

Multiple Sclerosis: The Safety–Efficacy Balance and Preventing Neurodegeneration

Introduction

The treatment landscape for multiple sclerosis (MS) has seen extensive growth over the last several decades. While the field still lacks universally accepted, algorithm-based treatment guidelines for the management of multiple sclerosis (MS),¹ available guidelines advocate that patients should have open access to any currently approved disease-modifying therapies (DMTs).^{2,3}

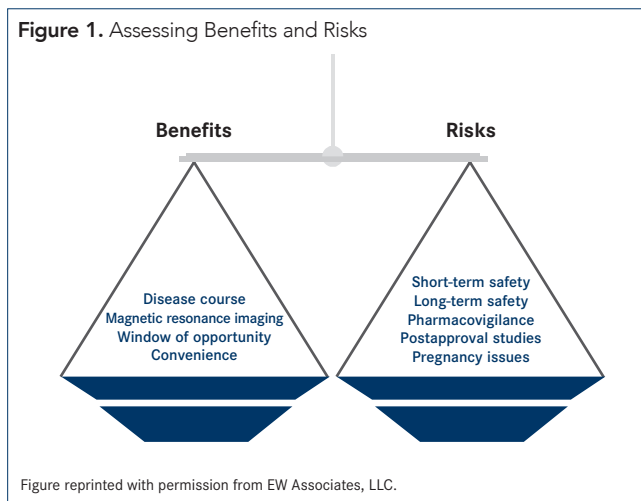
Historically, initial treatment with DMTs begins with first-generation injectable products (ie, interferon beta products and glatiramer acetate), as the efficacy and safety of these products are well understood.⁴ Treatment with first-generation injectable products require frequent subcutaneous or intramuscular injections, are moderately effective, and are not associated with rare, life-threatening adverse reactions (such as infections and cancers).^{4,5} Although oral agents and recently approved injectable products are associated with improved efficacy, they have been associated with serious adverse reactions, some of which are life-threatening.⁴ (See **Figure 1** and **Figure 2**.)

When patients are diagnosed with MS and have their first neurological symptoms, axonal loss has already occurred.⁶ Because brain atrophy, specifically gray matter atrophy, creates permanent damage and correlates with physical and cognitive disability, there is a need to treat the disease process as early as possible.

When evaluating currently approved DMTs, those that modulate CD8+ T cell proliferation (eg, dimethyl fumarate) appear to have neuroprotective benefits.⁷ Much of the current research in MS involves the identification of remyelination therapies that can reverse the neurodegenerative damage that occurs in MS.

Evidence-Based Treatment Guidelines

Despite the lack of universally accepted algorithm-based treatment guidelines for MS, the 2007 Consensus Statement from the National Clinical Advisory Board of the National Multiple Sclerosis Society made suggestions regarding the use of interferon beta products, glatiramer acetate, and mitoxantrone.² According to the guidelines, a patient's access to medication should not be limited by their age, frequency of relapses, or level of disability. Moreover, treatment should not be delayed or discontinued while insurers evaluate for continuing treatment coverage, as this would put patients at increased risk for recurrent disease activity. The guidelines also note that therapy should be continued indefinitely except if patients experience a clear lack of benefit,

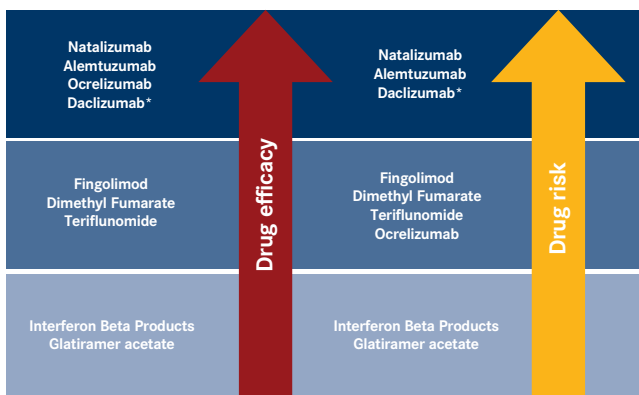


intolerable adverse effects, or if better therapy becomes available. Changing from one DMT to another should be medically justifiable, according to the guidelines.²

Additionally, the guidelines indicate that all FDA-approved agents should be included in formularies and covered by third-party payers to help physicians and patients determine the most appropriate agent on an individual basis; failure to do so is unethical and discriminatory.² Importantly, none of these therapies have been approved for use for women who are pregnant or trying to become pregnant, or for nursing mothers.² **Figure 1** and **Figure 2** offer information on the risks and benefits that should be taken into consideration when selecting therapy.

Although the algorithm portion of this consensus statement is outdated, the recommendations related

Figure 2. Relative Efficacy and Risk of FDA-Approved Disease-Modifying Therapies



FDA indicates Food and Drug Administration. Figure reprinted with permission from EW Associates, LLC.

to access to DMTs are still applicable. A more recent Consensus Paper from the MS Coalition, released in 2014, also addresses access to DMTs.³ Both guidelines advocate that patients should have open access to any currently approved DMTs.

Evaluating Efficacy

Efficacy plays an important role in the choice of an initial DMT treatment.⁸ For patients with mild or moderate disease, efficacy may be among many considerations, but for patients with more aggressive disease, efficacy may be more important than other factors.⁸

Patients with more aggressive disease are generally characterized by¹:

- Disease onset >40 years
- Male gender
- Initial symptoms being motor or cerebellar; polysymptomatic
- High attack frequency in early disease
- Incomplete recovery after first event
- High load of T2 lesions and T1 black holes
- Rapid growth of lesions
- Multiple locations of lesions

Because there are no currently available biomarkers that predict response to particular DMTs, efficacy must be discussed at the population level using clinical trial data.⁸ However, head-to-head data are scarce. Additionally, it is difficult to compare results among trials because of the differences in trial characteristics (eg, differences in study populations and outcome measures).⁸ For example, earlier trials (prior to the millennium), included patients with higher Expanded Disability Status (EDS) and who had more disease activity compared with the trials conducted in the postmillennium period. (For more information regarding EDS, see **Figure 3**.)

When evaluating efficacy, it is also important for clinicians to understand that the relationship among inflammatory activity, concurrent or subsequent neurodegeneration, and disease progression that leads to disability remains inconclusive.⁸ Because long-term trial data are limited for the majority of DMTs, it not possible to ascertain the long-term benefits (>2 years) of DMTs on these parameters.

Evaluating response to DMTs is most commonly accomplished using relapse rates, magnetic

resonance imaging (MRI) scans, EDS scoring, and Multiple Sclerosis Functional Composite (MSFC) scoring.⁹ For more information on assessing a patient's therapeutic response, see **Table 1**.^{9,11-13}

Safety Considerations

The currently available DMTs exert their effects on the immune system either by immunomodulatory or immunosuppressant effects, with some producing both.¹ Risk can be mitigated through careful patient selection and close monitoring. Since the interferon beta products and glatiramer acetate have been on the market the longest, the safety risks for those products are well documented.⁸ Likewise, after 10-plus years of postmarketing data, the safety profile of natalizumab is also well documented.⁸ While the safety concerns with the oral agents and newer injectable DMTs are generally known, it is possible that new safety concerns could arise in postmarketing surveillance, either because exposure has not yet reached the required threshold of total patient years or because long-term data are insufficient.^{8,10}

The interferon beta products and glatiramer acetate are generally associated with the fewest adverse events, in terms of number and severity. Products such as natalizumab, daclizumab*, and alemtuzumab, which have Risk Evaluation and Mitigation Strategies (REMS), are associated with more adverse events, in terms of number and severity, and require increased monitoring.^{8,10} See **Table 2** for more information on monitoring considerations and use in pregnancy and lactation.^{4,14-23}

Preventing Neurodegeneration

White Matter Versus Gray Matter Pathology

Multiple sclerosis has traditionally been considered a disease of white matter.²⁴⁻²⁶ More recent data suggest that there is also gray matter involvement, as the development

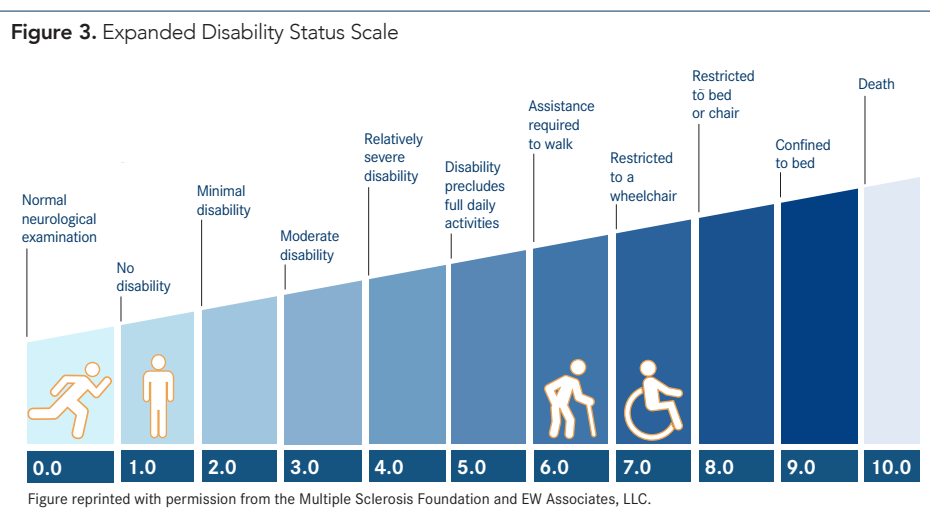


TABLE 1. Assessing Therapeutic Response^{9,10}

Relapse rates	<ul style="list-style-type: none"> Relapses are defined as new or worsening neurological symptoms that are objectified on neurological examination in the absence of fever and last >24 hours, and have been preceded by a period of clinical stability of ≥30 days, with no other explanation than MS The relationship between relapses and disability worsening is not completely clear. Limitations <ol style="list-style-type: none"> Subjective Requires patient reporting Recovery of signs and symptoms may occur before confirmation of relapse Newly reported symptoms may not be clearly depicted as a change of EDSS
MRI scans	<ul style="list-style-type: none"> MRI is sensitive in detecting, characterizing, and quantifying lesions in the white matter. MRI is highly sensitive in detecting disease activity. The most commonly used MRI measures of disease activity in clinical practice include new or enlarging T2 lesions (white spots observed on MRI) in serial scans, Gd-enhancing T1 lesions, hypointense T1 lesions (black holes), and disease burden, which is based on the total T2 lesion volume. Limitation: Widespread changes, such as neurodegeneration or possible remyelination, are not adequately assessed by conventional MRI.
EDSS	<ul style="list-style-type: none"> Assesses response using an ordinal scale, 0-10 (0 = normal neurological exam; 10 = death from MS) Limitations <ol style="list-style-type: none"> Subjective Scoring is nonlinear Only measures ambulation Cognitive impairment is not taken into consideration
MSFC	<ul style="list-style-type: none"> Developed because of limitations associated with EDSS Covers leg function/ambulatory, arm/hand function, and cognitive function Results are depicted in an interval scale and can be converted to a Z-score Limitations <ol style="list-style-type: none"> Moderate reliability, sensitivity, and responsiveness of the PASAT Does not assess several functional domains Lack of clear dimension of the overall score

EDSS indicates Expanded Disability Status Scale; Gd, gadolinium; MRI, magnetic resonance imaging; MSFC, Multiple Sclerosis Functional Composite; PASAT, paced auditory serial addition task.

of some clinical features, such as cognitive impairment, cannot be fully explained by the severity of white matter pathology alone.²⁵ Gray matter lesions are clearly defined areas of demyelination within the cerebral cortex, basal ganglia, and gray matter of the spinal cord and brainstem.²⁵ A growing body of evidence suggests that gray matter involvement and the mechanism of neurodegeneration are at least partially independent from inflammation.^{6,25}

MRI is the most important diagnostic and monitoring tool to assess the onset and progression of MS.⁹ Since the introduction of MRI, white matter lesions tend to be easily and accurately visualized.²⁵ In contrast, gray matter lesions are more difficult to visualize through traditional MRI scans and have a different underlying pathology.²⁶ Gray matter is less inflammatory (with limited infiltration of immune cells), small and potentially undetectable (with insufficient spatial resolution), and hard to distinguish from normal surrounding tissues due to volume effects of nearby cerebrospinal fluid (CSF).²⁶

Nonconventional MRI techniques are required to assess pathogenic processes associated with disease activity

and progression, including the presence of gray matter pathology.^{24,25} These techniques can identify the underlying pathology within lesions and brain tissue which appear to be normal (such as edema, inflammation, demyelination, axon loss, and neurodegeneration). While newer imaging sequences (including ultra-high-field MRI and magnetic resonance spectroscopy) have greatly improved detection of gray matter lesions,²⁵ these technologies are not readily available/accessible. Thus, a “gold standard” imaging model has not yet been developed for gray matter demyelination.

Gray Matter Atrophy Leads to Neurodegeneration and Cognitive Impairment

Over the past decade, results of several studies have demonstrated that brain volume reduction (atrophy), which is a measure of neurodegeneration, occurs faster in people with MS.^{9,10} Average brain volume loss per year is 0.5% to 1.0% in patients with MS compared with 0.1% to 0.3% in healthy individuals.⁹ The pathogenesis of brain atrophy in MS is complex and not completely clear.

TABLE 2. Monitoring Considerations and Use in Pregnancy/Lactation^{4,14-23}

Drug	Monitoring Consideration	Use in Pregnancy/Lactation
First-Generation Injectable Products		
Interferon beta products	<ul style="list-style-type: none"> Obtain MRI scans, CBC, and LFTs prior to treatment. Monitor LFTs at 1, 3, and 6 months, and then periodically as clinically necessary; for LFTs >3x ULN, reduce dose or pause therapy. Measure neutralizing antibodies after 6, 12, and 24 months; repeat for positive results. 	<ul style="list-style-type: none"> Pregnancy Category C
Glatiramer acetate	<ul style="list-style-type: none"> Obtain MRI scans, CBC prior to treatment. Monitor for postinjection reaction 	<ul style="list-style-type: none"> Pregnancy Category B
Orally Administered Products		
Fingolimod	<ul style="list-style-type: none"> Obtain prior to initiating treatment: MRI scan, CBC, LFTs, ECG, ophthalmic examination, VZV antibody assay (provide vaccine if no antibodies are present), and negative pregnancy test. Requires 6-hour post-dose infusion observation Avoid live attenuated viruses. Monitor CBC, LFTs, and BP routinely. Ophthalmic examinations 3-4 months after starting therapy Spirometry and diffusion lung capacity for carbon monoxide testing when clinically indicated 	<ul style="list-style-type: none"> Pregnancy Category C Unknown whether fingolimod is excreted in human milk Pregnancy registry has been established
Dimethyl fumarate	<ul style="list-style-type: none"> Obtain prior to initiating treatment: MRI, CBC, and LFTs, lymphocyte count, and negative pregnancy test. Monitor lymphocyte counts every 3 months; if lymphocyte counts decrease to <0.5x10⁹/L for 6 months, temporarily discontinue treatment. 	<ul style="list-style-type: none"> There are no adequate data on development risk in pregnant women. There are no data on the presence in human milk. Pregnancy registry has been established.
Teriflunomide	<ul style="list-style-type: none"> BLACK BOX WARNING: Hepatotoxicity Obtain prior to initiating treatment: MRI, CBC, LFTs, and negative pregnancy test. Monitor LFTs every 2 weeks for 6 months. If patients want to become pregnant, wait 2 years from last dose (until plasma levels are <0.02 mg/L) or use accelerated elimination procedure. Use accelerated elimination procedure if patients become pregnant or develop serious infections or hepatotoxicity. 	<ul style="list-style-type: none"> BLACK BOX WARNING: Risk of Teratogenicity Contraindicated for use in pregnant women and females of reproductive potential not using effective contraception. Unknown whether excreted in human milk Detected in human semen; if wanting to father a child, wait 2 years from last dose (until plasma levels are <0.02 mg/L) or use accelerated elimination procedure Pregnancy registry has been established.
Postmillennial Injectable Products		
Natalizumab	<ul style="list-style-type: none"> BLACK BOX WARNING: PML REMS Program Obtain prior to initiating treatment: MRI, CBC, and JCV antibodies Anti-natalizumab antibody testing if there are ongoing infusion reactions; stop therapy if test is positive JCV testing every 6 months in JCV-positive patients Yearly MRIs in JCV-negative patients Discontinue if PML is suspected 	<ul style="list-style-type: none"> No adequate data on the developmental risk in pregnant women Has been detected in human breast milk
Alemtuzumab	<ul style="list-style-type: none"> BLACK BOX WARNING: Autoimmunity, Infusion Reactions, and Malignancies REMS Program Obtain prior to initiating treatment: MRI, CBC, serum creatinine, urinalysis, thyroid function tests, screening for latent viruses (ie, TB, HBV, and HIV), screening for VZV antibodies, and negative pregnancy test Avoid live attenuated viruses Monthly CBC, creatinine, and urinalysis Thyroid function tests every 3 months HPV screening (female patients) 	<ul style="list-style-type: none"> Pregnancy Category C There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should use contraception while receiving and for 4 months after the last dose. Unknown whether excreted in human milk

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TABLE 2. Monitoring Considerations and Use in Pregnancy/Lactation^{4,14-23} (continued)

Ocrelizumab ⁴	<ul style="list-style-type: none"> • Obtain prior to initiating treatment: MRI, LFTs, bilirubin, CBC, serum creatinine, urinalysis, HBV; screen for TB • Monitor patients closely during and for at least 1 hour after infusion • Avoid live attenuated viruses • Routine breast examinations 	<ul style="list-style-type: none"> • There are no adequate data on the developmental risk associated with use in pregnant women. • There are no data on the presence in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. • Women of childbearing potential should use contraception while receiving and for 6 months after the last infusion.
Daclizumab*	<ul style="list-style-type: none"> • BLACK BOX WARNING: Autoimmune Hepatitis and Other Immune-Mediated Disorders • REMS Program • Obtain prior to initiating treatment: MRI, LFTs, bilirubin, CBC, serum creatinine, urinalysis, screening for TB • Avoid live attenuated viruses • Monitor LFTs and bilirubin • Monitor CBC and serum creatinine every 3 months 	<ul style="list-style-type: none"> • There are no adequate data on the developmental risk in pregnant women. • Unknown whether excreted in human milk

*In March 2018, daclizumab was withdrawn worldwide following reports of inflammatory encephalitis and meningoencephalitis.

BP indicates blood pressure; CBC, complete blood count; ECG, electrocardiogram; HBV, hepatitis B virus; HPV, human papillomavirus; JCV, John Cunningham virus; LFT, liver function tests; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; REMS, Risk Evaluation and Mitigation Strategy; TB, tuberculosis; ULN, upper limit of normal; VZV, varicella zoster virus.

Importantly, emerging evidence suggests gray matter atrophy may be a more sensitive marker of the neurodegenerative process in MS than whole brain atrophy.²⁴ The atrophy rate of gray matter in patients with relapsing MS is 3 to 4 times that of healthy patients; in secondary-progressive MS, it is 14 times that of healthy people.^{9,24}

The relationship between atrophy measures and clinical presentation has been extensively investigated.⁹ Whole brain atrophy and gray matter atrophy correlate strongly with disability and cognitive impairment, both cross-sectionally and longitudinally. Atrophy associated with gray matter structures may even be more closely related to clinical signs than white matter lesions or whole brain atrophy. Atrophy of several structures correlate with certain clinical symptoms, including^{9,25}:

- Cerebral gray matter atrophy with cerebellar symptoms and hand function
- Upper cervical cord area with ambulatory dysfunction
- Hippocampal atrophy with ambulatory deficits
- Thalamic volume with cognitive impairment

While brain atrophy is considered a marker of advanced stages of MS, it also occurs in patients with clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS).⁶ Because brain atrophy creates permanent damage and correlates with physical and cognitive disability, it is important that patients with MS be treated as early in the disease process as possible with DMTs.²⁷ Results from a meta-analysis conducted evaluating the impact of controlling degenerative

activity with the currently FDA-approved DMTs found that a greater reduction in brain atrophy led to reduced disability progression at the 2-year follow-up period.²⁸ Brain atrophy may therefore have a greater predictive value than traditional MRI scans in preventing physical disability progression.⁶

Effect of Disease-Modifying Therapies on Brain Atrophy

Brain atrophy is now a recognized endpoint in phase 3 clinical trials for MS.^{6,24} It can be evaluated using traditional MRI scans. These atrophy measurements do have some limitations.⁹ Because atrophy occurs slowly, longer follow-up may be required to detect significant changes. Additionally, immunosuppressive DMTs may decrease brain volume as inflammation resolves in the short term. With no loss of neuronal tissue, this volume loss cannot be considered a sign of neurodegeneration; this effect can last up to 12 months after starting the DMT. Brain volume can also be affected by physiological variations in the content of intra- and extra-cellular compartments as well as non-MS factors such as dehydration, alcohol consumption, smoking, genetic variation, comorbidities, and age.⁹

The effect of currently-approved DMTs on decreasing the rate at which the brain atrophies is unclear.⁶ There is an unmet need to identify DMTs that both decrease the inflammatory processes that occur with MS and decrease brain atrophy progression and neurodegeneration. In the pivotal trials for fingolimod, dimethyl fumarate, and alemtuzumab, measures of brain atrophy were assessed as a secondary

endpoint.²⁷ In these studies, significant differences in atrophy reduction were observed when compared with no treatment or active drug. Atrophy has also been assessed with other DMTs (ie, interferon beta-1a intramuscular, glatiramer acetate, and natalizumab). In these studies, atrophy was decreased at certain time points.²⁷ The most significant limitation to using brain atrophy as an endpoint is that it is more commonly measured during clinical trials than in clinical practice.

Myelin and Axonal Repair Strategies and the Future of MS Treatment

Much of the current research in MS involves prevention of demyelination, limiting damage in areas already affected, and identifying promising remyelination therapies.⁷ Understanding the complex etiology of MS and the importance of the axon integrity are essential for clinicians. When patients are diagnosed with MS and have their first neurological symptoms, axonal loss has already occurred. Consequently, there is a need to treat early and to use multiple strategies that target remyelination and preservation of axons and oligodendrocytes.⁶

When evaluating currently approved DMTs, those that modulate CD8+ T-cell proliferation (eg, dimethyl fumarate and fingolimod) appear to have the most neuroprotective benefits.⁷ These results suggest that immunotherapy directed against active CD8+ cells using anti-CD8 antibodies could suppress the immune-mediated reactions in patients with MS.^{29,30}

Clinicians must weigh several factors related to efficacy, safety, tolerability, route of administration, cost, and finally patient-specific needs. The interferon beta products and glatiramer acetate are moderately effective and are associated with the fewest adverse events, in terms of number and severity. The oral agents and the more recently approved injectable products are associated with improved efficacy but have been associated with serious adverse reactions, some of which are life-threatening.⁴

*** In March 2018, Biogen withdrew daclizumab (Zinbryta) worldwide following reports of inflammatory encephalitis and meningoencephalitis.**

REFERENCES

- Bainbridge J, Miravalle A, Wong P. Multiple sclerosis. In: DiPiro J, Talbert R, Yee G, Matzke G, Wells B, Posey L, eds. *Pharmacotherapy: A Pathophysiological Approach*. 10th edition. New York, NY: McGraw-Hill Education; 2017:815-836.
- 2007 Disease Management Consensus Statement. National Clinical Advisory Board of the National Multiple Sclerosis Society. main.nationalmssociety.org/docs/HOM/Exp_Consensus.pdf. Accessed February 9, 2018.
- Costello K, Halper J, Kalb R, Skutnik L, Rapp R. The use of disease-modifying therapies in multiple sclerosis principles and current evidence. a consensus paper by the multiple sclerosis coalition. 2014. http://ms-coalition.org/cms/images/stories/dmt_consensus_ms_coalition_web_color2.pdf. Accessed February 10, 2018.
- Weinstock-Guttman B, Nair KV, Glajch JL, Ganguly TC, Kantor D. Two decades of glatiramer acetate: from initial discovery to the current development of generics. *J Neuro Sci*. 2017;376: 255-259.
- Grebenciucova E, Pruitt A. Infections in patients receiving multiple sclerosis disease-modifying therapies. *Curr Neurol Neurosci Rep*. 2017;17(11):88.
- Rojas JL, Patrucco L, Miguez J, Cristiano E. Brain atrophy in multiple sclerosis: therapeutic, cognitive and clinical impact. *Arq Neuropsiquiatr*. 2016;74(3):235-243.
- Kremer D, Küry P, Dutta R. Promoting remyelination in multiple sclerosis: current drugs and future prospects. *Mult Scler*. 2015;21(5):541-549.
- Farber RS, Sand IK. Optimizing the initial choice and timing of therapy in relapsing-remitting multiple sclerosis. *Ther Adv Neurol Disord*. 2015;8(5):212-232.
- van Munster C, Uitdehaag BM. Outcome measures in clinical trials for multiple sclerosis. *CNS Drugs*. 2017;31(3):217-236.
- Aurichio F, Scavone C, Cimmaruta D, et al. Drugs approved for the treatment of multiple sclerosis: review of their safety profile. *Exp Opin Drug Safety*. 2017;16(12):1359-1371.
- Giorgio A, De Stefano N. Effective utilization of MRI in the diagnosis and management of multiple sclerosis. *Neurol Clin*. 2018;36(1):27-34.
- Kurtzke J. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1452.
- Fischer JS, Rudick RA, Cutter GR, Reingold SC; National MS Society Clinical Outcomes Assessment Task Force. The multiple sclerosis functional composite measure (MSFC): an integrated approach to MS clinical outcome assessment. *Mult Scler*. 1999;5(4):244-250.
- Avonex [package insert]. Cambridge, MA: Biogen, Inc; March 2016.
- Plegridy [package insert]. Cambridge, MA: Biogen, Inc; July 2016.
- Copaxone [package insert]. Overland Park, KS: Teva Neuroscience, Inc; August 2016.
- Gilenya [package insert]. Novartis Pharmaceutical Corporation: East Hanover, NJ; December 2017.
- Tecfidera [package insert]. Cambridge, MA: Biogen, Inc; December 2017.
- Aubagio [package insert]. Cambridge, MA: Genzyme Corporation; November 2016.
- Tysabri [package insert]. Cambridge, MA: Biogen, Inc; August 2017.
- Lemtrada [package insert]. Cambridge, MA: Genzyme Corporation; December 2017.
- Ocrevus [package insert]. South San Francisco, CA: Genentech, Inc. March 2017.
- Zinbryta [package insert]. Cambridge, MA: Biogen, Inc; August 2017.
- Riley C, Azevedo C, Bailey M, Pelletier D. Clinical applications of imaging disease burden in multiple sclerosis: MRI and advanced imaging techniques. *Expert Rev Neurother*. 2012;12(3):323-333.
- van Munster C, Jonkman J, Weinstein H, Uitdehaag B, Geurts J. Gray matter damage in multiple sclerosis: impact on clinical symptoms. *Neuroscience*. 2015;303:446-461.
- Jacobsen C, Hagemeyer J, Myhr KM, Nyland H, Lode K. Brain atrophy and disability progression in multiple sclerosis patients: a 10-year follow-up study. *J Neurol Neurosurg Psychiatry*. 2014;85(10):1109-1115.
- Vidal-Jordana A, Sastre-Garriga J, Rovira A, Montalban X. Treating relapsing-remitting multiple sclerosis: therapy effects on brain atrophy. *J Neurol*. 2015;262(12):2617-2626.
- Sormani MP, Arnold DL, DeStefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. *Ann Neurol*. 2014;75(1):43-49.
- Vidal-Jordana A. New advances in disease-modifying therapies for relapsing and progressive forms of multiple sclerosis. *Neurol Clin*. 2018; 36(1):173-183.
- Lemus HN, Warrington AE, Rodriguez M. Multiple sclerosis: mechanisms of disease and strategies for myelin and axonal repair. *Neurol Clin*. 2018;36(1):1-11.