Progressive Multiple Sclerosis

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ABSTRACT

Purpose of Review: Many therapeutic advances for relapsing-remitting multiple sclerosis (MS) have occurred in the past 25 years. Although similar advances in disease-modifying therapies have not been realized in progressive MS, many symptomatic therapeutic strategies can benefit patients with progressive MS. Few guidelines exist for management of patients with progressive MS.

Recent Findings: The classification of progressive MS was revised in 2013 to include a description of inflammatory disease activity determined by clinical relapses or imaging findings. Developing knowledge about the pathogenesis of progressive MS and the role of comorbidities in modifying the disease course has implications for the clinical management of patients with progressive MS as well as for clinical trial design. Current and upcoming clinical trials will assess a wide range of interventions, including immunomodulatory agents, putative neuroprotective molecules, stem cell therapy, nutrition, and rehabilitation techniques.

Summary: None of the therapies currently approved for use in relapsing-remitting MS have been shown to slow the gradual progression of disability that occurs in the absence of recent relapses or changes in MRI. A multidisciplinary approach is needed to address the many symptoms that impact quality of life for patients with progressive MS.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic disorder of the central nervous system that typically presents in the third to fifth decades of life. The symptoms are variable, and the long-term course is often difficult to predict. The 1996 US National Multiple Sclerosis Society (NMSS) Advisory Committee on Clinical Trials in Multiple Sclerosis defined four clinical subtypes of MS: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing.[1] In 2013, the International MS Phenotype Group revised these criteria to separate active inflammation (ie, clinical relapses, new or active lesions on MRI) from gradual insidious clinical progression (**Figure 5-1**).[2] MS is now classified by these two characteristics in parallel instead of the separate distinct relapsing-remitting MS versus secondary progressive MS. Additionally, the progressive-relapsing MS category was eliminated from general use. These modifications recognize the variability in disease course within each subtype as well as the similarities between groups. This article discusses an approach to the management of patients across the spectrum of progressive MS and reviews the evidence available to guide management recommendations.

CLINICAL FEATURES OF PROGRESSIVE MULTIPLE SCLEROSIS

By definition, the clinical courses from onset are distinct for primary

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Dr Willis serves on the board of directors of the Multiple Sclerosis Association of America and on the editorial board of the *International Journal of MS Care*. Dr Willis has received personal compensation for speaking engagements from Biogen and Sanofi Genzyme and research support from Biogen. Dr Fox serves on the scientific advisory board of MedDay Pharmaceuticals and on the editorial boards of the *Multiple Sclerosis Journal* and *Neurology*. Dr Fox serves as a consultant for Actelion Pharmaceuticals Ltd, Biogen, Mallinckrodt Pharmaceuticals, Novartis AG, Teva Pharmaceutical Industries Ltd, and XenoPort, Inc. Dr Fox receives royalties from Elsevier B. V. and research support from the National Institutes of Health, the National Multiple Sclerosis Society, and Novartis AG.

Unlabeled Use of Products/Investigation Use Disclosure:
Drs Willis and Fox discuss the unlabeled/investigational use of pharmaceuticals for the treatment of progressive multiple sclerosis. Mitoxantrone is the only medication approved by the US Food and Drug Administration for secondary progressive multiple sclerosis.

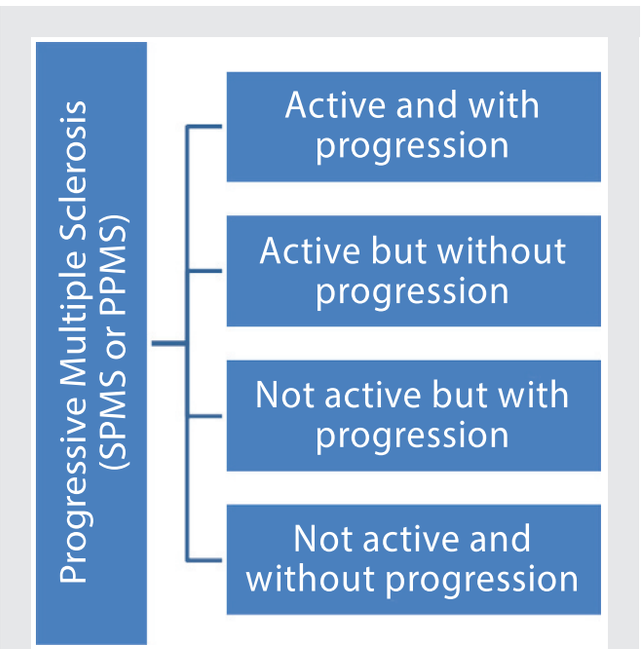

FIGURE 5-1 2013 Multiple sclerosis disease modifier phenotypes. Determination of ''active'' status includes assessment for relapses and MRI activity (eg, new or enlarging T2 lesions, gadolinium-enhancing lesions). ''Progression'' refers to gradually progressive neurologic dysfunction in the absence of clinical relapses.

PPMS = primary progressive multiple sclerosis;
SPMS = secondary progressive multiple sclerosis.

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KEY POINTS

- The clinical subtypes of multiple sclerosis have been revised to include description of two parallel components: disease activity and disease progression.
- No clear clinical criteria exist to determine when a patient transitions from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis.
- Relapses and gadolinium-enhancing lesions can occur in progressive multiple sclerosis.

progressive MS and secondary progressive MS. A diagnosis of secondary progressive MS requires a history of at least one clinical relapse and then at least 6 to 12 months of continuous disability progression that is independent of clinical relapses. No clear clinical criteria exist to determine when a patient transitions from relapsing-remitting MS to secondary progressive MS. On the other hand, the criteria for diagnosis of primary progressive MS are well defined. The 2010 criteria for diagnosis of primary progressive MS specify that a combination of 1 year of disease progression (prospective or retrospective) plus MRI or CSF findings as outlined in **Table 5-1** must be present (**Case 5-1**).[3] Superimposed relapses and gadolinium-enhancing lesions can occur in both types of progressive MS. **Table 5-2** compares the characteristics of secondary progressive MS and primary progressive MS.

As in patients with secondary progressive MS, the average age at the time of primary progressive MS diagnosis is in the fifth to sixth decades of life. Unlike secondary progressive MS, males seem to develop primary progressive MS as frequently as females.[4] The rate of disability progression from the onset of progressive disease is similar for primary progressive and secondary progressive MS, although the course of primary progressive MS is more variable.[5,6] MRI characteristics for primary progressive MS and secondary progressive MS are comparable, although patients with primary progressive MS generally have more diffuse brain lesions and more spinal cord lesions when compared with patients with relapsing-remitting MS and secondary progressive MS.[5] Athough confluent T2-hyperintense lesions, the presence of T1-hypointense lesions, and brain volume loss are frequently seen in patients with progressive MS, these findings alone do not distinguish patients with a relapsing versus a progressive course.

DIFFERENTIAL DIAGNOSIS

Gradually worsening neurologic function in a patient with MS warrants consideration of other explanations, even in patients with established MS. For example, cervical spondylosis or vitamin B_{12} deficiency may contribute to worsening sensory abnormalities or gait impairment. In addition, many conditions can mimic primary progressive MS, which most often presents as a gradually worsening myelopathy. A search for alternative diagnoses should be considered prior to confirmation of

TABLE 5-1 2010 McDonald Criteria for the Diagnosis of Primary Progressive Multiple Sclerosis[a]

Primary Progressive Multiple Sclerosis May Be Diagnosed in Patients With:
1. One year of disease progression (retrospectively or prospectively determined)
2. Plus two of the following three criteria[b]:
A. Evidence for dissemination in space in the brain based on ≥1 T2 lesions in at least one area characteristic of multiple sclerosis (periventricular, juxtacortical, or infratentorial)
B. Evidence for dissemination in space in the spinal cord based on ≥2 T2 lesions in the cord
C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

CSF = cerebrospinal fluid; IgG = immunoglobulin G.
[a] Reprinted with permission from Polman CH, et al, Ann Neurol.[3] *onlinelibrary.wiley.com/doi/10.1002/ana.22366/abstract*. © 2011 American Neurological Association.
[b] Gadolinium-enhancing lesions are not required, and symptomatic lesions in the brainstem or spinal cord are excluded.

primary progressive MS or secondary progressive MS (**Table 5-3**).

PATHOLOGY OF PROGRESSIVE MULTIPLE SCLEROSIS

All phenotypes of MS share the following pathologic findings: inflammation, demyelination, remyelination, axonal loss, and glial scar formation.[7–9] It has been suggested that progressive forms of MS largely represent a neurodegenerative process with comparably little of the infiltrative inflammation that is pronounced in relapsing-remitting MS. Unlike relapsing-remitting MS, the inflammation in secondary progressive

KEY POINTS

- Progression of disability occurs at a similar rate for secondary progressive multiple sclerosis and primary progressive multiple sclerosis.
- Gradually worsening neurologic function in a patient with multiple sclerosis warrants consideration of other explanations, even in patients with established multiple sclerosis. Patients with multiple sclerosis may have cervical spondylosis, vitamin B_{12} deficiency, or other conditions contributing to worsening neurologic function.
- All subtypes of multiple sclerosis are characterized by inflammation, demyelination, remyelination, axonal loss, and glial scar formation.

Case 5-1

A 35-year-old man presented because of a 2-year history of frequent tripping with his right foot. He had no numbness or tingling, but his entire right leg felt stiff upon awakening in the morning or after prolonged sitting. His neurologic examination revealed moderate spasticity in the knee extensors and ankle plantar flexors on the right. Mild spasticity was present in the left lower extremity. In the right lower extremity, power in the hip flexor was 4/5, knee flexor 4+/5, and ankle dorsiflexor 4/5. Left lower extremity strength was normal. His gait was slow (timed 25-foot walk: 14.4 seconds [normal time approximately 4 seconds]) with short steps, slight circumduction on the right, and poor toe clearance on the right. Vibration and proprioception were impaired in the right lower extremity, with no reproducible sensory level to pinprick. Reflexes were normal in the upper extremities and hyperactive in the lower extremities, right more than left. Sustained clonus was present at the right ankle. Plantar response was extensor bilaterally. His brain MRI (**Figure 5-2**) showed multiple fluid-attenuated inversion recovery (FLAIR) hyperintense periventricular lesions and one lesion that enhanced with gadolinium on T1-weighted imaging. Cervical spine MRI showed multiple short-segment T2/short tau inversion recovery (STIR) hyperintense lesions.

CSF analysis revealed three nucleated cells (98% lymphocytes), normal glucose and protein, IgG index 1.01 (upper limit of normal = 0.61), and eight oligoclonal bands in the CSF with 0 in the serum (upper limit of normal = 1). All other laboratory tests were normal. He was diagnosed with primary progressive multiple sclerosis and chose to enroll in a clinical trial.

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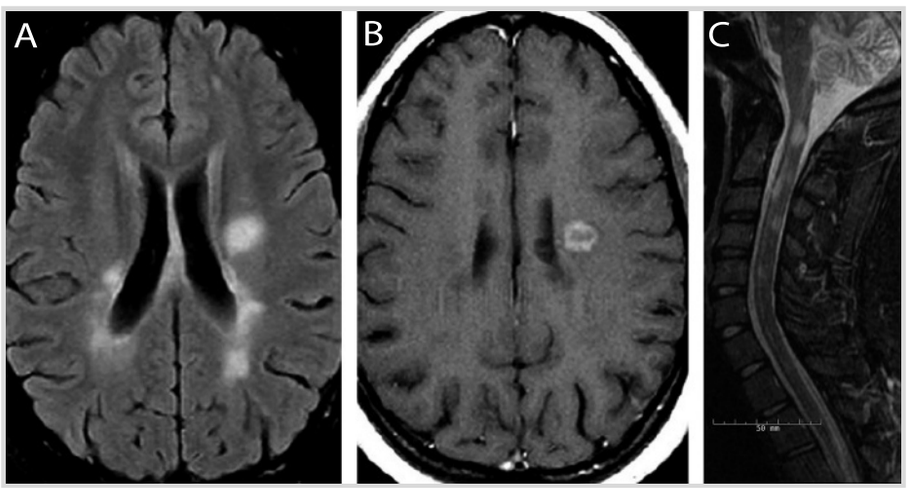

FIGURE 5-2 MRI of the patient in **Case 5-1** showing periventricular, enhancing, and short segment spinal cord lesions typical of multiple sclerosis. *A*, Axial fluid-attenuated inversion recovery (FLAIR) brain image; *B*, axial postgadolinium T1-weighted brain image; *C*, sagittal T2-weighted cervical spine image.

Comment. Progressive gait impairment is the most common presentation of primary progressive multiple sclerosis. Initial misdiagnosis is also common. Several features of this patient's presentation suggest that he may benefit from disease-modifying therapy: young age, recent disability progression, and presence of gadolinium-enhancing lesions. Management of spastic myelopathy will also be important to improve his current functioning.

TABLE 5-2 Characteristics of Secondary Progressive Multiple Sclerosis and Primary Progressive Multiple Sclerosis

	Secondary Progressive Multiple Sclerosis	Primary Progressive Multiple Sclerosis
Criteria	No clearly defined criteria	International diagnostic criteria
Disease course	Follows a relapsing disease course	No preceding relapses
Pathology	Diffuse inflammation and axonal injury, cortical demyelination, little focal inflammation	Diffuse inflammation and axonal injury, cortical demyelination, little focal inflammation
Treatment	In the absence of active inflammation, initiation of immune-modulating therapy is not indicated	In the absence of active inflammation, initiation of immune-modulating therapy is not indicated

TABLE 5-3 Other Diagnostic Considerations in Patients With Multiple Sclerosis With Progressive Neurologic Disability

▶ **Structural Causes**
Cervical stenosis
Tumor
Dural arteriovenous fistula or arteriovenous malformation
▶ **Nutritional Deficiencies**
Vitamin B_{12} deficiency
Copper deficiency
Vitamin E deficiency
▶ **Infections**
Human immunodeficiency virus
Progressive multifocal leukoencephalopathy
Lyme disease
Human T-cell lymphotropic virus type 1
▶ **Other**
Neurosarcoidosis
Neuromyelitis optica
Paraneoplastic myelopathy
Adrenomyeloneuropathy
Primary lateral sclerosis
Hereditary spastic paraparesis

MS and primary progressive MS appears to be less robust and is usually dissociated from breakdown in the blood-brain barrier.[9,10] Cortical demyelination is present in relapsing and progressive forms of MS but may be more prominent in progressive MS.[9] Axonal loss and decreased brain volume is present in patients with early relapsing-remitting MS but is more pronounced in patients with progressive disability.[8]

Several mechanisms have been proposed to explain the underlying neurodegeneration of progressive MS.[8,9] It is hypothesized that progressive disability occurs when a patient reaches a threshold of accumulated damage for which compensation is no longer possible (ie, exhaustion of functional reserve). Potential underlying mechanisms include mitochondrial injury related to prolonged oxidative stress, brain iron accumulation, and altered expression of ion channels that may amplify neurodegeneration.[9] Another hypothesis is that MS is a primary neurodegenerative disease with a superimposed inflammatory process that causes further destruction.[8]

ROLE OF DISEASE-MODIFYING THERAPY

The uncertainties regarding the pathogenesis of progressive MS and the timing of transition to a progressive

KEY POINT

■ Peripheral immune modulation is not sufficient to alter the course of progressive multiple sclerosis.

course present a challenge when making decisions about disease-modifying therapy. With the exception of mitoxantrone (which is rarely used in MS anymore), none of the MS medications approved by the US Food and Drug Administration (FDA) carries an indication for progressive MS. Clinical trials using immune-modulating therapies in patients with progressive MS have been uniformly disappointing (**Table 5-4**[11–24]). Smaller studies evaluating the effects of pulse IV methylprednisolone[25] and other immunosuppressive agents such as methotrexate[26] did not show an impact on disease course. Only the European interferon beta-1b trial showed delayed disability progression, while a similar North American trial was negative.[13] It seems clear that peripheral immune modulation alone is not sufficient to alter the course of progressive MS. Some researchers have proposed that inflammation in progressive MS is compartmentalized and thus not easily

TABLE 5-4 Agents That Have Been Tested in Phase 3 Clinical Trials in Progressive Multiple Sclerosis

Type of Progressive Multiple Sclerosis	Reference
Secondary progressive multiple sclerosis	
Interferon beta-1a IM	Cohen et al, 2002[11]
Interferon beta-1a SC	Li et al; University of British Columbia MS/MRI Analysis Research Group, 2001[12]
Interferon beta-1b SC	Kappos et al; European Study Group on Interferon β-1b in Secondary Progressive MS, 1998[13]
Mitoxantrone	Hartung et al, 2002[14]
IV immunoglobulin	Hommes et al, 2004[15]
Cladribine	Rice et al; Cladribine MRI Study Group, 2000[16]
Cyclophosphamide	Weiner, Cohen, 2002[17]
Myelin basic protein 8298	Freedman et al, 2011[18]
Dronabinol	Zajicek et al, 2013[19]
Linomide	Noseworthy et al; North American Linomide Investigators, 2000[20]
Primary progressive multiple sclerosis	
Glatiramer acetate	Wolinsky et al, 2007[21]
Rituximab	Hawker et al, 2009[22]
IV immunoglobulin	Pöhlau et al, 2007[23]
Dronabinol	Zajicek et al, 2013[19]
Fingolimod	Miller et al, 2013[24]

IM = intramuscular; IV = intravenous; SC = subcutaneous.

modified by systemic immune-modulating therapy, although this has yet to be demonstrated.

Recent recommendations from the American Academy of Neurology included advice against using interferon beta or glatiramer acetate for patients with disability from progressive nonrelapsing forms of MS.[27] Although this recommendation seems appropriate for patients with untreated progressive MS without evidence for active inflammation, its application to patients in whom active inflammation stopped while taking disease-modifying therapy is probably inappropriate, since we currently are unable to identify those patients who do not have active inflammation because they are taking disease-modifying therapy. At this time, no consensus guidelines exist regarding switching or discontinuation of disease-modifying therapy for patients with progressive MS. A 2011 survey of practice patterns among neurologists (42% academic, 58% community) treating patients with progressive MS revealed variable approaches to the use of disease-modifying therapy for primary progressive MS and secondary progressive MS. Ninety-five percent of responders would switch therapy for a patient with secondary progressive MS with MRI activity and gradual progression. Only 60% felt that disability progression alone was enough to constitute a treatment failure. A small majority (56%) of respondents would start disease-modifying therapy in a patient with primary progressive MS, but 85% would start therapy in the same patient if gadolinium-enhancing lesions were present.[28]

In previous clinical trials of progressive MS, some subgroups appeared to benefit from immune-modulating therapies. Characteristics of those patients included younger age, more recent disability progression, recent relapse, and MRI activity.[12,21,22] A clinical relapse or MRI activity (ie, new T2 lesions or gadolinium-enhancing lesions) in a patient with progressive MS warrants consideration of a change in MS immune-modulating therapy (including initiation of therapy in a patient who is not currently receiving immune-modulating therapy). A change in therapy when gradually progressive disability occurs in the absence of these inflammatory markers is unlikely to alter the gradually progressive course of progressive MS. Patients should be advised that no evidence exists to guide such changes and no currently approved therapy is expected to restore function.

The risks of escalating disease-modifying therapy, such as the risk of progressive multifocal leukoencephalopathy, should be discussed frankly with patients who seek to change therapy when potential benefit is thought to be low. As described earlier, screening for other conditions that could contribute to disability progression would be prudent. Treatment should include management of current symptoms, rehabilitation strategies, and identification of needed resources (**Case 5-2**).

Evidence guiding discontinuation of disease-modifying therapy is sparse. The decision to stop therapy should not be solely guided by age or level of disability. In general, discontinuation of disease-modifying therapy should be considered if the cost, side effects, or other burden of treatment outweighs the perceived benefits (**Case 5-3**). For more information on discontinuing disease-modifying therapies, refer to the article ''Switching or Discontinuing Disease-Modifying Therapies for Multiple Sclerosis'' by Aaron E. Miller, MD, FAAN,[29] in this issue of *Continuum*. Clinical and

KEY POINTS

- A recent survey of practice patterns revealed variable approaches to the use of disease-modifying therapy in progressive multiple sclerosis.
- No evidence exists to guide changes in immune-modulating therapy for patients who have gradual progression in the absence of inflammation.
- The decision to stop therapy in progressive multiple sclerosis should not be solely guided by age or level of disability.

KEY POINT

- None of the currently approved therapies have been shown to repair preexisting damage or to reverse the persistent symptoms often present in persons with multiple sclerosis.

Case 5-2

A 50-year-old woman with no other medical problems was diagnosed with relapsing-remitting multiple sclerosis (MS) at age 40. Despite treatment with an injectable therapy for 7 years followed by an oral disease-modifying therapy for 3 years, she developed severe myelitis with paraplegia and bladder and bowel incontinence. She received 5 days of IV methylprednisolone and a course of plasma exchange (five exchanges of 1.5 liters) with no immediate improvement. She was nonambulatory upon discharge to acute rehabilitation. Her disease-modifying therapy was changed to natalizumab. Six months after her myelitis episode, she still had residual sensory and motor deficits but could walk with a cane. Although she had no further relapses or new lesions on MRI, she reported gradual worsening of spastic paraparesis and required a rollator for safe ambulation. She reported persistent tightness and heaviness in both arms as well as frequent urinary incontinence. MRI of the brain, cervical spine, and thoracic spine repeated after 24 months of natalizumab showed no new lesions when compared to her studies before starting natalizumab. Moderate cervical spondylosis was present but no cord compression was seen. Laboratory testing for metabolic causes of myelopathy was normal. She inquired about changing her disease-modifying therapy because of her progressive walking difficulties.

Comment. This patient had a very active relapsing-remitting MS disease course, followed by evolution into secondary progressive MS without evidence for active inflammation. A significant decline in function or change in symptoms in the absence of relapse warrants consideration of other etiologies, including compressive myelopathy. After other etiologies are excluded, the management should focus on management of the symptoms of progressive myelopathy. In the absence of active inflammation in this patient, it is unlikely that changing to another immune-modulating therapy will be effective in slowing her gradually progressive myelopathy. Instead, management should focus on her current symptoms, rehabilitation strategies, adjustment to the diagnosis of progressive MS, workplace accommodations, and the potential need for other resources.

radiographic monitoring should continue after therapy has been stopped.

BEYOND IMMUNE-MODULATING THERAPY

As with relapsing-remitting MS, treatment of progressive MS should not be limited to just immune-modulating therapy. None of the currently approved therapies have been shown to repair preexisting damage or to reverse the persistent symptoms often present in persons with MS. Patients with progressive MS often have complex care needs that are best managed by a multidisciplinary team.[30] **Figure 5-3** shows the authors' approach to management of patients with progressive MS.

Table 5-5 describes symptom frequency in patients with progressive MS.[31] Fatigue; pain; depression; weakness; walking difficulty; incoordination; bowel, bladder, and sexual dysfunction; cognitive impairment; and visual impairment directly impact function and quality of life. Assessment and management of these symptoms are important components of comprehensive care for patients with progressive MS. Strategies for management of many of these individual symptoms are discussed in the article "Symptom Management and Lifestyle

Case 5-3

A 66-year-old woman with hypertension and osteoporosis was diagnosed with relapsing-remitting multiple sclerosis (MS) 25 years earlier. Despite treatment with interferon beta for the past 15 years, she developed a progressive myelopathy over the past 8 years and now had secondary progressive MS without relapses or new lesions on MRI. Her cognitive function gradually declined over the past 10 years to the point that she had required total assistance with activities of daily living for the past several years. Her daughter reported that her wandering and agitation improved after starting adult daycare and improving her sleep. Her other medical conditions were well managed by her primary care physician, and age-appropriate screenings and immunizations were up-to-date. The daughter stated that her mother slept excessively, was depressed, and did not eat at all on the day following her interferon injection. Because of changes in her Medicare plan, the family was now responsible for $3000 of medication costs before the remainder was covered. The daughter asked if her mother's interferon therapy was necessary.

Comment. This case illustrates a scenario in which discontinuation of immune-modulating therapy would be favored. This patient has secondary progressive MS and dementia, and has significant side effects and out-of-pocket expense for her immune-modulating therapy. Because of her age and history of disease stability, she may no longer need an MS immune-modulating therapy. Additionally, interferon may be contributing to her sleep disruption, depression, and anorexia. It would be appropriate to discontinue immune-modulating therapy and follow clinically and with imaging to monitor for reactivation of MS inflammation.

KEY POINT

- Rehabilitation techniques are a cornerstone of comprehensive care in progressive multiple sclerosis.

Modifications in Multiple Sclerosis'' by Patricia K. Coyle, MD, FAAN,[32] in this issue of *Continuum*.

Rehabilitation techniques are a cornerstone of comprehensive care in progressive MS. Occupational therapy may be helpful in addressing decreased upper extremity function, cognitive impairment, and energy conservation techniques. Physical therapy may include lower extremity strengthening, gait evaluation and retraining, assessment for orthotics, development of a home exercise program, and evaluation of functional capacity for disability assessment. Speech therapists can evaluate and manage language, speech, and swallowing impairment. Physiatrists may offer comprehensive rehabilitative evaluation and management, including botulinum toxin injections, intrathecal baclofen therapy, and other interventions.

Management of gait disorders common in progressive MS often combines rehabilitation strategies, assistive devices, and symptomatic medications. Dalfampridine, an extended-release formulation of the potassium channel blocker 4-aminopyridine, has been shown to improve walking speed in some patients with MS. Approximately 35% to 43% of subjects in two phase 3 randomized controlled trials demonstrated a clinically relevant improvement on the timed 25-foot walk test with dalfampridine 10 mg extended-release tablets taken every 12 hours.[33] Response to treatment appears to be independent of the disease course, baseline walking speed, or baseline Expanded Disability Status Scale (EDSS)

KEY POINT

■ Prevention and treatment of medical comorbidities are important in progressive multiple sclerosis.

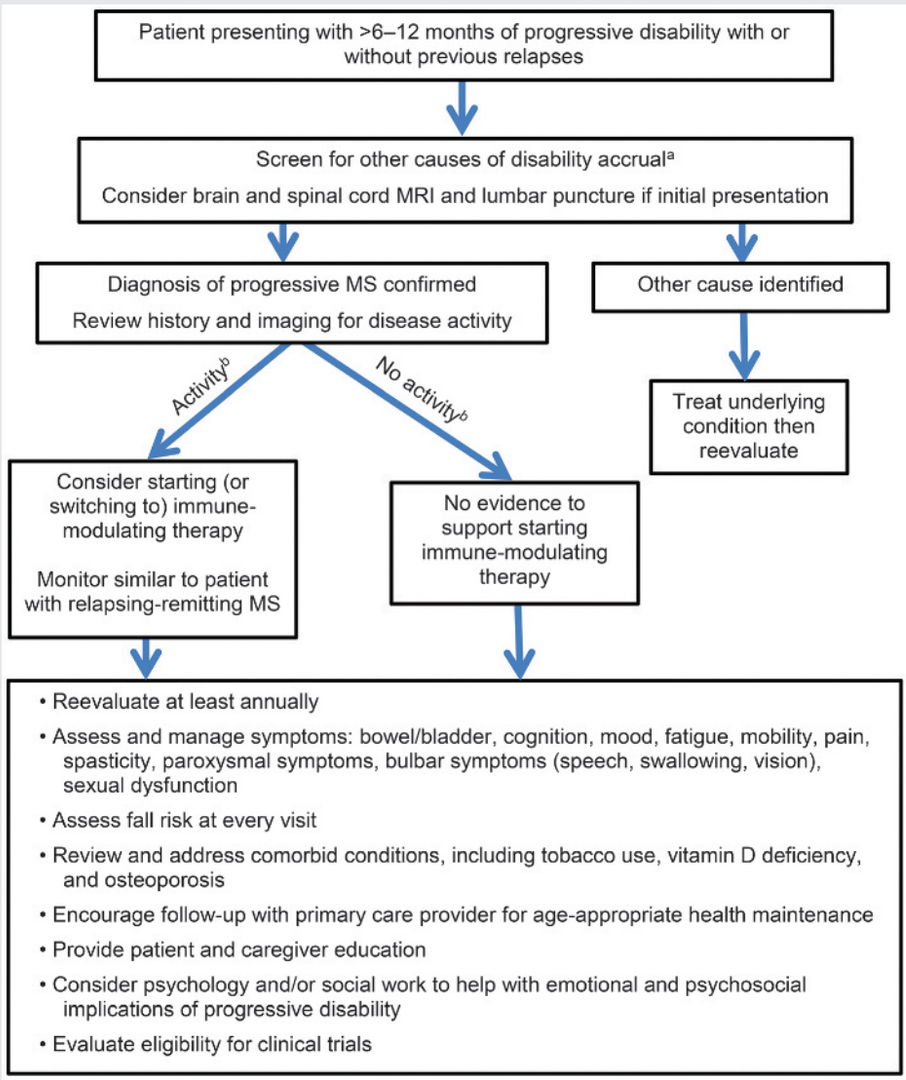

FIGURE 5-3 Approach to management of patients with possible progressive multiple sclerosis.

MRI = magnetic resonance imaging; MS = multiple sclerosis.

[a] For more information, refer to **Table 5-3** in this article.

[b] Activity is defined by relapses, gadolinium-enhancing lesions, or new or unequivocally enlarging T2 lesions during the assessment period.[2]

score.[33] Although the improvement of walking speed is the sole approved indication for use in the United States, other proposed effects of dalfampridine include improved performance in walking endurance measured by the 6-minute walk test,[34,35] improvement of internuclear ophthalmoparesis,[36] and improved manual dexterity.[35] Moderate to severe renal impairment (creatinine clearance of 50 mL/min or lower) and a personal history of seizure are contraindications to the use of dalfampridine.

Review, discussion, prevention, and treatment of other medical comorbidities are important in progressive MS. Quality of life decreases with increasing

TABLE 5-5 Common Symptoms in Progressive Multiple Sclerosis[a]

Symptom	Frequency
Mobility impairment	80%
Fatigue	80%
Weakness	70%
Ataxia	80%
Spasticity	60–90%
Bladder dysfunction	58–75%
Cognitive dysfunction	60–70%
Pain	55–70%
Depression	25–50%
Pseudobulbar affect	10%

[a] Modified with permission from Feinstein A, et al, Lancet Neurol.[31] *www.thelancet.com/journals/laneur/article/PIIS1474-4422(14)70231-5/abstract*. © 2015 Elsevier Ltd.

numbers of comorbidities.[37] The presence of comorbid health conditions or habits can also impact treatment decisions as well as affect disability progression and disease severity.[38–41] Comorbid conditions of particular concern include smoking, vitamin D deficiency, obesity, hypertension, hyperlipidemia, sleep disorders, osteoporosis, osteoarthritis, depression, anxiety, and thyroid disease.[38,39] Both smoking and vitamin D deficiency have been associated with disability progression in MS.[40,41] Routine health maintenance visits with a primary care provider should be encouraged.

Education and social needs change as progressive disability causes limitations in performing activities of daily living, reduced or loss of driving ability, loss of employment, and changing family roles. Education and support should not be limited to patients with MS but should also include family members and caregivers. Psychologists and social workers should be consulted where needed.

FUTURE DIRECTIONS

Our incomplete understanding of the pathophysiology of progressive MS presents a significant challenge in developing effective therapies for this

KEY POINT

- Proposed strategies for altering the course of progressive multiple sclerosis include remyelination, axonal repair, and therapies targeting mitochondria and compartmentalized inflammation.

TABLE 5-6 Interventions in Planned or Ongoing Trials in Progressive Multiple Sclerosis

Intervention	Estimated Year of Completion
Secondary progressive multiple sclerosis (SPMS)	
Imilecleucel-T	2016
Siponimod	2017
Lipoic acid	2015[a]
MIS416	2016
Rituximab (intrathecal and IV)	2017
Amiloride, fluoxetine, or riluzole	2017
TCR peptide vaccine	2018
Domperidone	2019
Primary progressive multiple sclerosis (PPMS)	
Laquinimod	2017
Ocrelizumab	2015[a]
Idebenone	2018
SPMS and PPMS	
Masitinib	2015[a]
Lithium	2015[a]
MD1003	2016
Sunphenon epigallocatechin-gallate	2016
Ibudilast	2017
Adrenocorticotropic hormone	2018
Mesenchymal stem cells	2018

IV = intravenous.
[a] Trial completed, but data not available at the time of final article review.

form of MS. Although previous trials of immune-modulating therapies have failed, ongoing and upcoming trials of putative neuroprotective therapies hold promise for altering the ultimate course of progressive MS. Potential strategies include remyelination, axonal repair, and therapies targeting mitochondria and compartmentalized inflammation. As shown in **Table 5-6**, a wide range of interventions are currently under investigation.[42,43] Trials aimed at addressing symptoms and rehabilitation techniques solely in patients with progressive MS have been limited. Studies involving robot-assisted gait training, functional electrical stimulation, vestibular rehabilitation, and dietary interventions are planned or enrolling.[43]

CONCLUSION

While many new treatments for relapsing-remitting MS have been developed in the past 10 to 20 years, advances in management of progressive MS lag far behind. While no consensus exists on the use of immune-modulating therapies for patients with progressive MS, the revised diagnostic classification may help identify patients likely to benefit from these treatments. Furthermore, patients with progressive MS typically have therapeutic needs beyond use of immune-modulating therapy. A multidisciplinary approach is often needed to address these treatment needs. Ongoing research may inform best practices for symptomatic management as well as use of neuroprotective agents, repair-promoting agents, and disease-modifying therapies.

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