medication.

between the first and second attacks reached moderate disability in about half the time and required a cane in less than one-third the time.[3,4]

INCOMPLETE RECOVERY FROM ATTACKS. In natural history population studies, disability milestones such as moderate disability or requiring a cane were reached in about half the time in those with incomplete recovery.[1,2] The proportion of people reaching these milestones was increased about tenfold in those with incomplete recovery.[3,4] Residual disability as indicated by EDSS score after the onset exacerbation was the single strongest predictor of having difficulty walking after 10 years.[8]

PYRAMIDAL, CEREBELLAR, SPHINCTER, OR COGNITIVE SYMPTOMS. The proportion of people reaching disability requiring a cane is higher if pyramidal or cerebellar systems are involved.[3] The proportion of patients reaching disability milestones is almost 4 times higher in those with residual pyramidal symptoms, 2 times higher in those with residual sphincter dysfunction, 1.5 times higher in those with residual cerebellar dysfunction, and 1.25 times higher in those with brainstem dysfunction.[8] Having motor or cerebellar symptoms at onset increased the risk of disability.[6] However, motor symptoms are highly correlated with age, sex, and progressive onset, which confounds the association.[9] Baseline cognitive changes also predicted greater disability on the EDSS, although the EDSS is primarily a scale of motor dysfunction.[16] Vision symptoms have a more benign prognosis, but this effect was modest after controlling for age, male sex, and progressive onset.[9] Similarly, sensory symptoms have a better prognosis.[6] Sensory symptoms decrease the risk of reaching disability milestones by half.[8] Brainstem symptoms have been associated with disability in some studies but not in others.[1,15]

MULTIFOCAL ONSET. Many studies have suggested that multifocal symptoms at onset increase the risk of disability. However, this has not been found in all studies.[15]

Rapidly Worsening Disability

Those with shorter times from onset to moderate disability have faster onset of disability and more severe disabilities.[15] Baseline EDSS and EDSS progression during the first 24 months were strongly correlated with several measures of disability 8 years later.[10]

Progression From Onset

Progression from onset more than doubles the risk of disability compared to relapsing-onset MS.[8,11] Patients with progressive onset reach disability milestones in approximately one-third to half the time of those with relapsing-remitting onset.[1,2,9] Progressive onset strongly correlates with a nonbenign course.[5]

MRI Characteristics

Characteristics seen on MRI that may indicate a more aggressive MS course include the number and volume of T2 lesions; the presence of gadolinium-enhancing lesions; the volume of T1-hypointense lesions; and the presence of atrophy, infratentorial lesions, or spinal cord lesions.

T2 BURDEN. The number of baseline T2 lesions and new T2 lesions developing over time correlates with future disability.[17] In a study of people with clinically

KEY POINTS

- Rapidly worsening disability and multiple sclerosis that is progressive from onset predict an aggressive course.
- MRI characteristics that predict more aggressive course include the number and volume of T2 lesions; the presence of gadolinium-enhancing lesions; the volume of T1-hypointense lesions; and the presence of atrophy, infratentorial lesions, or spinal cord lesions.

isolated syndrome, the proportion of people reaching moderate disability at 20 years after disease onset was 36% for those with one to three T2 lesions at baseline, 50% for those with four to nine T2 lesions at baseline, and 65% for those with 10 T2 lesions at baseline.[18] In a large European database, having three or more new T2 lesions over 1 year best predicted future disability compared to other MRI parameters.[14] Baseline volume of T2 lesions also predicted future disability,[19] as did the growth of lesion volume over time.[18]

In a multivariate model, the number of new T2 lesions over time was the best MRI predictor of future disability, followed by new enhancing lesions, baseline enhancing lesions, baseline T2 lesion number, and baseline T2 lesion volume.[17] Two measures of lesion location (spinal cord and infratentorial) and two measures of disease activity (baseline gadolinium enhancement and new T2 lesions at 3 months) correlated best with subsequent disability.[17] Other studies suggest that baseline brain volume may be a better predictor than T2 lesion parameters.[10]

GADOLINIUM-ENHANCING LESIONS. Gadolinium-enhancing lesions at baseline and newly developing over time are associated with increased risk of future disability.[17]

T1-HYPOINTENSE LESIONS. Patients with clinically isolated syndrome who were destined to have moderate disability by 5 years had triple the baseline T1 lesion volume compared to those not reaching this level of disability. T1 lesion volume also increased more quickly over time in those developing disability.[19] However, T1 lesion volume may not be as accurate in predicting aggressive MS as T2 lesion number.[17]

ATROPHY. In some studies, brain atrophy correlates poorly with disability.[17] However, in other studies, brain volume strongly correlates with several markers of poor clinical outcome.[10] Patients with higher rates of atrophy were more likely to reach moderate levels of disability at 5 years than those with less atrophy. However, atrophy accounts for only a small portion of the risk of developing disability.[19]

INFRATENTORIAL LESIONS. Infratentorial lesion location is associated with disability, but the strength of the association is weak.[17]

SPINAL CORD LESIONS. The proportion of patients who develop moderate disability is over 5 times greater in those with spinal cord lesions compared to those without spinal cord lesions.[20] Baseline spinal cord lesions and spinal cord lesions that develop over time correlate with disability.[19] Of the MRI locations commonly used in MS diagnosis, the spinal cord correlates the best with disability.[17] However, in patients with clinically isolated syndrome, brain and spinal cord factors were highly correlated, and adding spinal cord factors improved the prediction of disability only slightly.[19]

Cerebrospinal Fluid Characteristics

Oligoclonal bands, indicating active B-cell clones within the central nervous system (CNS), are associated with several markers for aggressive MS.[21] However, the number of bands does not add additional prognostic information

beyond their presence. The production of IgG by CNS plasma cells, as indicated by the IgG index or IgG synthesis rate, increases the risk of an aggressive course[22] with an approximately 50% increase in the rate of developing disability over time.[23] IgM oligoclonal bands and CSF free kappa light chains also predict a more severe course, but these studies are not usually available from clinical laboratories.[24,25]

KEY POINT

● Oligoclonal bands are associated with several markers for aggressive multiple sclerosis.

Neurofilament Light Chain

Many biomarkers have been proposed for MS. However, most have performed poorly or are not available for use in the clinic. Currently, the marker with the most promise is neurofilament light chain. This has usually been measured in CSF, making it impractical as a longitudinal marker. However, an assay using serum is now available. Standardized percentiles based on age (serum neurofilament light chain increases with age) correlate with current EDSS score and with EDSS score worsening at 1 year.[26] This test is not yet commercially available.

Integration of Risk Factors for Future Disability

Using these risk factors to determine future disability in an individual patient remains problematic. Risk factors are often highly correlated and cannot simply be added together. For example, later age of onset, male sex, pyramidal involvement, and progressive onset often occur together, and each factor would not independently contribute to risk. Furthermore, known risk factors account for only a small part of the overall risk in an individual patient. Multivariate analyses found an R^2 of only 0.35 in an 8-year follow-up of a clinical trial cohort.[10] This means that only 35% of the variability between patients could be accounted for based on the included risk factors. Better prediction may be found in combining both initial evaluations and ongoing monitoring. This results in an emphasis on early disabling symptoms (motor, sphincter, increasing EDSS score) and disease activity (clinical or MRI attacks) as the best models.[27]

DEFINING AGGRESSIVE MULTIPLE SCLEROSIS

Many definitions of aggressive MS have been used in clinical research settings.[28] These generally emphasize three markers for aggressive disease: clinical attacks, disability, and MRI activity. The three most common schemata for identifying aggressive disease, the Canadian MS Working Group Assessment, the modified Rio score, and the Multiple Sclerosis Decision Model, are outlined in TABLE 6-2, TABLE 6-3, and TABLE 6-4.[29]

The Canadian MS Working Group Assessment rates changes in relapses, disability, and MRI as having low, medium, or high levels of concern (TABLE 6-2). The Working Group recommends switching to more aggressive therapy if a high level of concern is present in any one domain, a medium level of concern is present in any two domains, or a low level of concern is present in all three domains.[30]

The modified Rio score was developed in patients newly starting disease-modifying therapies.[31] Many measures were analyzed to determine which best predicted outcomes over years 2 to 4. Because many measures were interrelated, the final model retained only two criteria: new T2 lesions and clinical relapses, with points assigned in each category (TABLE 6-3). A patient with a score of 0 has a 24% probability of disability worsening by the end of year 4.

TABLE 6-2 **Canadian Multiple Sclerosis Working Group Assessment for Suboptimal Response to Disease-Modifying Therapies**

	Level of Concern		
Criteria	**Low**	**Medium**	**High**
Relapses			
Rate	One in second year of treatment	One in first year of treatment	More than one in first year of treatment
Severity	Mild: Steroids not required Minimal effect on activities of daily living One functional domain affected No or mild motor/cerebellar involvement	Moderate: Steroids required Moderate effect on activities of daily living More than one functional domain affected Moderate motor/cerebellar involvement	Severe: Steroids/hospitalization required Severe effect on activities of daily living More than one functional domain affected Severe motor/cerebellar involvement
Recovery	Prompt recovery; no functional deficit	Incomplete recovery at 3 months; some functional impairment	Incomplete recovery at 6 months; functional impairment
Disability progression			
EDSS ≤3.5	≤1 point	2 points at 6 months	>2 points at 6 months 2 points at 12 months
EDSS 4.0–5.0	<1 point	1 point at 6 months	>1 point at 6 months 1 point at 12 months
EDSS ≥5.5	NA	0.5 points at 6 months	>0.5 points at 6 months
Clinically documented progression	No motor symptoms; minor sensory symptoms	Some motor, cerebellar, or cognitive symptoms; multiple EDSS domains affected	Pronounced motor, cerebellar, or cognitive symptoms; multiple EDSS domains affected
Timed 25-foot walk	≤20% confirmed at 6 months	>20% and <100% increase confirmed at 6 months	≥100% increase confirmed at 6 months
MRI activity			
New gadolinium-enhancing lesions *OR* Accumulation of new T2 lesions per year	1 lesion	2 lesions	≥3 lesions

EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; NA = not applicable.

Those with scores of 1 have a 33% probability, and those with scores of 2 or higher have a 65% probability.

The Multiple Sclerosis Decision Model (TABLE 6-4) is designed to identify patients who do not attain "no evidence of disease activity" (NEDA). NEDA means no relapse, disability, or MRI activity.[32] This model identifies patients with even minimal activity in these areas.[29] The interpretation scores are color coded for each domain. If all four domains are green, therapy remains unchanged. If one domain is yellow, the patient should be reassessed in 3 months. If two domains are yellow or one is red, an immediate change in therapy should be considered.

TREATMENTS FOR AGGRESSIVE MULTIPLE SCLEROSIS

Currently, seven aggressive treatments for MS are approved by the US Food and Drug Administration (FDA). Phase 3 study results are impossible to compare between these medications because of differences in study design, comparator arm treatments, outcome measures, inclusion criteria, and baseline patient characteristics. The six commonly used aggressive medications are discussed here in order of FDA approval.

Natalizumab

Natalizumab is a humanized monoclonal antibody that binds to the α_4 subunit of two integrin adhesion molecules, $\alpha_4\beta_1$ and $\alpha_4\beta_7$. An IgG4 subclass, it does not fix complement or lyse cells. $\alpha_4\beta_1$ and $\alpha_4\beta_7$ are proteins expressed on the surface of all leukocytes except neutrophils. They bind complementary proteins expressed on endothelial cells: $\alpha_4\beta_1$ to VCAM-1 and $\alpha_4\beta_7$ to MAdCAM-1. Leukocytes exiting the bloodstream bind their complementary molecules on endothelial cells, allowing them to stop, go between the endothelial cells, and enter the target tissue. Natalizumab, by binding to the α_4 subunit, prevents the

Modified Rio Score TABLE 6-3

Criteria	Points Assigned
MRI done at 6 months	
≤5 new T2 lesions	0
>5 new T2 lesions	1
MRI done at 1 year	
≤4 new T2 lesions	0
>4 new T2 lesions	1
Relapse over 1 year	
0 relapses	0
1 relapse	1
≥2 relapses	2

MRI = magnetic resonance imaging.

TABLE 6-4

The Multiple Sclerosis Decision Model[a]

Criteria	Points Assigned	Interpretation[b]
Relapse		0 points = green
Each relapse	3	1–4 points = yellow
Characteristics		≥5 points = red
Functionally relevant	1	
Residual symptoms after 3–6 months	2	
Interval since start or change of therapy		
>12 months	0	
6–12 months	1	
>3 to <6 months	2	
Disability		0 points = green
MS Functional Composite[c]		1 point = yellow
Each test with worsening by 20%	1	≥2 points red
Each test with worsening by 40%	2	
Symbol Digit Modality Test		
Worsening by ≥4 points	1	
Worsening by ≥8 points	2	
Neuropsychology		0 points = green
Fatigue Scale for Motor and Cognitive Functions		1 point = yellow
Worsening by 1 category	1	≥2 points = red
Worsening by 2 categories	2	
Worsening by 3 categories	3	
Depression (HADS)	−1	
Anxiety (HADS)	−1	
Quality of life (MSIS-29)	No points	
MRI		0–2 points = green
Each gadolinium-enhancing lesion	1	≥3 points = yellow
Each new/enlarging T2 lesion	1	

HADS = Hospital Anxiety and Depression Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale-29.

[a] Modified from Stangel M, et al, Ther Adv Neurol Disord.[29] © 2014 The Authors.

[b] The interpretation scores are color coded for each domain. If all four domains are green, therapy remains unchanged. If one domain is yellow, the patient should be reassessed in 3 months. If two domains are yellow or one is red, an immediate change in therapy should be considered.

[c] The MS Functional Composite includes the timed 25-foot walk, the 9-hole peg test, and the low-contrast Sloan letter chart.

leukocyte from adhering to the endothelium cell, thus blocking its exit from the bloodstream. Thus, natalizumab prevents leukocytes from entering the CNS. Natalizumab was approved by the FDA in 2004 for relapsing forms of MS based on the results of the AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis) study, which compared the medication to placebo, and the SENTINEL (Safety and Efficacy of Natalizumab in Combination With Interferon Beta-1a in Patients with Relapsing-Remitting Multiple Sclerosis) study, which compared the medication to weekly interferon beta-1a.[33,34] Common adverse effects of natalizumab are listed in TABLE 6-5.

The most serious adverse effect of natalizumab is progressive multifocal leukoencephalopathy (PML). PML is an infection of oligodendrocytes by the JC virus. The JC virus commonly infects the kidneys, where it remains latent but intermittently becomes active. JC virus entering the bloodstream is easily controlled by the immune system. However, in the setting of mutations making the JC virus more likely to infect the CNS (neurotrophic) and immunosuppression, the virus may gain access to the brain, causing PML. Symptoms of PML resemble MS, including cognitive, motor, sensory, and visual symptoms (CASE 6-2). However, PML slowly worsens over weeks, whereas most MS symptoms worsen over days (for acute exacerbations) or months (for progressive forms of MS). Suspected PML is diagnosed by MRI and confirmed by an ultrasensitive

Important Adverse Effects of Natalizumab TABLE 6-5

Allergic Reactions

- Hypersensitivity 1.9–4%, urticaria 2%
- Anaphylactic/anaphylactoid 0.8%

Liver Injury/Failure

Malignancies

- Melanoma
- Primary central nervous system lymphoma

Infection

- Herpes simplex virus type 1 encephalitis, meningitis
- Varicella-zoster meningovasculitis
- Acute retinal necrosis: herpes simplex virus types 1 and 2, varicella-zoster virus, Epstein-Barr virus
- *Mycobacterium avium* intracellulare
- Aspergillosis
- Cryptococcal fungemia/meningitis
- *Candida* pneumonia
- *Pneumocystis carinii* pneumonia
- *Burkholderia cepacia*
- Cryptosporidial gastroenteritis
- Progressive multifocal leukoencephalopathy

Rebound After Stopping Medication

CASE 6-2

A 52-year-old woman with multiple sclerosis presented with several weeks of difficulty focusing her eyes and subtle cognitive slowing.

Her initial care was at a different institution. When initially diagnosed with multiple sclerosis 8 years ago, she was treated with interferon beta-1a, but she had three additional attacks over 2 years and was switched to natalizumab after 4 years. Her CD4:CD8 ratios were tracked monthly and trended about 1400:750, or approximately 2.0 (normal). She was positive for antibodies against the JC virus at the time that she started the natalizumab, but a JC virus antibody index was not performed. She had received 40 doses of natalizumab at the time of this presentation.

MRI demonstrated changes consistent with progressive multifocal leukoencephalopathy (PML) in the right posterior temporal white matter (FIGURE 6-2). After recognizing that she likely had PML, she was transferred to this institution for specialty care. An ultrasensitive polymerase chain reaction (PCR) for JC virus was positive in her CSF with 272 copies/mL. The natalizumab was discontinued, and five courses of plasma exchange were given. She stabilized and remained stable 3 years later, with fixed cognitive and visual deficits.

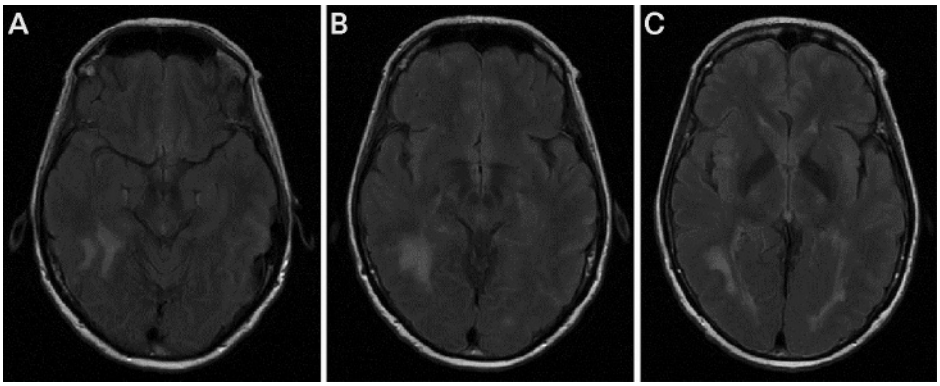

FIGURE 6-2
Axial fluid-attenuated inversion recovery (FLAIR) brain MRI shows a confluent lesion in the white matter of the inferior (*A*), middle (*B*), and superior (*C*) temporal lobe and adjacent regions of the right parietal lobe.

COMMENT

PML presents with symptoms developing over a few weeks. It is diagnosed by MRI and confirmed by ultrasensitive PCR for JC virus in CSF. Risk factors include time on natalizumab, prior use of immunosuppressive medications, and a high JC virus antibody index (>0.9). The JC virus antibody test is reported as positive or negative, but an index may be requested from the clinical laboratory. The index should be followed every 6 months. CD4:CD8 ratios, as had been previously followed in this patient, do not predict PML risk with natalizumab and should not be used for that purpose.

polymerase chain reaction (PCR) test on CSF for the JC virus. Typical MRI findings in PML are one or more hyperintense lesions on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences with a sharp border at the gray-white junction and less distinct borders toward the white matter. Lesions from PML may affect white matter areas of the hemispheres, basal ganglia, external capsule, or posterior fossa. Enhancement may or may not be present.[35] Standard sensitivity PCR testing from most laboratories is inadequate in this setting.

The risk of PML for patients on natalizumab is estimated using three factors: time on natalizumab, prior immunosuppressive medications, and JC virus antibody index. FIGURE 6-3 illustrates how to estimate PML risk.[36,37] Rare cases have occurred in patients without antibodies to the JC virus.[38] Some have advocated extending dosing intervals to 6 to 8 weeks in high-risk patients, but this remains controversial.[39]

Rebound may occur when discontinuing natalizumab, especially 3 to 6 months after the last dose.[40] Up to 27.9% of patients have rebound exacerbations within 6 months, and 37% of these are severe, with the median baseline EDSS score of 3.0 (moderate disability) increasing to 6.0 (requiring a cane). Rebound can be minimized by starting another disease-modifying therapy before the 3- to 6-month rebound period.[41] Many advocate starting another disease-modifying therapy about 4 weeks after the last natalizumab dose.

Before starting natalizumab, obtain liver function tests, a JC virus antibody index, and a brain MRI (for comparison if new PML symptoms develop). During treatment, obtain a JC virus antibody index every 6 months. The dose of natalizumab is 300 mg IV every 4 weeks.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody binding CD52. CD52 is expressed on lymphocytes, natural killer cells, monocytes, and dendritic cells.

KEY POINTS

- The most serious side effect of natalizumab is progressive multifocal leukoencephalopathy. The risk of progressive multifocal leukoencephalopathy is estimated by the duration of natalizumab therapy, prior immunosuppressive use, and JC virus antibody index.
- Rebound can occur between 3 and 6 months after stopping natalizumab. Other disease-modifying therapies should be started before this time to minimize rebound risk.

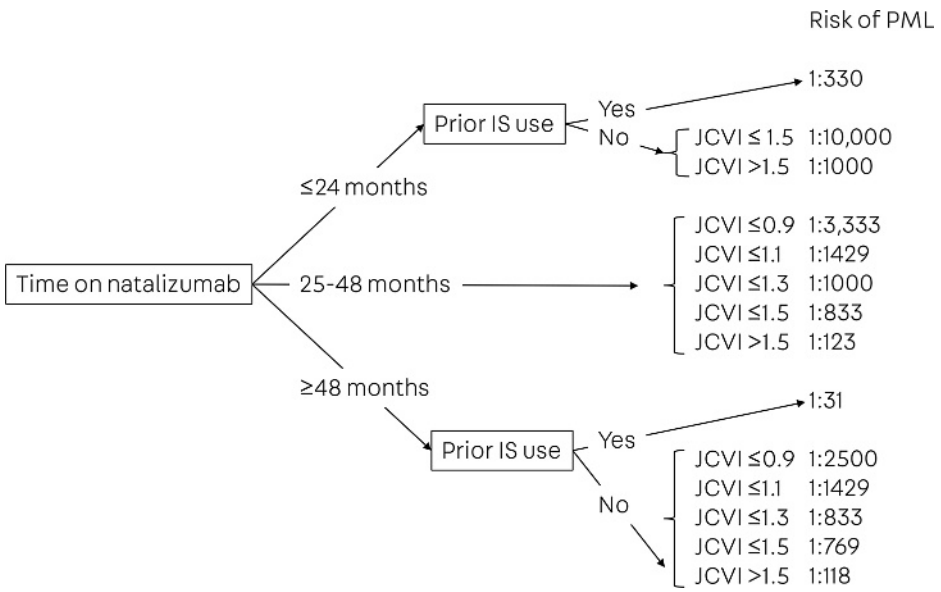

FIGURE 6-3

Risk of progressive multifocal leukoencephalopathy (PML) in patients taking natalizumab. Risk is determined by months on medication, prior use of immunosuppressive medications (IS), and JC virus antibody index (JCVI).[39]

The function of CD52 is poorly understood. Alemtuzumab, an IgG1 subclass, binds complement and lyses target cells. It causes a rapid depletion of all types of lymphocytes. Different lymphocyte types recover at different rates and degrees, causing long-term increases in regulatory and memory T cells, decreased T_H1 and T_H17 cells, and changes in cytokine profiles.[28]

Alemtuzumab was approved by the FDA in 2014 for relapsing forms of MS that had inadequate responses to two or more drugs indicated for the treatment of MS. Two pivotal studies, the CARE MS-I (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis, Study One) and CARE MS-II (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis, Study Two) compared alemtuzumab with interferon beta-1a 3 times a week.[42,43] The CARE MS-II study originally had an arm receiving alemtuzumab 24 mg/d, which was discontinued to increase recruitment into the other arms.

Common adverse effects of alemtuzumab are listed in TABLE 6-6. Infusion reactions with flushing are usually due to a lymphocyte lysis syndrome with cytokine release. However, true anaphylaxis with hives, airway constriction (wheezing), or cardiovascular instability can occur. Autoimmune diseases are

TABLE 6-6 **Important Adverse Effects of Alemtuzumab**

Infusion Reactions: 92%,

Anaphylaxis: 3%

Autoimmunity

- Graves disease: 34%
- Immune thrombocytopenia: 2%
- Autoimmune glomerular nephropathies: 0.3%
- Others (0.2% each): autoimmune hemolytic anemia and autoimmune pancytopenia, undifferentiated connective tissue disorders, anti-Factor VIII antibodies
- Others (0.2% each): rheumatoid arthritis, type 1 diabetes mellitus, vitiligo, retinal pigment epitheliopathy
- Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Malignancies

- Thyroid: 0.3%
- Melanoma: 0.3%
- Lymphoproliferative disorders: lymphoma, mucosa-associated lymphoid tissue lymphoma, Castleman disease, Burkitt lymphoma

Infections: Overall 71% Compared to 53% in Interferon Control

- Herpes: herpes simplex virus types 1 and 2, varicella-zoster virus, herpetic meningitis
- Human papilloma virus: cervical dysplasia (2%)
- Tuberculosis: 0.3%
- Vaginal candidiasis: 12% compared to 3% in interferon control
- *Listeria monocytogenes* meningitis, encephalitis, sepsis, and gastroenteritis

Acute Acalculous Cholecystitis

Hypersensitivity Pneumonitis, Pneumonitis With Fibrosis

presumably caused by imbalances in immune regulation as lymphocytes recover to different degrees. The risk of malignancy is due to decreased immune surveillance.

Before starting alemtuzumab, obtain a complete blood cell count with differential, liver function tests, blood urea nitrogen (BUN), creatinine level, varicella-zoster titer, urinalysis with microscopic examination, and purified protein derivative or QuantiFERON Gold test. A skin examination should also be performed to assess for baseline skin cancers, and all required vaccines should be administered 6 or more weeks before treatment.

During treatment, patients should be premedicated with methylprednisolone 1000 mg IV before each of the first 3 days of the series, an antihistamine (cetirizine 10 mg orally plus diphenhydramine 50 mg IV), and an antipyretic (acetaminophen 500 mg) and given acyclovir 400 mg to 800 mg 2 times a day. Acyclovir should be continued for 2 months or until the CD4 lymphocyte count is 200 cells/mm^3 or higher, whichever is longer. After treatment, a complete blood cell count with differential, creatinine level, and urinalysis with microscopic examination should be conducted monthly until 48 months after the last dose of alemtuzumab. A thyroid function test, including measurement of thyroid-stimulating hormone (TSH), and examination for thyroid nodules, should be performed every 3 months until 48 months after the last dose. A dermatologic examination and testing for the human papilloma virus in women (Papanicolaou test [pap smear]) should be conducted annually. The dose of alemtuzumab is 12 mg/d on 5 consecutive days. One year later, 12 mg/d is given for 3 consecutive days. Pivotal studies were halted before most people received additional doses because of thrombocytopenia. Many patients remain stable without additional doses. However, if relapses occur, 12 mg/d on 3 consecutive days can be given as often as annually.

KEY POINT

- **The side effects of alemtuzumab include immediate infusion reactions, autoimmune diseases, infections, and malignancies.**

Fingolimod

Fingolimod binds the sphingosine-1-phosphate receptor, causing it to be internalized and removed from the cell surface. It binds four of the five sphingosine-1-phosphate receptors but not sphingosine-1-phosphate receptor 2. These receptors are found on immune system cells, endothelial cells, neurons, oligodendrocytes, and astrocytes.[44] Fingolimod's benefit is attributed to its effect on lymphocytes. Naïve and central memory lymphocytes use the sphingosine-1-phosphate receptor to exit lymph nodes. Without this receptor, they get trapped in lymph nodes and removed from the circulation. Effector and effector memory lymphocytes do not traffic through lymph nodes and remain in circulation. Naïve lymphocytes comprise about 80% of circulating lymphocytes, so fingolimod decreases absolute lymphocyte counts by 80%. The 20% remaining are effector cells. The differential sequestration of naïve lymphocytes explains why leukocyte and lymphocyte levels do not correlate with the degree of immunosuppression or side effects with this medication.

Fingolimod was approved by the FDA in 2010 for relapsing forms of MS based on the results of the FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis) study, which compared the medication to placebo, and the TRANSFORMS (Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis) study, which compared the medication to interferon beta-1a weekly.[45,46] The pivotal trials contained a third arm dosed at 1.25 mg/d that was not commercialized (data are not included

here). The FREEDOMS II (Efficacy and Safety of Fingolimod [FTY720] in Patients With Relapsing-Remitting Multiple Sclerosis) study, conducted to include US patients, was used for safety but not efficacy during the FDA submission.

Common adverse effects of fingolimod are listed in TABLE 6-7. After the first dose, the patient's pulse slowly decreases, reaching a nadir at 4 to 5 hours before increasing again. This occurs because fingolimod initially has an agonist effect on cardiac sphingosine-1-phosphate receptors before their removal from the cell surface. After sphingosine-1-phosphate receptor removal, the drug has no effect on heart rate. Blood pressure and pulse should be monitored hourly for 6 hours after the first dose, with an ECG before and after. Symptomatic bradycardia, seen in 0.6%, is treated by having the patient lie recumbent since the pulse will increase over 1 to 2 hours in most cases without treatment. If patients are nonadherent to the medication for 14 days, receptors return in sufficient numbers that first-dose monitoring must be repeated. Drugs that prolong the QT interval are contraindicated before starting fingolimod. After about 2 weeks, most of these medications can be reinstated because the sphingosine-1-phosphate receptors are no longer present. Atrioventricular block can occur following the first dose, usually benign first-degree or Mobitz type I blocks, but rare third-degree blocks have occurred.

TABLE 6-7 **Important Adverse Effects of Fingolimod**

- **Cardiac**
  - **Bradycardia during first dose**
  - **Avoid medications that prolong the QT interval before first dose, including Class Ia and Class III antiarrhythmic medications**
- **Infections**
  - **Herpes**
    - Herpes simplex infection: encephalitis, disseminated infections
    - Varicella-zoster: shingles, disseminated zoster
    - Kaposi sarcoma: (human herpesvirus 8)
  - **Cryptococcal: meningitis, disseminated**
  - **Atypical mycobacteria**
  - **Progressive multifocal leukoencephalopathy**
- **Macular Edema**
- **Posterior Reversible Encephalopathy Syndrome (PRES)**
- **Respiratory Effects**
- **Hepatic Injury**
- **Blood Pressure**
- **Cutaneous Malignancies**
  - **Basal cell**
  - **Melanoma**
  - **Merkel cell**

Overall, infection rates are similar with fingolimod and placebo. However, opportunistic infections have been seen with fingolimod. Herpetic infections occur in 9% of patients treated with fingolimod and 7% of patients receiving placebo. Cryptococcal infections are seen in 1 in 20,000. The current rate of PML is approximately 1 per 12,000, increasing to 1 per 5,000 in those treated longer than 2 years (Overview of Fingolimod in Adults: Efficacy & Safety and Q4 2018 PML Update, November 2018, email communication April 1, 2019). Unlike with natalizumab, no markers are known to predict PML risk with fingolimod. Specifically, lymphocyte counts, CD4:CD8 ratios, and JC virus index do not predict risk.

Macular edema occurs in 0.5% of patients treated with fingolimod and 0.4% of patients on placebo but may be seen in 20% in those with diabetes mellitus or uveitis. Most cases occur within the first 3 to 4 months of treatment. Pulmonary spirometry measures are approximately 2% lower than in placebo and are usually clinically meaningful only in patients with severe baseline pulmonary dysfunction. Transaminase elevation is usually mild, with testing recommended only if hepatic symptoms occur. Elevations in blood pressure average 3 mm Hg systolic, 2 mm Hg diastolic. Basal cell carcinomas are seen in 2% of those treated with fingolimod and 1% on placebo. Periodic skin examination is recommended. Melanoma and Merkel cell carcinomas have been reported.[47]

Before starting fingolimod, obtain a complete blood cell count with differential, liver function tests, BUN and creatinine levels, and varicella-zoster titer. An eye examination for macular edema (optical coherence tomography) should also be performed. First-dose monitoring includes blood pressure and pulse hourly for 6 hours under medical observation and ECG immediately before and after the 6-hour first-dose monitoring. After treatment, eyes should be examined for macular edema 3 to 4 months after starting therapy and if visual symptoms are noted thereafter. Blood pressure should be monitored during office visits.

The dose of fingolimod is 0.5 mg/d. Fingolimod became the first disease-modifying therapy to receive FDA approval in pediatric patients age 10 or older.[48] Patients weighing more than 40 kg (88 lb) take the adult dose of 0.5 mg/d. Those weighing 40 kg (88 lb) or less take 0.25 mg/d.

KEY POINT

- The side effects of fingolimod include first-dose bradycardia. Fingolimod and siponimod may cause macular edema and opportunistic infections, including *Cryptococcus* and progressive multifocal leukoencephalopathy. Risk for infection cannot be assessed using absolute lymphocyte counts.

Siponimod

Similar to fingolimod, siponimod binds the sphingosine-1-phosphate receptor, but, unlike fingolimod, it only binds to subtypes 1 and 5. It was approved by the FDA on March 27, 2019, for relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. This was based on the results of the EXPAND (Exploring the Efficacy and Safety of Siponimod in Patients With Secondary Progressive Multiple Sclerosis) trial of patients with secondary progressive MS.[49]

Common adverse events are similar to those of fingolimod (TABLE 6-7). Variants of cytochrome P450 metabolize siponimod more slowly. This requires CYP2C9*1/*3 or *2/*3 genotype testing before initiation of therapy because patients with these variants should receive half of the normal dose. Patients who are homozygous for the CYP2C9*3/*3 genotype should not receive the drug. Unlike fingolimod, siponimod is initiated with a 4-day upward titration. As a result, first-dose monitoring is required only for those with sinus heart rates less than 55 beats/min, first- or second-degree atrioventricular block, or a history of myocardial infarction or heart failure. The maintenance dose of siponimod is 2 mg/d, except in those with CYP2C9*1/*3 or *2/*3 genotype, who should take 1 mg/d.

Ocrelizumab

Ocrelizumab, a humanized monoclonal antibody directed against CD20, is an IgG1 subclass that fixes complement and lyses cells. The function of CD20 is uncertain, but it is found predominantly on B cells. It is not expressed on stem cells, early pro-B cells, plasmablasts, or plasma cells. Since plasma cells are spared, antibody levels are minimally affected. It is assumed that ocrelizumab's mechanism of action relates to the role of B cells in presenting antigens to T cells and producing cytokines. A small subset of T cells have CD20, but their function is unclear.

Ocrelizumab was approved by the FDA in 2017 for relapsing MS based on the result of the OPERA (A Study to Evaluate the Efficacy and Safety of Ocrelizumab in Comparison to Interferon-β-1a in Patients With Relapsing Multiple Sclerosis) I and OPERA II studies, which compared the medication to interferon beta-1a 3 times a week.[50] It is also approved by the FDA for primary progressive MS based on the results of the ORATORIO (A Study of Ocrelizumab in Patients With Primary Progressive Multiple Sclerosis) study, which compared the medication to placebo.[51] Common adverse effects of ocrelizumab are listed in TABLE 6-8. Infusion reactions, seen in 34% to 40%, are primarily B-cell lysis syndromes with flushing and throat irritation. These are most common with the first infusion and less common with subsequent infusions because few B cells remain. Symptoms usually respond to slowing the infusion rate so that cells do not lyse so rapidly. Anaphylaxis with hives, airway obstruction, or cardiovascular instability is seen in 0.3%.

Infections are higher in ocrelizumab (58%) compared to interferon (52%). Upper and lower respiratory infections are modestly higher. Herpes infections are more common with ocrelizumab compared to interferon, including varicella-zoster (2.1 versus 1.0%), oral herpes (3.0 versus 2.2%), and genital herpes (0.1 versus 0%). PML and reactivation of hepatitis B are listed as risks with ocrelizumab, but no cases have been seen to date. They have occurred with rituximab, another anti-CD20 agent, but in people with hematologic

TABLE 6-8 **Important Adverse Effects of Ocrelizumab**

Infusion Reactions

Infections

- **Hypogammaglobulinemia**
- **Upper/lower respiratory infections**
- **Herpes**
  - Varicella-zoster
  - Human herpesviruses 1 and 2
  - Pasteurella
- **Progressive multifocal leukoencephalopathy**
- **Hepatitis B reactivation**

Malignancies

- **Breast (refer to article text for details)**

malignancies or in those receiving multiple immunosuppressive medications, both of which can contribute to the occurrence of these infections. The risk of PML is estimated to be 1 in 30,000 with rituximab.[52] It is uncertain whether ocrelizumab increases the risk of malignancies. The risk of all malignancies was 1.3% with ocrelizumab, 0.24% with interferon, and 0.8% with placebo. Breast cancer occurred in 6 of 781 women compared to none with placebo.[50,51] However, this number is well within the expected rate for age-matched women, and zero is lower than expected. Postmarketing breast cancer rates have remained stable and within the expected range.

Before starting ocrelizumab, obtain hepatitis B serology. Although not required, some obtain varicella-zoster virus titers and IgG levels. Ocrelizumab is given intravenously. The first course is two doses of 300 mg, given 2 weeks apart; subsequent courses are 600 mg given once every 6 months.

Cladribine

Cladribine, a purine analogue, is metabolized to its active form and concentrated in lymphocytes and monocytes but not in other cells. Single-stranded DNA breaks cannot be repaired, eventually resulting in cell death. The FDA application for cladribine was withdrawn in 2011 because of malignancy concerns. With additional data now available, cladribine was approved by the FDA on March 29, 2019. Approval was based on the results of the CLARITY (A Safety and Efficacy Study of Oral Cladribine in Subjects With Relapsing-Remitting Multiple Sclerosis [RRMS]) study that compared cladribine to placebo in patients with relapsing-remitting MS.[53] The ORACLE MS (Oral Cladribine in Early Multiple Sclerosis [MS]) study evaluated cladribine in those with clinically isolated syndrome, but side effects precluded an FDA approval for this indication.[54] It is approved for relapsing-remitting disease and active secondary progressive disease in those who have had an inadequate response to or are unable to tolerate an alternate drug.

Common adverse effects are listed in TABLE 6-9. Malignancies remain a concern, with 0.27 events per 100 person-years with cladribine and 0.13 events per 100 person-years with placebo. A variety of cancers was seen, consistent with

Important Adverse Effects of Cladribine TABLE 6-9

Lymphopenia

Neutropenia

Infections

- Varicella-zoster
- Progressive multifocal leukoencephalopathy
- Hepatitis B and C reactivation
- Tuberculosis reactivation

Malignancies

Rash

Alopecia

an effect on immunosurveillance rather than direct toxicity to a particular organ. Because of the risk of teratogenicity, both males and females should use effective contraception for 6 months after the last dose of treatment. Liver injury with transaminase elevations has been seen in 0.3% of patients. Cases of acute cardiac failure with myocarditis have been reported with cladribine.

The dose of cladribine is 1.75 mg/kg per year, taken as 10 mg/d to 20 mg/d for 4 to 5 days in week 1 and week 5. The dose is repeated 1 year later. No treatment is given in years 3 and 4. Oral tablets are 10 mg.

Mitoxantrone

Mitoxantrone, an anthracenedione chemotherapy agent, intercalates into DNA and blocks type II topoisomerase. This disrupts DNA replication, causes DNA strand breaks, and inhibits DNA repair. It is rarely used now in the United States because of toxicity, primarily cardiotoxicity and acute myelogenous leukemia, and the availability of safer alternative medications.

Daclizumab

Daclizumab received FDA approval in 2016 but was voluntarily withdrawn from the market in March 2018 because of inflammatory encephalitis/meningoencephalitis, some of which was eosinophilic. It is mentioned here for completeness.

INVESTIGATIONAL AND OFF-LABEL THERAPIES

In addition to FDA-approved therapies, several medications have been used off-label in patients with aggressive MS. These include cyclophosphamide, rituximab, and high-dose immunosuppressive therapy followed by hematopoietic stem cell transplantation.

Cyclophosphamide

Cyclophosphamide, a nitrogen mustard alkylating agent, cross-links DNA, leading to apoptosis independent of cell cycle. Aldehyde dehydrogenase, which catabolizes the drug, is present in most cells, including bone marrow stem cells. This allows the marrow to recover, even after large doses. It is a broad suppressor of immune cells and their cytokines.

Studies of cyclophosphamide in MS are relatively small. Some suggest very positive results, especially in earlier disease,[55] while others suggest little long-term effect.[56,57] A high-dose protocol has also been proposed.[58]

Side effects include immunosuppression, myelosuppression, gonadotoxicity, nausea, alopecia, ototoxicity, cardiac toxicity, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Hemorrhagic cystitis can be minimized with high levels of hydration and by administering mesna. Several types of malignancies, especially hematologic and bladder, are more common after cyclophosphamide. Malignancies and gonadotoxicity limit the lifetime cumulative dose to 80 g to 100 g.

Cyclophosphamide is typically dosed as follows:

- **Induction: 600 mg/m^2 IV plus methylprednisolone 1000 mg/d IV for 5 days (or every other day) followed by 700 mg/m^2 IV every other month for 2 years**
- **High-dose cyclophosphamide (HiCy) induction: 50 mg/kg/d IV for 4 days, then 5 mcg/kg/d IV granulocyte colony-stimulating factor**

Rituximab

Rituximab is a chimeric antibody against CD20, similar to ocrelizumab.[59,60] It has less antibody-dependent and more complement-dependent cytotoxicity than ocrelizumab and a different binding site on the CD20 molecule. It is more highly immunogenic than ocrelizumab. The mechanism of action is similar. Efficacy in relapsing-remitting MS was studied in the phase 2 HERMES (Helping to Evaluate Rituxan in Relapsing-Remitting Multiple Sclerosis) trial in 69 patients treated with rituximab and 35 patients who received placebo.[61] The primary end point, the mean number of gadolinium-enhancing lesions over 24 weeks, was 5.5 in the placebo arm and 0.5 in the rituximab arm. Benefit was also seen in T2 lesions and exacerbations. Rituximab is substantially cheaper than ocrelizumab. The typical dose used in MS is 500 mg or 1000 mg IV every 6 months. Rituximab is not approved for use in MS by the FDA.

High-dose Immunosuppressive Therapy With Stem Cell Transplantation

High-dose immunosuppressive therapy with stem cell transplantation uses high-dose chemotherapy to ablate the immune system, then reconstitutes the immune system with stem cells from the patient. This leads to long-lasting shifts in immune cell populations, cytokine profiles, and removal of dominant T-cell clones.[62] The effectiveness of high-dose immunosuppressive therapy with stem cell transplantation in producing NEDA approaches 70% at 5 years, about twice as effective as other highly aggressive therapies.[63] Serious side effects include 2.8% transplant-related mortality within the first 100 days.[64] Steps in the process include the following:

- Stem cell mobilization with granulocyte colony-stimulating factor or immunosuppressants
- Collection of stem cells by leukapheresis
- Conditioning regimen (high-dose chemotherapy); one of the following three regimens are commonly used:
  - Busulfan plus antithymocyte globulin, which is highly myeloablative and has risks of myelosuppression and veno-occlusive liver disease
  - Carmustine, etoposide, cytarabine, and melphalan plus antithymocyte globulin (BEAM/ATG), which has intermediate myeloablation and risk of myelosuppression
  - Cyclophosphamide plus antithymocyte globulin, which is nonmyeloablative and includes the same risks described in the cyclophosphamide section above
- Infusion of stem cells and reconstitution of the bone marrow

A Canadian study using the busulfan/antithymocyte globulin[65] conditioning regimen showed activity-free survival at 3 years of 69.6%; one death from veno-occlusive disease occurred. The HALT-MS (High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis) study used carmustine, etoposide, cytarabine, and melphalan /antithymocyte globulin[66] as the conditioning regimen and showed event-free survival at 5 years of 69.2%. In another study, patients for whom traditional therapy had failed either received another disease-modifying therapy determined by their treating physician or received a transplant using the cyclophosphamide/antithymocyte globulin[67] conditioning regimen. The primary end point, time to worsening of disability, was 24 months in the disease-modifying therapy arm. Time to worsening disability could not be calculated in the high-dose

KEY POINTS

- The side effects of ocrelizumab include infusion reactions, infections (especially herpes infections), and possible malignancy; progressive multifocal leukoencephalopathy and reactivation of hepatitis B are theoretical risks, but thus far no cases have been seen.
- Cladribine is an oral immunosuppressant that was recently approved by the US Food and Drug Administration. Side effects include infections and malignancies.
- Mitoxantrone's use has been limited by cardiotoxicity and acute myelogenous leukemia.
- Cyclophosphamide is widely available and has some evidence to support its use, but definitive trials have not been performed.
- Rituximab's mechanism of action and side effects are similar to those of ocrelizumab. Rituximab is not US Food and Drug Administration approved for multiple sclerosis, but many have used it off-label because it is less expensive than ocrelizumab.
- High-dose immunosuppressive therapy with stem cell transplantation is the most aggressive therapy available for multiple sclerosis today. Outcomes are possibly double the rate of "no evidence of disease activity" of other therapies. Thus far, only phase 2 studies have been completed.

immunosuppressive therapy with stem cell transplantation arm because there were too few events.

The more myeloablative regimens are believed to have better disease control, but this comes at the cost of side effects. Over half of the transplants for MS worldwide use intermediate myeloablative regimens, with 18.9% using high-intensity and 17.4% using low-intensity regimens.[64] The best results are seen in those younger than 32 years of age with relapsing-remitting MS for whom no more than two prior therapies have failed (CASE 6-3).[64]

APPROACH TO AGGRESSIVE THERAPY

Current knowledge is insufficient to predict which patients would most benefit from early aggressive therapy. Future studies, for example, TREAT-MS (Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial), comparing early aggressive therapy with traditional therapy should

CASE 6-3

A 17-year-old girl presented with diplopia in 2000. An MRI was obtained at that time, which showed multiple periventricular and juxtacortical lesions, one of which enhanced, leading to a diagnosis of multiple sclerosis. She had a relapsing-remitting course of diplopia, optic neuritis, leg weakness, paresthesia, and fatigue. Treatment with interferon beta-1a subcutaneous and glatiramer acetate were unsuccessful because of recurrent attacks. She was switched to mitoxantrone, receiving a 96 mg/m^2 total cumulative dose between 2002 and 2004. She went back on glatiramer acetate but continued to have attacks. She was then switched to natalizumab in 2010, but it was discontinued after 25 doses because she tested positive for JC virus antibodies. She continued to have attacks despite fingolimod, dimethyl fumarate, and cyclophosphamide. MRIs performed after these treatments showed multiple enhancing lesions in the cortical white matter (FIGURE 6-4).

She then underwent high-dose immunosuppressive therapy followed by autologous hematopoietic stem cell transplantation using a carmustine, etoposide, cytarabine, and melphalan plus antithymocyte globulin (BEAM/ATG) protocol in 2014. She had no new clinical exacerbations and stable MRI images without enhancement 4 years after this procedure.

COMMENT

This case illustrates the potential for high-dose immunosuppressive therapy with stem cell transplantation to control inflammatory disease activity in some patients with aggressive disease despite prior treatment with highly efficacious therapies. This patient had both clinical and MRI attacks. Early use of aggressive therapies included mitoxantrone, natalizumab, fingolimod, and cyclophosphamide. Despite these, she continued to have exacerbations. High-dose immunosuppressive therapy followed by autologous hematopoietic stem cell transplantation was successful in controlling her disease.

provide better guidance.[68] Until further data are available, the following approach is suggested:

- **Consider initial aggressive therapy (natalizumab, fingolimod, ocrelizumab, alemtuzumab) for patients who appear to be at high risk for aggressive disease and early disability**
- **Consider switching patients to more aggressive therapy in the presence of breakthrough disease (exacerbations, MRI activity, or worsening disability)**
- **Periodically evaluate neurologic examination and MRI to assess breakthrough disease**
- **Monitor patients so that side effects can be detected as early as possible**

Ultimately, the patient must participate in the decision-making process. This requires the physician to educate patients about benefits and side effects of each treatment option so that patients can decide what level of risk they want to assume in return for higher efficacy.

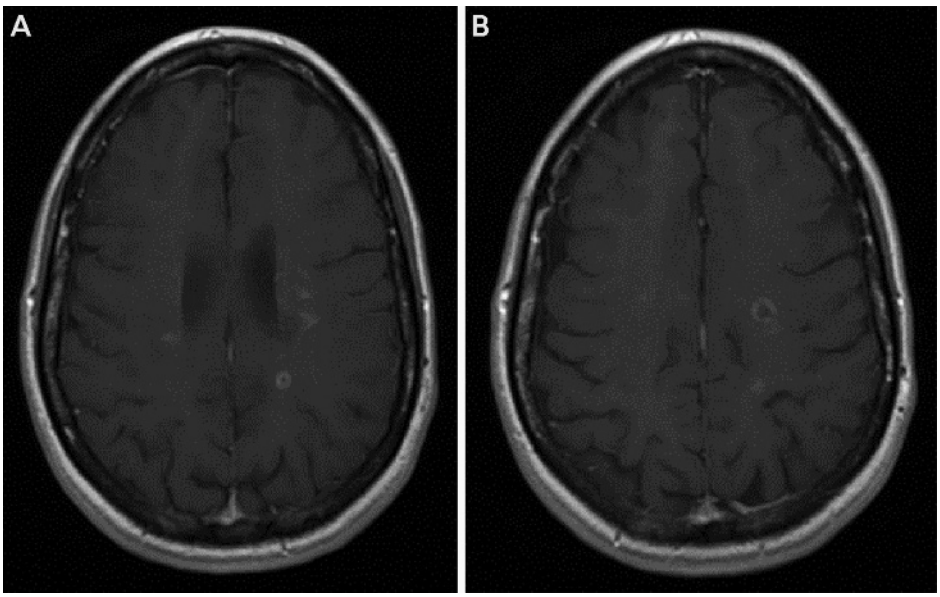

FIGURE 6-4
Axial postcontrast T1-weighted MRI demonstrates multiple enhancing lesions in the white matter of both periventricular regions (*A*) and the left periventricular region (*B*).

CONCLUSION

A number of factors can help identify patients at risk for aggressive MS. Older nonwhite males with motor, sphincter, and cognitive symptoms have more aggressive disease, as do those with disease activity on MRI. These patients can consider using early or even initial aggressive therapies. Patients for whom other therapies fail should consider switching to more aggressive disease-modifying therapies. However, these treatments have greater side effects that must be balanced against their increased efficacy. It is hoped that upcoming randomized trials will provide more answers on balancing efficacy and side effects during early use of these treatments. Until these results are available, use of these medications will require the participation of patients in decision making, monitoring of disease activity, and vigilance regarding complications.

REFERENCES

1 Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003;126(pt 4):770–782. doi:10.1093/brain/awg081.

2 Leray E, Yaouanq J, Le Page E, et al. Evidence for a two-stage disability progression in multiple sclerosis. Brain 2010;133(7):1900–1913. doi:10.1093/brain/awq076.

3 Vasconcelos CC, Aurenção JC, Thuler LC, et al. Prognostic factors associated with long-term disability and secondary progression in patients with multiple sclerosis. Mult Scler Relat Disord 2016;8:27–34. doi:10.1016/j.msard.2016.03.011.

4 Hampshire-Araújo F, Bergmann A, Alvarenga RM, Vasconcelos CC. Malignant multiple sclerosis: clinical and demographic prognostic factors. Arq Neuropsiquiatr 2017;75(3):139–141. doi:10.1590/0004-282X20170010.

5 Zivadinov R, Cookfair DL, Krupp L, et al. Factors associated with benign multiple sclerosis in the New York State MS Consortium (NYSMSC). BMC Neurol 2016;16(1):1–10. doi:10.1186/s12883-016-0623-2.

6 Gholipour T, Healy B, Baruch NF, et al. Demographic and clinical characteristics of malignant multiple sclerosis. Neurology 2011; 76(23):1996–2001. doi:10.1212/WNL.0b013e31821e559d.

7 Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. Ann Neurol 2016;80(1):89–100. doi:10.1002/ana.24682.

8 Amato MP, Ponziani G, Bartolozzi ML, Siracusa G. A prospective study on the natural history of multiple sclerosis: clues to the conduct and interpretation of clinical trials. J Neurol Sci 1999; 168(2):96–106. doi:10.1016/S0022-510X(99)00143-4.

9 Weinshenker BG, Rice GP, Noseworthy JH, et al. The natural history of multiple sclerosis: a geographically based study. 3. Multivariate analysis of predictive factors and models of outcome. Brain 1991;114(pt 2):1045–1056. doi:10.1093/brain/114.2.1045.

10 Traboulsee AL, Cornelissea P, Sandberg-Wollheim M, et al. Prognostic factors for long-term outcomes in relapsing-remitting multiple sclerosis. Mult Scler J Exp Transl Clin 2016;2: 205521731666640. doi:10.1177/2055217316666406.

11 Menon S, Shirani A, Zhao Y, et al. Characterising aggressive multiple sclerosis. J Neurol Neurosurg Psychiatry 2013;84(11):1192–1198. doi:10.1136/jnnp-2013-304951.

12 Cree BA, Khan O, Bourdette D, et al. Clinical characteristics of African Americans vs Caucasian Americans with multiple sclerosis. Neurology 2004;63(11):2039–2045. doi:10.1212/01.WNL.0000145762.60562.5D.

13 Heydarpour P, Manouchehrinia A, Beiki O, et al. Smoking and worsening disability in multiple sclerosis: a meta-analysis. Acta Neurol Scand 2018;138(1):62–69. doi:10.1111/ane.12916.

14 Sormani MP, Gasperini C, Romeo M, et al. Assessing response to interferon-β in a multicenter dataset of patients with MS. Neurology 2016;87(2):134–140. doi:10.1212/WNL.0000000000002830.

15 Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain 2010;133(pt 7): 1914–1929. doi:10.1093/brain/awq118.

16 Pitteri M, Romualdi C, Magliozzi R, et al. Cognitive impairment predicts disability progression and cortical thinning in MS: an 8-year study. Mult Scler 2017;23(6):848–854. doi:10.1177/1352458516665496.

17 Swanton JK, Fernando KT, Dalton CM, et al. Early MRI in optic neuritis: the risk for disability. Neurology 2009;72(6):542–550. doi:10.1212/01.wnl.0000341935.41852.82.

18 Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain 2008;131(pt 3):808–817. doi:10.1093/brain/awm329.

19 Brownlee WJ, Altmann DR, Alves Da Mota P, et al. Association of asymptomatic spinal cord lesions and atrophy with disability 5 years after a clinically isolated syndrome. Mult Scler 2017; 23(5):665–674. doi:10.1177/1352458516663034.

20 Arrambide G, Rovira A, Sastre-Garriga J, et al. Spinal cord lesions: a modest contributor to diagnosis in clinically isolated syndromes but a relevant prognostic factor. Mult Scler 2018;24(3): 301–312. doi:10.1177/1352458517697830.

21 Farina G, Magliozzi R, Pitteri M, et al. Increased cortical lesion load and intrathecal inflammation is associated with oligoclonal bands in multiple sclerosis patients: a combined CSF and MRI study. J Neuroinflammation 2017;14(1):1–11. doi:10.1186/s12974-017-0812-y.

22 Stendhal-Brodin L, Link H. Relation between benign course of multiple sclerosis and low-grade humoral immune response in cerebrospinal fluid. J Neurol Neurosurg Psychiatry 1980;43(2): 102–105. doi:10.1136/jnnp.43.2.102.

23 Izquierdo G, Angulo S, Garcia-Moreno JM, et al. Intrathecal IgG synthesis: marker of progression in multiple sclerosis patients. Acta Neurol Scand 2002;105(3):158–163. doi:10.1034/j.1600-0404.2002.1o009.x.

24 Villar LM, Sádaba MC, Roldán E, et al. Intrathecal synthesis of oligoclonal IgM against myelin lipids predicts an aggressive disease course in MS. J Clin Invest 2005;115(1):187–194. doi:10.1172/JCI22833.

25 Rinker JR 2nd, Trinkaus K, Cross AH. Elevated CSF free kappa light chains correlate with disability prognosis in multiple sclerosis. Neurology 2006; 67(7):1288–1290. doi:10.1212/01.wnl.0000238107.31364.21.

26 Disanto G, Barro C, Benkert P, et al. Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis. Ann Neurol 2017; 81(6):857–870. doi:10.1002/ana.24954.

27 Bergamaschi R, Berzuini C, Romani A, Cosi V. Predicting secondary progression in relapsing-remitting multiple sclerosis: a Bayesian analysis. J Neurol Sci 2001;189(1–2):13–21. doi:10.1016/S0022-510X(01)00572-X.

28 Fernández Ó. Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? Mult Scler Relat Disord 2017;17:75–83. doi:10.1016/j.msard.2017.07.003.

29 Stangel M, Penner IK, Kallmann BA, et al. Towards the implementation of 'no evidence of disease activity' in multiple sclerosis treatment: the multiple sclerosis decision model. Ther Adv Neurol Disord 2015;8(1):3–13. doi:10.1177/1756285614560733.

30 Freedman MS, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can J Neurol Sci 2013;40(3):307–323. doi:10.1017/S0317167100014244.

31 Sormani MP, Rio J, Tintorè M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. Mult Scler 2013;19(5):605–612. doi:10.1177/1352458512460605.

32 Hegen H, Bsteh G, Berger T. 'No evidence of disease activity'—is it an appropriate surrogate in multiple sclerosis? Eur J Neurol 2018;25(9): 1107–e101. doi:10.1111/ene.13669.

33 Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354(9):899–910. doi:10.1056/NEJMoa044397.

34 Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med 2006;354(9): 911–923. doi:10.1056/NEJMoa044396.

35 Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. Neurology 2013;80(15):1430–1438. doi:10.1212/WNL.0b013e31828c2fa1.

36 Plavina T, Subramanyam M, Bloomgren G, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol 2014;76(6):802–812. doi:10.1002/ana.24286.

37 Schwab N, Schneider-Hohendorf T, Melzer N, et al. Natalizumab-associated PML: challenges with incidence, resulting risk, and risk stratification. Neurology 2017;88(12):1197–1205. doi:10.1212/WNL.0000000000003739.

38 Gagne Brosseau MS, Stobbe G, Wundes A. Natalizumab-related PML 2 weeks after negative anti-JCV antibody assay. Neurology 2016;86(5): 484–486. doi:10.1212/WNL.0000000000002330.

39 Zhovtis Ryerson L, Frohman TC, Foley J, et al. Extended interval dosing of natalizumab in multiple sclerosis. J Neurol Neurosurg Psychiatry 2016;87(8):885–889. doi:10.1136/jnnp-2015-312940.

40 West TW, Cree BA. Natalizumab dosage suspension: are we helping or hurting? Ann Neurol 2010;68(3):395–399. doi:10.1002/ana.22163.

41 Kappos L, Radue EW, Comi G, et al. Switching from natalizumab to fingolimod: a randomized, placebo-controlled study in RRMS. Neurology 2015;85(1):29–39. doi:10.1212/WNL.0000000000001706.

42 Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012;380(9856): 1819–1828. doi:10.1016/S0140-6736(12)61769-3.

43 Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1829–1839. doi:10.1016/S0140-6736(12)61768-1.

44 Blaho VA, Hla T. An update on the biology of sphingosine 1-phosphate receptors. J Lipid Res 2014;55(8):1596–1608. doi:10.1194/jlr.R046300.

45 Kappos L, Radue EW, O'Connor PN, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362(5):387–401. doi:10.1056/NEJMoa0909494.

46 Cohen JA, Barkhof F, Comi G, et al. ral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010; 362(5):402–415. doi:10.1056/NEJMoa0907839.

47 Gilenya [package insert]. East Hanover, New Jersy: Novartis AG; 2012.

48 Chitnis T, Arnold DL, Banwell B, et al. PARADIGMS: a randomised double-blind study of fingolimod versus interferon β-1a in paediatric multiple sclerosis. In: Proceedings from the 7th Joint ECTRIMS-ACTRIMS Meeting; October 25–28, 2017; Paris, France. Abstract 276.

49 Kappos L, Bar-Or A, Cree BA, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018; 391(10127):1263–1273. doi:10.1016/S0140-6736(18)30475-6.

50 Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376(3):221–234. doi:10.1056/NEJMoa1601277.

51 Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017; 376(3):209–220. doi:10.1056/NEJMoa1606468.

52 Berger JR. Classifying PML risk with disease modifying therapies. Mult Scler Relat Disord 2017;12:59–63. doi:10.1016/j.msard.2017.01.006.

53 Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 2010; 362(5):416–426. doi:10.1056/NEJMoa0902533.

54 Leist TP, Comi G, Cree BA, et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. Lancet Neurol 2014;13(3): 257–267. doi:10.1016/S1474-4422(14)70005-5.

55 Weiner HL, Mackin GA, Orav EJ, et al. Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: final report of the Northeast Cooperative Multiple Sclerosis Treatment Group. Neurology 1993;43(5):910–918. doi:10.1212/WNL.43.5.910.

56 The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. The Canadian Cooperative Multiple Sclerosis Study Group. Lancet 1991;337(8739):441–446. doi:10.1016/0140-6736(91)93389-Q.

57 Likosky WH, Fireman B, Elmore R, et al. Intense immunosuppression in chronic progressive multiple sclerosis: the Kaiser study. J Neurol Neurosurg Psychiatry 1991;54(12):1055–1060. doi:10.1136/jnnp.54.12.1055.

58 Gladstone DE, Peyster R, Baron E, et al. High-dose cyclophosphamide for moderate to severe refractory multiple sclerosis: 2-year follow-up (investigational new drug no. 65863). Am J Ther 2011;18(1):23–30. doi:10.1097/MJT.0b013e3181b3ad95.

59 Piehl F, Hillert J. Rituximab is an acceptable alternative to ocrelizumab for treating multiple sclerosis—yes. Mult Scler 2018;24(9):1157–1159. doi:10.1177/1352458518757930.

60 Wallin MT. Rituximab is an acceptable alternative to ocrelizumab for treating multiple sclerosis—no. Mult Scler 2018;24(9):1159–1161. doi:10.1177/1352458518757931.

61 Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing–remitting multiple sclerosis. N Engl J Med 2008;358(7): 676–688. doi:10.1056/NEJMoa0706383.

62 Muraro PA, Robins H, Malhotra S, et al. T cell repertoire following autologous stem cell transplantation for multiple sclerosis. J Clin Invest 2014;124(3):1168–1172. doi:10.1172/JCI71691.

63 Sormani MP, Muraro PA, Saccardi R, Mancardi G. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. Mult Scler 2017;23(2):201–204. doi:10.1177/1352458516645670.

64 Muraro PA, Pasquini M, Atkins HL, et al. Long-term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis. JAMA Neurol 2017;74(4): 459–469. doi:10.1001/jamaneurol.2016.5867.

65 Atkins HL, Bowman M, Allan D, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. Lancet 2016;388(10044):576–585. doi:10.1016/S0140-6736(16)30169-6.

66 Nash RA, Hutton GJ, Racke MK, et al. High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. Neurology 2017;88(9):842–852. doi:10.1212/WNL.0000000000003660.

67 Burt RK, Balabanov R, Burman J, et al. Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a randomized clinical trial. JAMA 2019;321(2): 165–174. doi:10.1001/jama.2018.18743.

68 ClinicalTrials.gov. Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial (TREAT-MS). *clinicaltrials.gov/ct2/show/NCT03500328*. Accessed April 2, 2019.