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## Treatment of Multiple Sclerosis: A Review

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### Abstract

Multiple sclerosis (MS) is an autoimmune demyelinating and neurodegenerative disease of the central nervous system, and the leading cause of non-traumatic neurological disability in young adults. Effective management requires a multifaceted approach to control acute attacks, manage progressive worsening, and remediate bothersome or disabling symptoms associated with this illness. Remarkable advances in treatment of all forms of MS, and especially for relapsing disease, have favorably changed the long-term outlook for many patients. There also has been a conceptual shift in understanding the immune pathology of MS, away from a purely T-cell-mediated model to recognition that B cells have a key role in pathogenesis. The emergence of higher-efficacy drugs requiring less frequent administration have made these preferred options in terms of tolerability and adherence. Many experts now recommend use of these as first-line treatment for many patients with early disease, before permanent disability is evident.

### Keywords

Multiple Sclerosis; MS Therapy; B cell Therapy

## INTRODUCTION

The autoimmune disease multiple sclerosis (MS) is the leading cause of non-traumatic neurological disability arising in young adults.<sup>1,2</sup> MS is characterized by two pathological hallmarks: 1) inflammation with demyelination, and 2) astroglial proliferation (gliosis) and neurodegeneration. Tissue damage in MS is restricted to the central nervous system (CNS),

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#### Author Contributions

Both authors contributed equally to the literature search, figures, study design, data collection, data analysis, data interpretation, and writing of this manuscript.

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sparing the peripheral nervous system. Clinically, MS can follow two paths: relapsing or progressive. Most commonly, onset is a relapsing form of MS (RMS), manifested as discrete episodes of neurological dysfunction followed by partial, complete, or no remission. Over time, relapses usually decrease in frequency but a gradual worsening often supervenes, resulting in uninterrupted progression (termed secondary progressive MS [SPMS]); (Figure 1).<sup>3</sup> Less than 10% of patients with MS experience progression from onset, a category termed primary progressive MS (PPMS).<sup>3</sup> Despite these distinctions, all clinical forms of MS appear to reflect the same underlying disease process. And although inflammation is typically associated with relapses, and neurodegeneration with progression, it is now recognized that both pathologies are present in essentially all patients across the entire disease continuum.

MS is a global problem, and its prevalence is on the rise.<sup>4</sup> The prevalence is highest in North America, Western Europe and Australasia (>100 cases per 100,000 population), and lowest in countries centered around the equator (<30 cases per 100,000 population).<sup>4</sup> In the US, a recent study estimated that nearly 1 million individuals are affected. In RMS, women are affected nearly three times more often than men and the mean age of onset is ~30 years, whereas in PPMS the rates of men and women affected are similar and the mean age of onset is ~40 years.<sup>5-7</sup>

The development of increasingly effective therapies for RMS, and partially effective therapy for PPMS and SPMS, represents a profound success that has dramatically improved prospects for lives free from disability. For patients with RMS, the mean time to development of SPMS was historically estimated at approximately 19 years after onset but in the treatment era has been lengthened substantially. On highly effective therapy relapses are markedly reduced or eliminated. However, control of RMS has uncovered a relapse-independent “silent” progression that was previously obscured by attacks and remissions in RMS.<sup>8,9</sup> This recognition has also led to an increasing reliance on highly effective therapies early in the course of MS in order to maximally control both relapses and progression. In this review we summarize recent advances in MS treatment and speculate on future directions.

## DIAGNOSIS

### Clinical Manifestations

MS symptoms vary according to location and severity of lesions occurring within the CNS. Clinical features of RMS may present acutely or subacutely over hours to days, sometimes followed by gradual spontaneous remission over weeks to months. Conversely, PPMS is characterized by slowly progressive symptoms from onset. Table 1 summarizes common clinical and laboratory features of MS. Symptoms may be severe at onset or begin insidiously, sometimes unnoticed for months or years. Once the patient seeks medical attention, and if MS is suspected, prompt referral to a specialist is indicated.

## Investigation

Diagnosis requires objective evidence of inflammatory CNS injury and often additional details of dissemination of the disease process “in space and time”, i.e. affecting more than one CNS location with evolution over time (Table 2). Symptoms must last for >24 hours and occur as distinct episodes separated by at least 1 month. The main tests used to support diagnoses are magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis.

In most patients an abnormal MRI is observed.<sup>10</sup> Leakage of intravenous gadolinium is caused by breakdown in the blood-brain barrier that occurs early in the development of an MS lesion and is a marker of acute inflammation. Gadolinium enhancement typically persists for <1 month; however, the residual MS plaque remains visible indefinitely as a focal area of hyperintensity (a lesion) on fluid-attenuated inversion recovery or T2-weighted MRI scans. A periventricular (adjacent to the ventricles) distribution of lesions, indicative of perivenular inflammation, is characteristic. Lesions in juxtacortical (adjacent to the cerebral cortex) white matter, infratentorial white matter, and within the spinal cord are also suggestive of MS and contribute to “dissemination in space”. Although MS plaques can involve subcortical white matter, lesions in this location are considered non-diagnostic because other pathologies are associated with similar lesions.

Lumbar puncture is helpful, especially in uncertain cases and in all cases of suspected PPMS. CSF abnormalities include a mononuclear cell pleocytosis and an increased level of intrathecally synthesized IgG. Oligoclonal bands reflect the products of a highly focused immune response by activated B cells in the CNS. The abnormal intrathecal synthesis of gamma globulins, measured by an elevated IgG index or two or more discrete oligoclonal bands not present in a paired serum sample, is present in >90% of MS patients. Elevated intrathecal antibody production can also be used to fulfil “dissemination in time” criteria in patients presenting with their first clinical manifestation of MS. Although sensitive, elevated CSF antibody production is not specific for MS, and also occurs with CNS infections. More than 50 cells/mm<sup>3</sup> are rare in MS, and polymorphonuclear leukocytes, eosinophils or a markedly elevated total protein level should call the diagnosis into question.

Other useful tests include evoked potentials to assess nerve conduction in CNS pathways, and retinal imaging by optical coherence tomography.

## ADVANCES IN TREATMENT

Current management strategies are focused on treating acute attacks, ameliorating symptoms, and reducing biologic activity through disease-modifying therapies. The approach to treating acute attacks and symptom-based management is summarized in the supplement.

### Disease-Modifying Therapies

Disease-modifying therapies modify the course of MS through suppression or modulation of immune function. They exert anti-inflammatory activity primarily in the relapsing phase of MS; they reduce the rate of relapses, reduce accumulation of MRI lesions and stabilize, delay, and in some cases modestly improve disability.

The first approved therapies, the interferons and glatiramer acetate, were fortuitous discoveries. These well-tolerated drugs modestly reduce the frequency of MS relapses and soon became commonly prescribed.<sup>11</sup> Preclinical studies in experimental autoimmune encephalomyelitis, an animal model of MS, advanced our understanding of crucial steps in the pathogenesis of CNS autoimmune diseases, specifically early peripheral expansion of autoreactive immune cells in secondary lymphoid organs, subsequent infiltration of activated cells into the CNS, and generation of inflammatory lesions in white matter.<sup>12,13</sup> These studies showed that T cells play a critical role in experimental autoimmune encephalomyelitis;<sup>12</sup> however clinical trials with purely T-cell-based treatment approaches were ineffective in RMS.<sup>14,15</sup> In contrast, strategies that inhibited lymphocyte access to the CNS by blocking adhesion (natalizumab) or sequestering lymphocytes in primary lymphoid organs (the sphingosine-1-phosphate [S1P] receptor modulators fingolimod, siponimod, and ozanimod) were found to be effective in both MS and experimental autoimmune encephalomyelitis. A major advance was the development of disease models that more closely replicated the pattern of tissue damage in MS, leading to a new appreciation of the importance of humoral immunity in MS pathogenesis.<sup>16,17</sup> This paved the way for clinical trials of B-cell-depleting therapies, initially with the anti-CD20 monoclonal antibody rituximab and followed by the more successful development of ocrelizumab and ofatumumab. Anti-CD20-mediated B-cell depletion demonstrated a high level of success in limiting new relapses and silent progression in RMS,<sup>18–20</sup> and in reducing disability progression in PPMS.<sup>21</sup> Thus, the past decade has seen a shift in the conceptual framework of MS pathophysiology, from the earlier model that MS is a T-cell-mediated autoimmune disorder, to the understanding of a central role for B cells.<sup>22</sup> Although dramatic progress has been made against RMS, the development of highly effective therapies against progressive MS remains an unmet need (Figure 2).

## APPROACH TO TREATING PATIENTS WITH MS

Table 3 provides an overview of the characteristics and pivotal data associated with approved agents, stratified according to frequency of use and perceived level of efficacy. Given this large array of available therapies, it may be prudent for clinicians to become conversant with a few agents. As such, the following section is focused on detailing MS disease-modifying therapies that are widely used in clinical practice.

### Treating RMS

**Frequently used disease-modifying therapies for RMS—Ocrelizumab,** a humanized monoclonal antibody against the CD20 molecule on the surface of mature B cells,<sup>23</sup> has been widely used since its approval in 2017. Ocrelizumab is highly effective against relapses and silent progression in RMS patients, and has dramatic benefits in halting development of new white matter lesions detected by MRI. Ocrelizumab selectively depletes CD20-expressing B cells, preserving pre-existing humoral immunity and the capacity for B-cell reconstitution. B-cell depletion is associated with potent interruption in B-cell trafficking from the periphery to the CNS, reduced B cell antigen presentation to T cells, modulation of proinflammatory cytokine secretion by B cells, and reduced activation and differentiation to immunoglobulin secreting plasmablasts.<sup>24,25</sup> Ocrelizumab is administered

as an intravenous infusion every 24 weeks. Initial findings from the phase 3 trials indicated a possible low risk of increased malignancies including breast cancer, although longer follow-up revealed cancer rates identical to epidemiologic expectations. Post-marketing studies are generally consistent with the clinical trials although serious herpes virus infections have become a recognized complication.<sup>26</sup> Rituximab is a chimeric anti-CD20 monoclonal antibody that appears to be similarly effective against RMS and PPMS in preliminary trials and real world experience and is widely used despite never receiving approval from any regulatory body. Ofatumumab<sup>27</sup> is a fully human anti-CD20 monoclonal antibody administered by monthly subcutaneous injection at home and has an efficacy profile similar to ocrelizumab with a high degree of safety in the phase 3 trials for RMS.

Natalizumab, a humanized monoclonal antibody, is an inhibitor of the  $\alpha 4\beta 1$  integrin, an adhesion molecule expressed on the surface of lymphocytes and involved in transmigration across endothelia into the CNS.<sup>28</sup> Natalizumab is administered as an intravenous infusion once every 4 weeks. Natalizumab is highly effective in reducing relapses and slowing disease progression in RMS patients compared with placebo or IFN  $\beta$ -1a,<sup>29,30</sup> benefits sustained over longer-term in real-world studies.<sup>31</sup> Natalizumab is generally well tolerated; however, long-term treatment carries risk of progressive multifocal leukoencephalopathy (an opportunistic brain infection caused by the John Cunningham virus), occurring in ~0.4% of natalizumab-treated patients.<sup>32</sup> Progressive multifocal leukoencephalopathy incidence increases with natalizumab exposure and this risk can be stratified according to the levels of John Cunningham virus antibodies in serum. In antibody-negative patients, progressive multifocal leukoencephalopathy risk is minimal, <1:10,000. Conversely, in antibody-positive patients, risk may be as high as 1.1% annually.<sup>32</sup> Thus, natalizumab is generally recommended only for antibody-negative patients. Extending the dosing interval from 4 to 6 weeks appears to reduce the risk of progressive multifocal leukoencephalopathy by more than 90% in seropositive patients, providing a useful strategy in reducing risk.<sup>33</sup> A disadvantage of natalizumab is that discontinuation can trigger 'rebound' disease activity, a problem that may be encountered in patients who are noncompliant, or John Cunningham virus seroconvert, or who discontinue prior to attempting to conceive.

Fingolimod was the first oral therapy approved for RMS. It is a S1P inhibitor that prevents egress of lymphocytes from secondary lymphoid organs, blocking infiltration of autoreactive lymphocytes into the CNS. Fingolimod is well tolerated, although adverse events include mild abnormalities on routine laboratory evaluation (e.g. elevated liver function tests or lymphopenia).<sup>34-37</sup> Heart block and bradycardia can also occur when therapy is initiated, thus a 6-hour observation period (including electrocardiogram monitoring) is recommended for all patients receiving their first dose.<sup>38</sup> Other side effects include macular edema and, rarely, disseminated varicella-zoster virus, cryptococcal infections, and progressive multifocal leukoencephalopathy; prior to initiating therapy, an ophthalmic examination and varicella-zoster virus vaccination for seronegative individuals are indicated. Ozanimod, a recently approved selective S1P receptor modulator, was also shown to be effective in RMS, with favorable safety and tolerability.<sup>39,40</sup>

Dimethyl fumarate<sup>41,42</sup> exerts anti-inflammatory and cytoprotective effects through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway and Nrf2-

independent pathways.<sup>43,44</sup> Dimethyl fumarate is generally well tolerated, but treatment has been linked with some progressive multifocal leukoencephalopathy risk.<sup>45</sup> Most of these cases were lymphopenic, thus monitoring for lymphopenia every 6–12 months is recommended. Diroximel fumarate was recently approved and, like dimethyl fumarate, is metabolized to mono-methyl fumarate.<sup>46</sup>

Teriflunomide<sup>47</sup> is the active metabolite of leflunomide, an immune suppressant medication used in rheumatoid arthritis. Teriflunomide inhibits dihydroorotate dehydrogenase, an enzyme involved in pyrimidine synthesis. Teriflunomide inhibits proliferation of activated lymphocytes presumed to be autoreactive. Boxed warnings include risk of hepatotoxicity and teratogenesis. Common adverse events include headache, diarrhea, nausea, alopecia, and increase in hepatic alanine transferase. When necessary, teriflunomide can be rapidly eliminated by ingestion of cholestyramine.

Interferon beta (IFN- $\beta$ ) is a class I interferon whose mechanism of action likely involves immunomodulation through downregulating expression of MHC molecules on antigen-presenting cells, decreasing proinflammatory and increasing anti-inflammatory cytokines, inhibiting T-cell proliferation, and blocking trafficking of inflammatory cells to the CNS.<sup>48</sup> IFN- $\beta$  modestly reduces the relapse rate and MRI disease measures and slows accumulation of disability.<sup>49–53</sup> Common adverse events include flu-like symptoms and mild abnormalities on routine laboratory evaluation, as well as injection-site reactions with subcutaneous administration.<sup>50,53</sup> Side effects can usually be managed with nonsteroidal anti-inflammatory medications.

Glatiramer acetate is the acetate salt of a mixture of random polypeptides composed of four amino acids. Its mechanism of action may involve favorably altering the balance between proinflammatory and regulatory cytokines.<sup>54–56</sup> It modestly reduces relapse rates and some disease severity measures, and can be considered as an equally effective alternative to IFN- $\beta$  in RMS.<sup>54,55,57</sup> Common adverse events include injection-site reactions, flushing, chest tightness, dyspnea, palpitations, anxiety after injection, and less commonly, lipoatrophy that can rarely be disfiguring and require treatment cessation.<sup>54,55</sup>

**Infrequently used disease-modifying therapies for RMS**—These include mitoxantrone,<sup>58</sup> alemtuzumab,<sup>59–61</sup> and cladribine.<sup>62</sup> All are of proven benefit in RMS; however, serious treatment emergent adverse events limit their use. Finally, a growing body of evidence indicates that autologous hematopoietic stem cell transplantation can induce a prolonged remission in many RMS patients. Randomized trials comparing this procedure with other highly effective therapies are now underway. For the time being, autologous hematopoietic stem cell transplantation is recommended only for RMS patients who have exhausted all other reasonable treatment options, and is not recommended for patients with progressive MS because available data suggest that progression often continues despite this treatment.<sup>63</sup>

## Treating Progressive MS

**SPMS**—Siponimod<sup>64</sup> is a selective S1P modulator that is approved for relapsing forms of MS including active SPMS, meaning patients with SPMS who have had recent clinical

relapses and/or evidence of new or enlarging MRI lesions. Ocrelizumab, cladribine, and diroximel fumarate can also be used for patients with active SPMS.

**PPMS**—Ocrelizumab is the only approved disease-modifying therapy for the treatment of PPMS. Dosing is the same as for RMS. Ocrelizumab reduces progression of clinical disability by approximately one-quarter, and improves other clinical and MRI markers of inflammatory and degenerative disease activity in this population.<sup>21</sup>

### Decision Making for Treatment Of MS

Given the increasingly complex landscape of therapeutics for MS, the treatment algorithm in Figure 3 may aid in decision making. In general, therapy should be initiated in patients with a first attack who are at high risk for MS or in patients diagnosed with RMS.<sup>65</sup>

Although historically high-dose IFN  $\beta$ -1a and glatiramer acetate were the preferred first-line options, we now recommend the use of highly effective disease-modifying therapies as first-line options for the majority of patients with active MS. This approach supervenes the traditional “treat to target” method in which a treatment of modest or moderate effectiveness is first used, and therapy advanced to a more effective agent when breakthrough disease (evident clinically or by MRI) occurs. Observational studies suggest that early use of high efficacy therapy improves long-term outcomes. We favor initiating therapy for many patients with ocrelizumab or another anti-CD20 drug, or with natalizumab in John Cunningham virus negative patients. Anti-CD20 therapies represent an attractive option given their high level of efficacy, infrequent infusions or injections, favorable safety profile, and absence of rebound following discontinuation. Patients with PPMS with new or enlarging MRI lesions should also be considered for ocrelizumab treatment. Switching therapies may be required in the following situations: suboptimal response, experiencing more than one relapse with active MRI scans in the prior year while on treatment, and safety issues including development of persistent high-titer neutralizing antibodies in patients receiving IFN- $\beta$ . Discontinuation of disease-modifying therapies is required in cases of serious adverse events that may be drug-related and for many disease-modifying therapies in women who become pregnant while on treatment. Exceptions include glatiramer acetate that can be continued during pregnancy, and in some cases prior use of ocrelizumab, alemtuzumab and cladribine that have prolonged pharmacodynamic effects which persist after the drug has been eliminated.

### CONCLUSION

Spectacular progress has been made in the treatment of MS as a result of advances in understanding of the pathogenesis and course of this disease. The development of highly effective therapies has produced near-complete control of relapsing disease and focal brain inflammation. However, effective treatment of progression remains an unmet need because current therapies confer only partial protection against the neurodegenerative component of MS. Although natural history studies suggest that the long-term course of disease has been dramatically improved in the treatment era, further clinical and real-world assessments are needed to gather long-term efficacy and safety evidence for these therapies. Additional studies of the value of highly effective agents for early treatment and determination of

patients who benefit most will also be essential as we seek to achieve evidence-based and personalized approaches to MS treatment and management.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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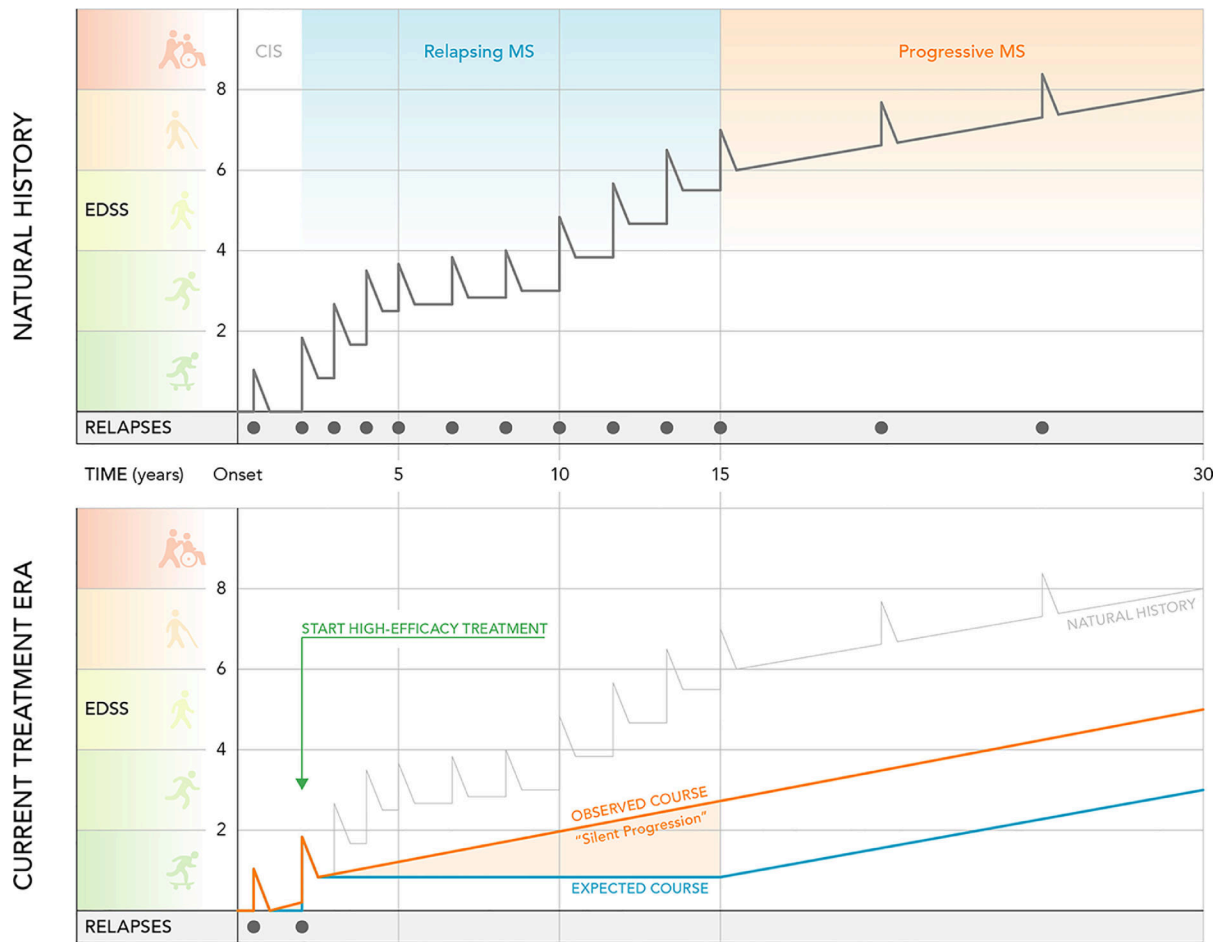
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**CLINICAL SIGNIFICANCE**

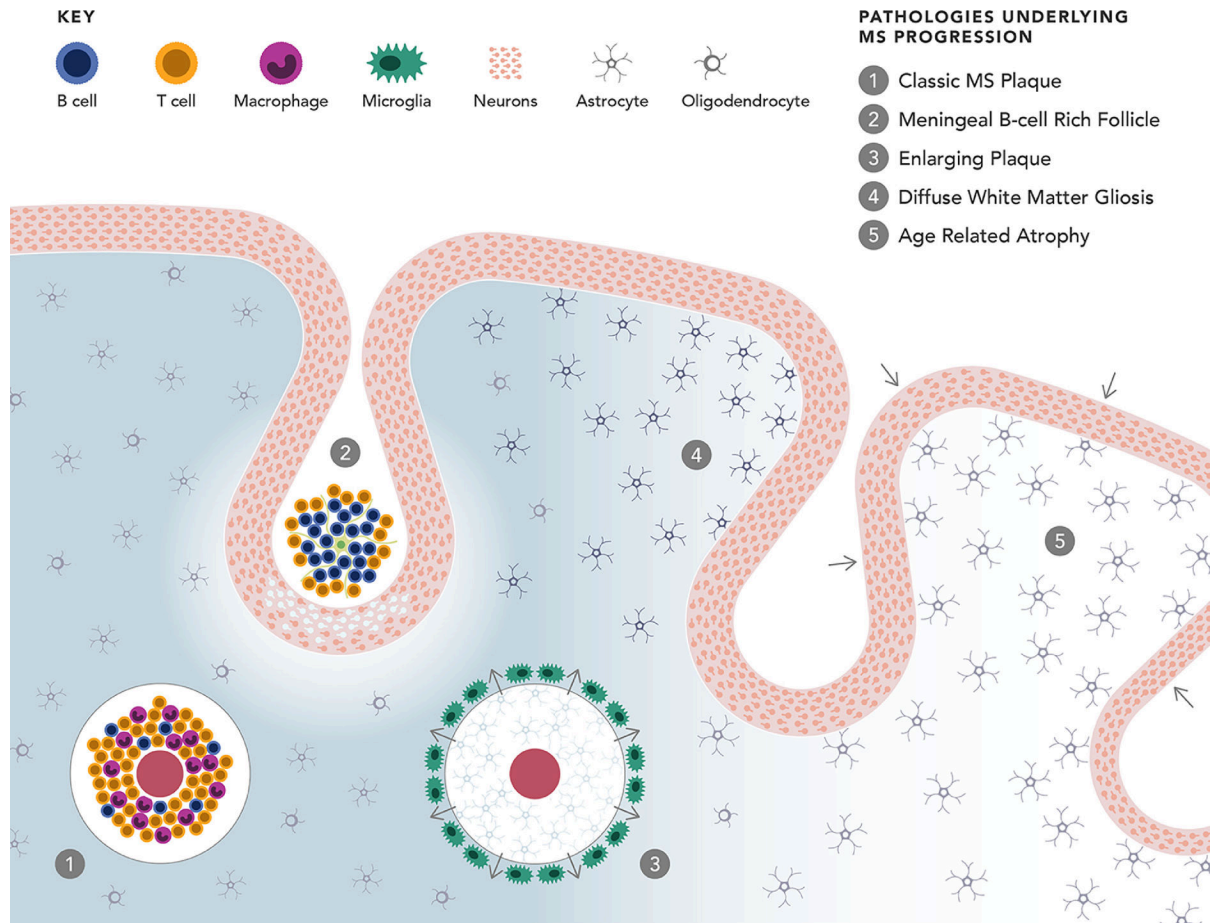
- Multiple sclerosis, a common autoimmune demyelinating disease of the central nervous system, has two major components: inflammation causing episodic attacks and neurodegeneration responsible for progressive worsening.
- Recently developed MS therapies are highly effective in preventing attacks and can partially protect against progression.
- Many experts now recommend the use of these therapies early in the disease course to protect against late disability.



**Figure 1. The New Natural History of MS**

The top half of the figure illustrates the natural history of relapse-onset MS in the pretreatment era. During the relapsing phase, disability accumulation was thought to result from incomplete recovery from relapses, until relapse-independent disability, designated SPMS, supervened. The “new” natural history of MS in the current treatment era is shown in the bottom half. With use of highly effective therapies, attacks are abolished in most patients, but insidious progression independent of relapse activity, termed “silent progression”, is now evident during the relapsing phase.

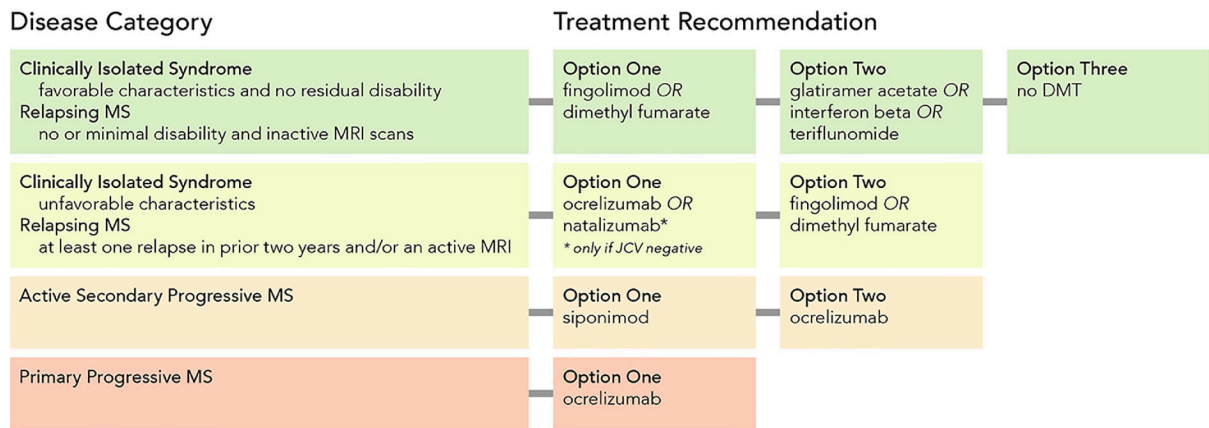
Abbreviations: EDSS, extended disability status score; CIS, clinically isolated syndrome; MS, multiple sclerosis; SPMS, secondary progressive multiple sclerosis.



**Figure 2. Five Distinctive Pathologies Likely Contribute to Progressive MS**

(1) Classic inflammatory white matter plaques are typically associated with relapses but also occur in patients who progress gradually without acute attacks. Hallmarks are perivenous inflammation dominated by lymphocytes and macrophages (detected by MRI as gadolinium enhancement indicating blood brain barrier disruption); demyelination associated with activated microglia; sharply demarcated plaques with glial scarring; and axonal loss with secondary retrograde and anterograde degeneration. (2) B cell rich lymphoid aggregates in the meninges, often in deep sulci, with underlying cortical demyelination and neuronal loss. (3) Slowly enlarging lesions due to gradual concentric expansion of chronic plaques, characterized by a rim of activated microglia at the leading edge, astrocytosis, stressed oligodendrocytes and progressive axonal injury. (4) Widespread diffuse microglial inflammation and astroglial changes throughout the CNS white matter, associated with decreased myelin density and ongoing axonal damage. (5) Age-related neurodegeneration. *For a more detailed discussion, readers may consult references<sup>66-68</sup>*

Abbreviations: CNS, central nervous system; MRI, magnetic resonance imaging; MS, multiple sclerosis.



**Figure 3. A Therapeutic Algorithm for Disease-Modifying Therapy Use in MS**

A simplified MS treatment algorithm based on the authors' practice pattern. Several drugs with proven effectiveness for MS are not mentioned, including: diroximel fumarate (presumably comparable to dimethyl fumarate); cladribine (reserved for MS refractory to at least two other treatments); alemtuzumab and mitoxantrone (not generally recommended due to severe toxicities); hematopoietic stem cell transplantation (reserved for severe treatment refractory disease unresponsive to high efficacy treatments); ozanimod (approved but not yet commercially available).

Abbreviations: DMT, disease-modifying therapy; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis.



**Table 1.**

Approach to the Diagnosis of Multiple Sclerosis

Symptoms	Magnetic Resonance Imaging (MRI)
<ul style="list-style-type: none"> <li>• Sensory loss or paresthesias (tingling)</li> <li>• Unilateral painful visual loss (optic neuritis)</li> <li>• Limb weakness (hyperreflexia, Babinski sign)</li> <li>• Facial weakness resembling Bell’s palsy</li> <li>• Visual blurring due to diplopia</li> <li>• Ataxia</li> <li>• Vertigo</li> <li>• Paroxysmal symptoms                             <ul style="list-style-type: none"> <li>– Lhermitte’s symptom (electric shock-like sensations evoked by neck flexion)</li> <li>– Trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia</li> <li>– Facial myokymia (rapid flickering contractions of the facial muscles)</li> </ul> </li> <li>• Heat sensitivity</li> <li>• Bladder dysfunction</li> <li>• Pain</li> <li>• Cognitive dysfunction, usually mild, “brain fog”, difficulty with multitasking.</li> <li>• Sexual dysfunction</li> <li>• Fatigue</li> </ul>	<ul style="list-style-type: none"> <li>• Multiple Lesions</li> <li>• White matter</li> <li>• Cerebral hemispheres, brainstem, spinal cord</li> <li>• Recent lesions enhance with gadolinium</li> <li>• Lesions perpendicular to ventricular surface and juxtacortical</li> </ul> <p><b>Cerebrospinal Fluid</b></p> <ul style="list-style-type: none"> <li>• Oligoclonal immunoglobulin</li> <li>• Modest inflammation (mononuclear cells)</li> </ul> <p><b>Evoked Potentials</b></p> <ul style="list-style-type: none"> <li>• Detect conduction delay in visual, auditory, and sensory pathways</li> </ul>
<b>Uncommon Symptoms (<i>Red Flags</i>)</b>	
<ul style="list-style-type: none"> <li>• Seizure</li> <li>• Dementia</li> <li>• Movement disorder</li> </ul>	

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**Table 2.**Diagnostic Criteria for Multiple Sclerosis<sup>65</sup>

<b>Criteria for diagnosis of multiple sclerosis in patients with an attack at onset</b>
2 attacks; objective clinical evidence of 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack
2 attacks; objective clinical evidence of 1 lesion <i>Dissemination in space, demonstrated by:</i> <ul style="list-style-type: none"> <li>• 1 T2 lesion on MRI in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• Await a further clinical attack implicating a different CNS site</li> </ul>
1 attack; objective clinical evidence of 2 lesions <i>Dissemination in time, demonstrated by:</i> <ul style="list-style-type: none"> <li>• Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• Await a second clinical attack</li> </ul>
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome) <i>Dissemination in space and time, demonstrated by:</i> <i>For dissemination in space</i> <ul style="list-style-type: none"> <li>• 1 T2 lesion in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• Await a second clinical attack implicating a different CNS site</li> </ul> <p style="text-align: center;">AND</p> <p><i>For dissemination in time</i></p> <ul style="list-style-type: none"> <li>• Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• Await a second clinical attack</li> </ul>
<b>Criteria for diagnosis of multiple sclerosis in patients with a disease course characterized by progression from onset (primary progressive multiple sclerosis)</b> Insidious neurologic progression suggestive of primary progressive multiple sclerosis <i>1 year of disease progression (retrospectively or prospectively determined)</i> <b>AND</b> <i>2 out of the 3 following criteria:</i> <ul style="list-style-type: none"> <li>• Evidence for dissemination in space in the brain based on 1 T2+ lesions in the MS-characteristic periventricular, juxtacortical, or infratentorial regions</li> <li>• Evidence for dissemination in space in the spinal cord based on 2 T2+ lesions in the cord</li> <li>• Positive cerebrospinal fluid (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)</li> </ul>

CNS, central nervous system; MRI, magnetic resonance imaging; MS, multiple sclerosis.

**Table 3.**

Summary of Approved Disease-Modifying Therapies for Multiple Sclerosis

Drug name	Mechanism of action	Indication	Route of and frequency of administration	Pivotal efficacy data	Common adverse events
<i>Highly effective</i>					
Ocrelizumab <sup>18,21</sup>	Anti-CD20 mAb	RMS and PPMS (1 <sup>st</sup> line)	IV infusion, every 6 months	RMS: Relative reduction in ARR compared with IFN $\beta$ -1a:47% PPMS: Relative reduction in 12-week CDP compared with placebo: 24%	RMS: Infusion-related reaction, nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection PPMS: Infusion-related reaction, upper respiratory tract infection, and oral herpes infection
Ofatumumab <sup>27</sup>	Anti-CD20 mAb	RMS (1 <sup>st</sup> line)	SC injection, every 4 weeks	Relative reduction in ARR compared with teriflunomide: 54%	Injection-related reaction, nasopharyngitis, headache, upper respiratory tract infection, and urinary tract infection
Natalizumab <sup>30</sup>	$\alpha$ 4 $\beta$ 1 integrin inhibitor	RRMS (2 <sup>nd</sup> line)	IV infusion, every 4 weeks	Relative reduction in ARR compared with placebo: 68% Relative reduction in sustained disease progression compared with placebo: 42%	Fatigue and allergic reaction
Alemtuzumab <sup>59-61</sup>	Anti-CD52 mAb	RMS (1 <sup>st</sup> line)	IV infusion, once daily	Relative reduction in ARR compared with placebo: 49–69%	Headache, rash, nausea, and pyrexia
Mitoxantrone <sup>58</sup>	DNA intercalator	RMS, SPMS (2 <sup>nd</sup> or 3 <sup>rd</sup> line)	IV infusion, every month or 3 months	Relative reduction in relapses compared with placebo: 61%	Dose-related cardiomyopathy, promyelocytic leukemia
<i>Moderately effective</i>					
Fingolimod <sup>34,36</sup>	Sphingosine 1-phosphate inhibitor	RMS (2 <sup>nd</sup> line)	Oral, once daily	Relative reduction in ARR compared with placebo: 48–60%	Bradycardia, atrioventricular conduction block, macular edema, elevated liver-enzyme levels, and mild hypertension
Siponimod <sup>64</sup>	Sphingosine 1-phosphate receptor modulator	CIS, RMS, active SPMS (1 <sup>st</sup> Line)	Oral, once daily	Relative reduction in 12-week CDP compared with placebo: 21%	Headache, nasopharyngitis, urinary tract infection, and falls
Ozanimod <sup>39,40</sup>	Sphingosine 1-phosphate receptor modulator	CIS, RMS, active SPMS	Oral, once daily	Relative reduction in ARR compared with placebo: 48%	Headache and elevated liver aminotransferase
Dimethyl fumarate and diroximel Fumarate <sup>41,42</sup>	Nuclear factor (erythroid-derived 2)-like 2 pathway inhibitor	RMS (1 <sup>st</sup> line)	Oral, twice daily	Relative reduction in ARR compared with placebo: 48–53%	Flushing, diarrhea, nausea, upper abdominal pain, decreased lymphocyte counts, and elevated liver aminotransferase
Cladribine <sup>62</sup>	Not fully known	RMS (2 <sup>nd</sup> or 3 <sup>rd</sup> line)	Oral, 4–5 days over 2-week treatment courses	Relative reduction in ARR compared with placebo: 55–58%	Headache, lymphocytopenia, nasopharyngitis, upper respiratory tract infection, and nausea
<i>Modestly effective</i>					

Drug name	Mechanism of action	Indication	Route of and frequency of administration	Pivotal efficacy data	Common adverse events
Teriflunomide <sup>47</sup>	Dihydroorotate dehydrogenase inhibitor	RMS (1 <sup>st</sup> line)	Oral, once daily	Relative reduction in ARR compared with placebo: 32–36%	Nasopharyngitis, headache, diarrhea, and alanine aminotransferase increase
Glatiramer Acetate <sup>35</sup>	Not fully known	RMS (1 <sup>st</sup> line)	SC injection, once daily or 3 times weekly	Relative reduction in ARR compared with placebo: 29%	Injection-site reactions
IFN $\beta$ -1a (Rebif) <sup>69</sup>	Not fully known	CIS and RMS (1 <sup>st</sup> line)	SC injection, 3 times weekly	Relative reduction in ARR compared with placebo: 33%	Injection-site inflammation, flu-like symptoms, rhinitis, and headache
IFN $\beta$ -1a (Avonex) <sup>51</sup>	Not fully known	CIS and RMS (1 <sup>st</sup> line)	IM injection, once weekly	Relative reduction in 24-week CDP compared with placebo: 37%	Flu-like symptoms, muscle aches, asthenia, chills, and fever
PegIFN $\beta$ -1a (Plegridy) <sup>70</sup>	Not fully known	CIS and RMS (1 <sup>st</sup> line)	SC injection, every 2 weeks	Relative reduction in ARR compared with placebo: 39%	Injection-site erythema, influenza-like illness, pyrexia, and headache
IFN $\beta$ -1b (Betaseron) <sup>50</sup>	Not fully known	CIS and RMS (1 <sup>st</sup> line)	SC injection, every other day	Relative reduction in ARR compared with placebo: 31%	Lymphopenia, flu-like symptoms, and injection-site reactions

ARR, annualized relapse rate; CDP, confirmed disability progression; CIS, clinically isolated syndrome; IFN  $\beta$ -1a, interferon beta 1a; IM, intramuscular; IV, intravenous; mAb, monoclonal antibody; PPMS, primary progressive multiple sclerosis; RMS, relapsing forms of multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis.