Multiple Sclerosis Update

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Abstract

Multiple sclerosis (MS) is a chronic but incurable disease of the central nervous system (CNS) that is often diagnosed in the second or third decade of life. It is more common among women than men, significantly impairs patient quality of life, and is associated with substantial costs to patients, healthcare systems, and society. Of the approximately 2.3 million individuals worldwide that have MS, more than 400,000 reside in the United States. Although the etiology of MS is not completely understood, a great deal of evidence suggests a complex relationship between environmental and genetic factors. The pathophysiology of MS involves an aberrant attack by the host immune system on oligodendrocytes, which synthesize and maintain myelin sheaths in the CNS. There are 4 identified disease courses in MS, and approximately 85% of people with MS present with relapsing-remitting MS, which is characterized by discrete acute attacks followed by periods of remission. Signs and symptoms of MS are dependent on the demyelinated area(s) of the CNS and often involve sensory disturbances, limb weakness, fatigue, and increased body temperature. The criteria for a diagnosis of MS include evidence of damage in at least 2 separate areas of the CNS, evidence that the damage occurred at different time points, and the ruling out of other possible diagnoses. Disease-modifying drugs (DMDs) that reduce the frequency of relapses, development of brain lesions, and progression of disability are the standard of care for relapsing forms of MS, and the use of DMDs should be initiated as early as possible.

(Am J Manag Care. 2013;19(16):S294-S300)

For author information and disclosures, see end of text.

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) in which inflammation and breakdown occur in the protective insulation that surrounds nerve fibers (myelin), thereby disrupting signals from within the brain, as well as between the brain and the host body. It results in a variety of neurological symptoms that depend upon which pathways are disrupted.[1,2] While the onset of MS for most individuals typically occurs between their 20s and 50s, with 2 to 3 times as many women as men being diagnosed with MS, approximately 2% and 5% of patients encounter disease onset before the ages of 10 and 16 years, respectively.[2,3] Although life expectancy with MS is at least 25 years from disease onset, with most patients dying from unrelated causes,[3] those with MS have worse health-related quality-of-life scores than the general population with regard to physical functioning, vitality, and general health.[4-6] Additionally, several studies have evaluated the economic burden associated with MS in the United States, with results indicating that MS is very costly to individuals, healthcare systems, and society.[7-10]

Epidemiology

Approximately 2.3 million individuals worldwide have MS, which includes more than 400,000 in the United States.[2] In addition, an estimated 200 persons are diagnosed with MS each week in the United States, which translates to roughly 1 diagnosis of MS every hour.[2] The largest and most recent examination of the worldwide prevalence of this often unpredictable and debilitating disease was conducted in a large international study from 2005 to 2007, and included over 100 countries that spanned all World Health Organization (WHO) regions and continents.[11]

Data from the WHO study indicated that the global median estimated prevalence of MS was 33 cases per 100,000 persons. While MS is present in all regions of the world, its prevalence varies greatly; the highest rates per 100,000 persons were found in North America (140) and Europe (108), and the lowest rates were found in sub-Saharan Africa (2.1) and East Asia (2.2).[11] Furthermore, the prevalence of MS may also vary substantially within each region; for instance, in Europe, the highest prevalence per 100,000 persons is found in Sweden (189), whereas the lowest is found in Albania (22).[11] Reasons for the observed variation

in worldwide prevalence and incidence of MS are not well understood, and although environmental and genetic explanations have been offered, it is widely accepted that both factors likely play important roles.

Etiology and Pathophysiology

The etiology of MS is not completely understood, but epidemiological and association studies do suggest a relationship between multiple environmental and genetic factors.[3,12] Several environmental risk factors for MS that have been identified include high Epstein-Barr virus immunoglobulin G antibody titers, low levels of vitamin D and/or ultraviolet radiation exposure, and cigarette smoking.[12-14] In addition to these environmental factors, genetic components are thought to be involved in the etiology of MS. The disease is known to aggregate in families,[15] and has higher concordance rates in monozygotic twins (up to 30.8%) compared with dizygotic twins (2.4%-4.7%), ordinary siblings (3%),[16,17] or half-siblings (1.32%).[18] Although children of 2 parents with MS have a 5.8% chance of developing MS,[19] no increased risk was observed among adoptive relatives.[20]

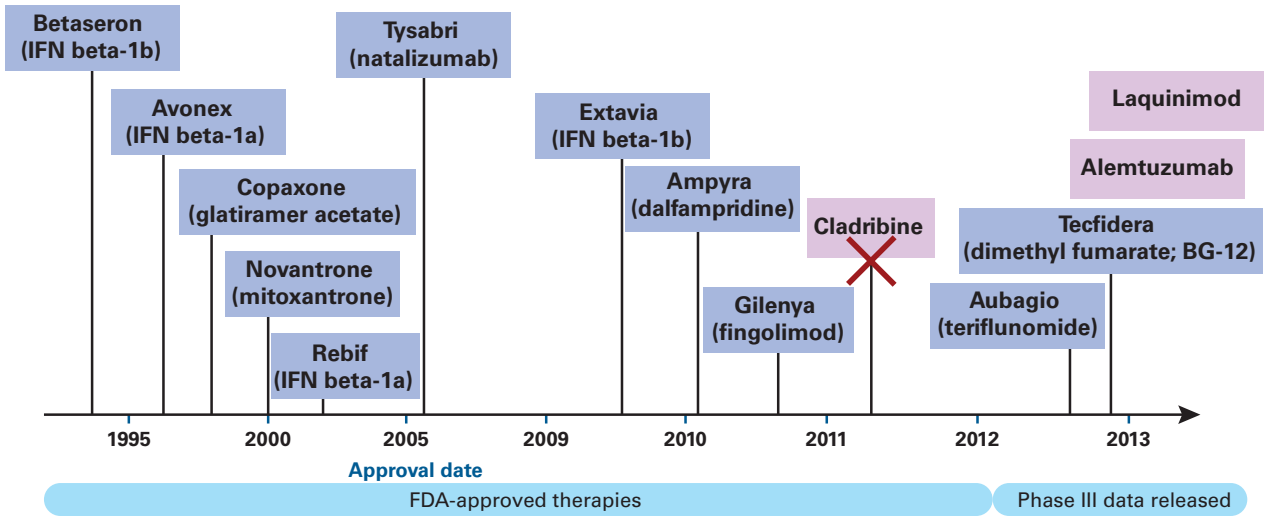
Multiple sclerosis is characterized by acute focal inflammatory demyelination and axonal loss with limited remyelination, which results in chronic multifocal sclerotic plaques. The atrophy and accelerated loss of brain gray matter has also been correlated with disability progression in MS.[3,21] Regarding the pathophysiology of MS, oligodendrocytes, which synthesize and maintain the myelin sheath of up to 40 neighboring nerve axons in the CNS, is the principal target of immune attacks in MS.[3] The breakdown of immune regulation in autoimmune diseases such as MS is thought to be attributable to molecular mimicry, in which a peptide presented to the peptide-binding groove of a specific class II molecule is immunologically indistinguishable from a self-antigen. Therefore, in MS, an appropriate immunological response to infection can inadvertently generate inappropriate inflammation against a component of the oligodendrocyte-myelin unit, which results in temporally and spatially segregated inflammatory lesions. This breakdown of host immune regulation can lead to the proliferation and activation of autoreactive T cells and their subsequent entry into circulation. These cells can express adhesion molecules and induce reciprocal changes in endothelia, allowing the T cells to cross the blood-brain barrier (BBB) into the CNS. Once within the host CNS, the activated T cells initiate a proinflammatory loop by re-encountering the antigen and activating the microglia, causing the expression of class II molecules and re-presenting of antigen to T cells. Toxic inflammatory mediators are then released, sustaining a breakdown of the BBB and leading to injury of axons and glia. Although cytokines and growth-promoting factors, which are released by reactive astrocytes and microglia as part of the acute inflammatory process, can promote endogenous remyelination, astrocyte reactivity and gliosis can lead to a physical barrier that prevents further remyelination.[3]

Clinical Course and Diagnosis

Four disease courses have been identified in MS: (1) relapsing-remitting MS (RRMS); (2) primary-progressive MS (PPMS); (3) secondary-progressive MS (SPMS); and (4) progressive-relapsing MS (PRMS).[22] Although the course of the disease in an individual is largely unpredictable, approximately 85% of people with MS begin with a relapsing-remitting course and experience discrete, acute attacks, which are followed by periods of remission.[2,22] These exacerbations may occur at random intervals with a limited annual frequency that steadily decreases over time, and in some cases, patients may recover fully; however, in some patients a residual deficit will remain and continue to worsen with each exacerbation.[3,22] Although most patients with MS will begin with relapsing-remitting disease, more than 50% of untreated patients will develop SPMS within 10 years, and 90% within 25 years. During this time, those patients will lose the ability to fully recover following exacerbations, which results in a disease and symptomatology that progressively worsens.[2,22] Patients with SPMS may also experience relapses, minor remissions, and plateaus.[22] PRMS, which is detected in approximately 5% of individuals with MS at diagnosis, is defined as disease that progresses from the onset of MS, with patients experiencing acute exacerbations and continuing disease progression during the periods between relapses.[2,22] PPMS, which is diagnosed in approximately 10% of patients with MS, is defined as disease that demonstrates a gradual and nearly continuous progression from onset, without relapses and remissions.[2,22] Although some patients may experience an almost steady progression from the beginning, other patients may encounter an occasional plateau during which no progression is noted, and some may even experience minor but temporary improvements.[22]

MS is associated with a wide array of signs and symptoms that are largely attributable to the affected and damaged area(s) of the CNS. Based on the location(s) of the lesion(s), such as the cerebrum, optic nerve, cerebellum, brain stem, or spinal cord, RRMS can be accompanied by limb weakness, clumsiness, gait ataxia, symptoms of neurogenic bladder and/or bowel, sensory disturbances, unilateral optic neuritis, diplopia (internuclear ophthalmoplegia), and trunk and limb paresthesias that are evoked by neck flexion (and referred to

Figure. The Evolving MS Treatment Landscape



FDA indicates US Food and Drug Administration; IFN, interferon; MS, multiple sclerosis.

as Lhermitte's sign).[3,23] Another common feature of RRMS is fatigue that worsens in the afternoon, coupled with increased body temperature.[3,23] The characteristic appearance of signs and symptoms following exercise or a hot bath, which is referred to as Uhthoff's phenomenon, is partially due to the demyelinated axons that cannot sustain a reduction of membrane capacitance that is induced by a rise in temperature, which results in conduction failure.[3,23] Due to the overlap of signals from neighboring demyelinated axons, some patients may experience a brief (1-2 minutes) but recurrent stereotypical phenomenon that is often triggered by touch or movement, referred to as paroxysmal symptoms, which includes trigeminal neuralgia, ataxia, dysarthria, and a painful tetanic posturing of the limbs.[3,23] Although more prominent cortical signs (eg, visual field loss, early dementia, aphasia, recurrent seizures, apraxia, chorea, and rigidity) are rarely primary manifestations of CNS dysfunction, other manifestations of CNS dysfunction (eg, cognitive impairment, depression, emotional lability, dysarthria, dysphagia, vertigo, progressive quadriparesis and sensory loss, ataxic tremors, pain, sexual dysfunction, and spasticity) may develop and become increasingly troublesome.[3,23] The signs and symptoms of PPMS are characterized by a slowly evolving upper motor neuron syndrome of the legs, referred to as chronic progressive myelopathy, which worsens gradually and may result in the development of quadriparesis, cognitive decline, visual loss, and brain-stem syndromes, as well as cerebellar, bowel, bladder, and sexual dysfunction.[23]

Unfortunately, there are no stand-alone symptoms, physical findings, or laboratory tests that can be utilized independently to conclusively determine whether or not an individual has MS.[2] Therefore, the diagnosis of MS is based upon established clinical[24,25] and, when necessary, laboratory criteria.[24] Diagnosis of MS entails a careful review of medical history, a neurologic exam, and various other assessments, including magnetic resonance imaging (MRI), evoked potential (EP) testing, and cerebrospinal fluid (CSF) analysis.[2] In general, the criteria for a confirmed diagnosis of MS must include evidence of damage in at least 2 separate areas of the CNS (disseminated in space [DIS]), evidence that the damage occurred at different time points (disseminated in time), and the ruling out of all other possible diagnoses.[2,24]

An essential component of MRI analysis in MS is the presence of gadolinium-enhancing lesions. Gadolinium is a chemical contrast agent used during MRI scans to highlight areas of inflammation, which may indicate active lesions and/or sites of presumed inflammatory demyelination. It is important to note that some tissues may appear to be brighter or darker than other tissues on an MRI scan. This contrast depends on the density of protons in that area such that areas with an increased density appear darker on the scan. Furthermore, relaxation times for protons may vary, and therefore 2 times are commonly measured, T1 and T2. In T1-weighted MRI images, white matter (ie, fat, water, and other fluids) is darker than gray matter, whereas in T2-weighted images, white matter is brighter than gray matter.[25]

EP analysis may also be useful in identifying DIS by providing physiologic evidence of subclinical dysfunction of the optic nerves and spinal cord through changes in visual evoked responses and somatosensory EPs.[26] Further, CSF analysis may

Table. Selected Information on DMDs and Other Agents Approved by the US Food and Drug Administration for MS[42-52]

Generic name	Brand name(s)	Dosing information	Proposed mechanism of action
Interferon beta-1b	Betaseron Extavia	0.0625 mg (0.25 mL) subcutaneously every other day, with dose increases over a 6-week period to the recommended dose of 0.25 mg (1 mL) every other day	Unknown
Interferon beta-1a	Avonex	7.5 µg intramuscularly once a week, with dose increases over a 3-week period to the recommended dose of 30 µg once a week	Unknown
	Rebif	4.4 or 8.8 µg subcutaneously 3 times a week with dose increases over a 5-week period to the recommended dose of 22 or 44 micrograms 3 times a week	Unknown
Glatiramer acetate	Copaxone	20 mg subcutaneously every day	Not fully understood; however, glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of multiple sclerosis
Mitoxantrone	Novantrone	12 mg/m^2 given as a short (approximately 5-15 min) intravenous infusion every 3 months	• Deoxyribonucleic acid (DNA)-reactive agent, intercalates into DNA through hydrogen bonding, causes crosslinks and strand breaks • Also interferes with ribonucleic acid and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA • Has a cytocidal effect on both proliferating and nonproliferating cultured human cells, suggesting lack of cell cycle phase specificity • Has been shown in vitro to inhibit B-cell, T-cell, and macrophage proliferation and impair antigen presentation, and decrease the secretion of interferon gamma, tumor necrosis factor α, and interleukin-2
Natalizumab	Tysabri	300 mg intravenous infusion over approximately 1 hour every 4 weeks	• Binds to the α4 subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptor(s) • Receptors for the α4 family of integrins include vascular cell adhesion molecule-1, which is expressed on activated vascular endothelium, and mucosal addressin cell adhesion molecule-1 present on vascular endothelial cells of the gastrointestinal tract • Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue • In vitro, anti-α4-integrin antibodies also block α4-mediated cell binding to ligands such as osteopontin and an alternatively spliced domain of fibronectin connecting segment-1 • In vivo, may further act to inhibit the interaction of α4-expressing leukocytes with their ligand(s) in the extracellular matrix and on parenchymal cells, thereby inhibiting further recruitment and inflammatory activity of activated immune cells • Specific mechanism(s) in multiple sclerosis have not been fully defined

(Continued)

Table. Selected Information on DMDs and Other Agents Approved by the US Food and Drug Administration for MS[42-52] *(Continued)*

Generic name	Brand name(s)	Dosing information	Proposed mechanism of action
Dalfampridine	Ampyra	≤10 mg orally twice daily	• Mechanism in multiple sclerosis has not been fully elucidated • Is a broad spectrum potassium channel blocker • Has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels in animal studies
Fingolimod	Gilenya	0.5 mg orally once daily	• Metabolized by sphingosine kinase to the active metabolite • Is a sphingosine 1-phosphate receptor modulator, and binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5 • Blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood • Mechanism in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system
Teriflunomide	Aubagio	7 mg or 14 mg orally once daily	• Is an immunomodulatory agent with anti-inflammatory properties • Inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis • Exact mechanism in multiple sclerosis is unknown but may involve a reduction in the number of activated lymphocytes in the central nervous system
Dimethyl fumarate	Tecfidera	120 mg twice a day orally for 7 days, then increase to the maintenance dose of 240 mg twice a day orally	• Mechanism in multiple sclerosis is unknown • Dimethyl fumarate and the metabolite, monomethyl fumarate (MMF), have been shown to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist in vitro

DMD indicates disease-modifying drug; MS, multiple sclerosis.

assist in the diagnostic process, as those with MS typically have increased intrathecal synthesis of immunoglobulins of restricted specificity, as well as occasional, moderate lymphocytic pleocytosis (fewer than 50 mononuclear cells). The use of the aforementioned diagnostic techniques is particularly important in evaluating patients who present with a clinically isolated syndrome (CIS), which is defined as the first neurologic episode that persists for a minimum of 24 hours and is caused by inflammation/demyelination in 1 (monofocal) or more (multifocal) sites in the CNS.[24,27] Patients with MS who experience a CIS that is characterized by cerebellar or brainstem dysfunction, or incomplete transverse myelitis, as their first event have an increased risk of both recurrent events and disability within a decade if changes are seen in clinically asymptomatic regions of the brain on MRI.[28] It is interesting to note that modern diagnostic techniques for MS are also being used to assess the possibility of MS in persons with MRI findings that are suggestive of the disease but do not have the typical symptoms associated with MS, a condition referred to as radiologically isolated syndrome (RIS).[29] In the first study of patients with RIS, published in 2009, 18 of 27 patients (66.6%) had CSF measures that were indicative of MS, and 24 of 41 (58.5%) demonstrated radiological progression in the form of new T2 lesions, gadolinium enhancement, or enlarging T2 lesions over a median time period of 2.7 years.[29]

Treatment

Traditionally, therapies for MS have been divided into 2 categories: (1) treatments for exacerbations and relapses, such as glucocorticoids and plasmapheresis (not recommended by current treatment guidelines), which is also referred to as apheresis, plasma exchange, or "plex"; and (2) immuno-

modulatory disease-modifying drugs (DMDs) that reduce the frequency of relapses, the development of brain lesions, and the progression of disability.[30] In patients with MS, treating only the exacerbations has been associated with a variety of negative outcomes. In studies that examined the natural course of the disease, clinical progression of RRMS resulted in SPMS within 10 years in more than 50% of all cases, and in 90% within 25 years,[2,31] with 29% of patients worsening by 1 to 1.5 points (from an initial score of 0) on the Expanded Disability Status Scale (EDSS) within 2 years.[24,32-36] (The EDSS score is a common end point in MS clinical trials, and a 1-point increase has been used to define disability progression.[37,38]) Although these data suggest that treatment beyond exacerbations and relapses is essential for improved patient outcomes, further research examining the pathophysiology of MS led to several other observations that underscore the need for early treatment. For example, inflammatory activity, which is the precursor of irreversible neurodegeneration, occurs early in the clinical sequelae of MS.[39,40] Therefore, it is critical to initiate therapies that inhibit the inflammatory process early. As such, the disease management consensus statement from the National Multiple Sclerosis Society recommends that DMDs be made available early in the disease process to the appropriate candidates.[41]

A timeline that depicts the history of DMD availability, as well as DMDs in development, is shown in the **Figure**, with selected information about DMDs approved by the US Food and Drug Administration (FDA) listed in the **Table**.[42-52] Currently, 11 agents have been approved by the FDA for use in MS.[42-52] Since 2009, a wave of newer agents gained FDA approval, nearly doubling the therapeutic armamentarium.[43,49-52] In addition to the current repertoire of DMDs, the drug pipeline for MS, which has seen increased activity in recent years, contains several novel agents for MS that are currently under investigation, including 1 oral agent (laquinimod) and 2 intravenous agents (alemtuzumab and ocrelizumab).[53-55]

Conclusion

MS is a progressive and incurable disease that substantially decreases patient quality of life and is associated with a clinical and economic burden that weighs heavily on the affected individual, healthcare and managed care systems, and society as a whole. CIS is the first recognizable clinical event that a patient may experience, and it should be treated as the first event of MS. Similarly, RIS is associated with a high risk of progressing to CIS/MS and should therefore be monitored closely. The use of MRI has greatly benefited the therapeutic space for MS, allowing clinicians to make a diagnosis sooner, and providing the opportunity to consider appropriate treatment earlier in the course of the debilitating disease. Additionally, our improved and increasing understanding of the host immune system and its role in the pathogenesis of MS is paving the way for novel, targeted immunotherapies. With new therapies for MS on the horizon, clinicians will have more treatment options for their patients, but are simultaneously faced with additional therapeutic complexity. It is likely that novel mechanisms of action and new agents for MS will raise concerns about the unknown, rare, or long-term safety and efficacy issues, and undoubtedly, additional long-term studies, data collection and analysis, and post marketing surveillance are necessary. However, it is clear that the therapeutic landscape for MS is evolving and will continue to progress, with notable implications for further personalized medicine and improved outcomes.

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Funding source: This activity is supported by educational grants from Bayer HealthCare Pharmaceuticals; Biogen Idec; EMD Serono, Inc; Genzyme Corporation; and Questcor Pharmaceuticals, Inc.

Author disclosure: Dr Markowitz reports serving as a consultant/paid advisory board member for Bayer HealthCare Pharmaceuticals; Biogen Idec; Acorda; EMD Serono, Inc; Genentech; Genzyme Corporation; Novartis; and Teva.

Authorship information: Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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