Sphingosine-1-Phosphate Modulators for Multiple Sclerosis

Sphingosine-1-phosphate modulators may act through more than just inhibition of neuroimmune and neuroinflammatory effects of multiple sclerosis.

By Mark B. Skeen, MD

The past 20 years have seen a revolution in multiple sclerosis (MS) treatment with new agents approved regularly. Despite this revolution in therapy, treatment choices are complicated by many factors, including lack of well-controlled comparative trials; differences in efficacy, tolerability, safety, and mode of administration; and patient and physician preferences. Additional challenges include how to measure MS disease activity, differences in disease subtypes, and a lack of a basic understanding of disease progression mechanisms. We now have several highly effective anti-inflammatory therapies for MS, but there is a growing desire to understand the additional noninflammatory mechanisms of disease progression and develop therapies that also limit or reverse those aspects of the disease.

Traditionally, MS has been understood as an autoimmune relapsing inflammatory demyelinating disease of white matter. We are increasingly aware that this is only partially correct. Early rather than late axonal loss and gray matter atrophy in areas that do not demonstrate inflammation clinically or radiographically suggest additional processes may be responsible for disease progression. Early axonal loss occurs not just after extensive white matter disease and in normal-appearing white matter. Gray matter injury is associated with many of the clinical manifestations of progressive disease. There is a growing appreciation of progressive disability, which is not relapse dependent and may not be inflammation dependent.

Treatments for progressive forms of MS remain the great unmet need. Sphingosine-1-phosphate receptor (S1PR) modulators are a newer class of therapies that includes the first oral therapy for MS, the first approved therapy for children with MS, and the first therapy to demonstrate efficacy in secondary progressive MS (SPMS). The recognized mechanism of action of S1PR modulation is limiting lymphocyte egress from lymph nodes, which effectively limits T-cell migration to tissues. The S1PR is ubiquitous and expressed on the cell surface of many cells throughout the body, including the central nervous system (CNS). Recognition of the role of S1PRs within the nervous system also begs the question as to whether there are additional direct CNS effects of S1PR modulation in addition to limiting lymphocyte migration, and whether those effects provide additional therapeutic benefit.

This review explores the mechanism of action of S1PR modulators focusing on potential direct CNS effects that may be pertinent to treatment effects separate from immunomodulation. We also review the clinical data upon which recent regulatory decisions have been made and practical aspects of S1PR modulator use.

Sphingosine-1-Phosphate Receptor Modulation

The story of S1PRs as immunomodulators is said to have begun with traditional Chinese medicine and a fungus, *Isaria sinclairii*, said to promote youthfulness. A natural immunosuppressive molecule, myriocin, was isolated from the culture broth of the fungus and demonstrated immunosuppressive properties during in vitro and in vivo studies. Myriocin was then chemically modified to fingolimod, which became the first approved S1PR modulator for MS. Of the 5 recognized S1PR subtypes (Figure 1), S1PR1 is expressed on lymphocytes and is part of the signaling process that promotes egress of lymphocytes from lymph nodes into the circulation. Although the S1PR modulators are agonists of the receptor, binding to the S1PRs causes internalization of the receptor-modulator complex into the lymphocyte, making the modulator an effective antagonist, reducing lymphocyte egress into the circulation, and limiting lymphocyte effects in tissues. The

reduction in lymphocyte migration is believed to be responsible for the therapeutic immunomodulatory effects of S1PR modulators.

Sphingosine in the Central Nervous System

Sphingosine is a major constituent of myelin, long considered just a structural component of the cellular membranes.

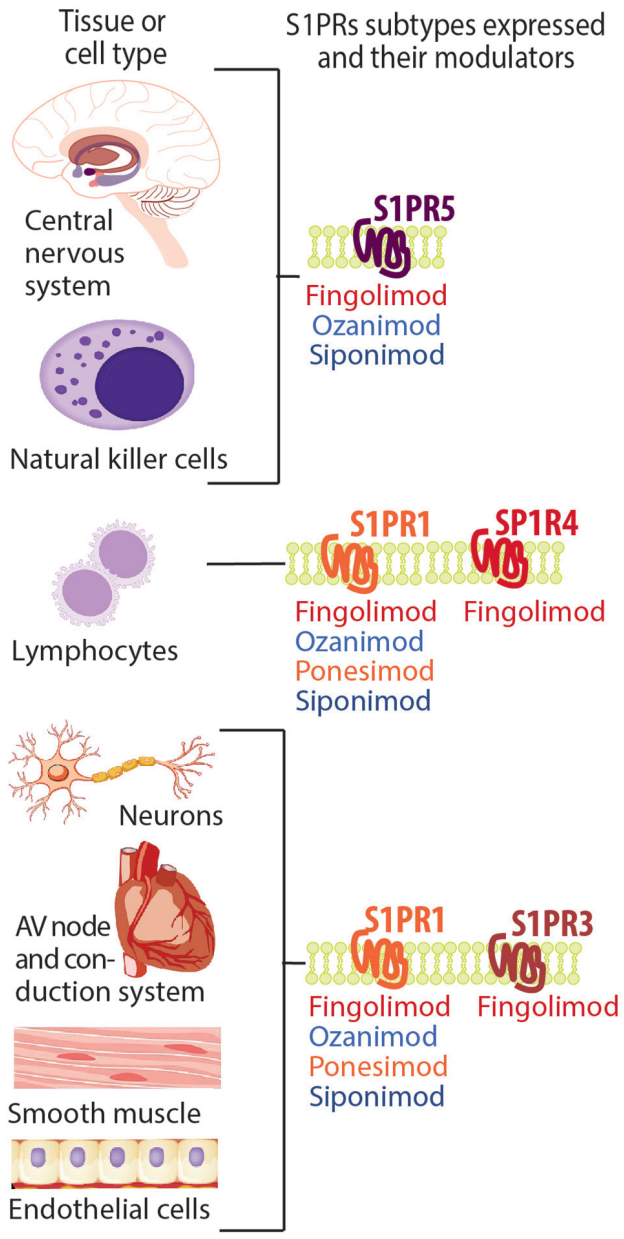

Figure 1. Sphingosine-1-phosphate receptor (S1PR) modulator therapies approved or being studied for treatment of multiple sclerosis (MS) have different S1PR subtype specificities. All these S1P modulators bind to S1P1R on lymphocytes but additional effects in other tissues may be mediated by other S1PR subtypes.

We now know, however, that sphingosine metabolites, such as ceramide and sphingosine-1-phosphate (S1P), play crucial roles as signaling molecules. These metabolites are implicated in the control of many CNS processes including cell migration, differentiation, apoptosis, cellular maturation, proliferation, myelination, and neurotransmitter release.[1] A review of S1PR signaling in the CNS is beyond the scope of this review, but a brief look at certain aspects helps convey the complexity of issues and potential direct therapeutic effects of S1PR modulation in the CNS.

The brain has the highest concentration of S1PRs. Cellular levels of S1P are tightly regulated by the balance between synthesis by sphingosine kinase and degradation by hydrolysis or cleavage, suggesting a critical role within the CNS.[2,3] The S1PR receptors are expressed on neurons, oligodendrocytes, astrocytes, and microglia. Each of the 5 different S1PR subtypes is bound to specific G proteins, each of which activates different intracellular signaling cascades. Several lines of evidence suggest that S1P functions as an intracellular second messenger using both S1PR-independent and S1PR-dependent pathways.[3] The effect of S1PR stimulation in the CNS depends on many factors, including which S1PR subtype(s) is (are) expressed by the cell, which cells are stimulated, the state of cell maturation, the milieu of stimulation (including the presence of other cytokines), and the state of cell activation.[1,3,4] Some effects of S1PR stimulation depend on S1P concentration and the balance of stimulation among various S1PR subtypes, which sometimes have opposing effects.[5-7]

Observed effects of S1P signaling within the CNS include the ability to modulate Nogo A-mediated inhibition of neuronal plasticity and neurite growth; neuronal autophagy; microglial proinflammatory cytokine release; oligodendrocyte migration, myelination, and survival; and astrocyte control of blood-brain--barrier permeability.[1,5-12] In animal models of MS, the S1PR modulator fingolimod reduced the production of microglial proinflammatory cytokines, increased microglial expression of neurotrophic factor, improved oligodendrocyte survival and differentiation, and inhibited or blocked many inflammatory responses. Siponimod has shown effects on modulating glial cell function and attenuating demyelination in animal models, and ozanimod inhibits astrocytic proinflammatory cytokines.[12-17] The direct CNS effect of various therapeutic S1PR modulators may not be equivalent. For example, fingolimod and siponimod induce different astrocytic transcription products in vivo.[18]

We do not yet understand CNS S1P effects well enough to predict the therapeutic effects of S1PR modulation therapies, and clinical use will continue to depend on demonstrable clinical benefit demonstrated in well-controlled clinical trials. The above observations should, however, serve to demonstrate that S1PR modulation likely has a significant impact in many CNS functions and in many, if not all, CNS cell types.

Some of those effects could be therapeutically important and independent of lymphocyte sequestration peripherally.

Fingolimod

The therapeutic benefits of fingolimod were first explored in clinical trials for renal transplantation before being developed as a potential therapy for MS. Fingolimod was approved by the Food and Drug Administration (FDA) for the treatment of relapsing MS in September 2010. Fingolimod reduced the risk of disability progression compared with placebo (hazard ratio [HR]=0.70, *P*=.02) over 24 months.[19] The cumulative probability of disability progression (confirmed after 3 months) was 17.7% with fingolimod and 24.1% with placebo for the same period and fingolimod vs placebo resulted in fewer new or enlarged T2 lesions, fewer gadolinium-enhancing lesions, and less brain volume loss (*P*<.001 for all at 24 months).[19] Fingolimod reduced the annualized relapse rate (ARR) (0.21; 95% CI, 0.17-0.25) compared with placebo (0.40; 95% CI, 0.34-0.48; *P*<.0001) as well.[20] Fingolimod also improved ARR (0.16; 95% CI, 0.12-0.21) compared with intramuscular interferon b-1a (0.33; 95% CI, 0.26-0.42; *P*<0.001).[21] In children age 10 to 17 years, fingolimod vs interferon β-1a reduced the ARR by 82% (0.12 vs 0.67, *P*=.0001) and significantly reduced new or newly enlarged T2 lesions on brain MRI.[22] Fingolimod did not, however, significantly reduce disability progression compared with placebo in people with primary progressive MS (PPMS).[23]

Fingolimod is generally well-tolerated, and the most concerning adverse effects include transient cardiac rhythm disturbances at initiation of treatment. Fingolimod is contraindicated in people who have had transient ischemic attacks (TIAs) or have certain cardiac conditions. A first-dose observation procedure is required at initiation of therapy. Macular edema has occurred in a small number of people, and screening is required before starting fingolimod and 3 to 4 months later because macular edema may be asymptomatic. Opportunistic infections including progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis have occurred rarely. Vaccination for varicella zoster virus (VZV) is recommended prior to initiation in individuals who are negative for antibodies to VZV. Monitoring for lymphopenia and transaminase elevations is recommended. In the appropriate patients with relapsing forms of MS, fingolimod is generally considered a rather efficacious well-tolerated therapy with rare serious adverse effects when the prescribing information is followed.

Siponimod

In March 2019, the FDA approved siponimod to treat adults with relapsing forms of MS, to include clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and active secondary progressive MS (aSPMS). This FDA approval represented a somewhat different approach compared with prior approvals because the pivotal trial had enrolled only people with SPMS.[24] See *Point-Counterpoint: Food and Drug Administration Multiple Sclerosis Categorization Changes* p. 44 this issue).

In a clinical trial of siponimod, 903 (82%) participants treated with siponimod and 424 (78%) given placebo completed the study. Of those who received siponimod, 26% (288/1096) and 32% (173/545) of those receiving placebo had 3-month confirmed disability progression (HR=0.79, 95% CI, 0.65-0·95; relative risk reduction 21%; *P*=.013).[24] This was the first phase 3 trial in SPMS to achieve the predesignated primary endpoint. The Center for Drug Evaluation and Research (CDER) summary review is available online and is a very instructive document with a thorough and insightful review of the data and extensive subset analyses.[25]

Because other S1PR modulators are effective anti-inflammatory treatments for MS and siponimod demonstrated significant efficacy in a phase 2 study for relapsing MS,[26] this author's perspective is that the question to answer is whether there is additional benefit of siponimod for reducing disability in SPMS that is perhaps attributable to direct CNS or other effects. As Figure 2 (from the CDER summary review) shows, the hazard ratio for time to confirmed disability progression was in favor of siponimod in every subset. The largest effects were seen in the subsets of participants who had: relapses in the 2 years prior to the study, relapses during the study, younger relative age, shorter disease duration, and lower Expanded Disability Status Scale (EDSS) score at baseline. These subsets are more likely to have active, relapsing, or inflammatory disease.

These and other analyses in the CDER summary review led the FDA to conclude that efficacy was only adequately demonstrated in people with aSPMS. Another approach to this data would be to recognize that even subsets of participants without relapses in the 2 years prior to the study, without relapses during the study, baseline age 60, EDSS=6.0, and disease duration of 30 years had an apparent delay in disease progression, even if it was not statistically significant in a subset analysis. It is not surprising that a therapy with demonstrated efficacy for relapsing inflammatory disease would show greater benefit in patients with relapsing inflammatory disease than in those without. Indeed, this finding would be expected. Other statistical analyses have suggested siponimod's effect on disability is largely independent from the effect on relapses.[27] For comparison, natalizumab is recognized as a highly efficacious therapy for MS therapy for relapsing or active disease, although it did not demonstrate efficacy in the primary outcome measures for SPMS in trials with a similar population to those studied in the siponimod SPMS trial.[24,28] At present, siponimod appears to have the best efficacy data for treating SPMS. Clinicians and patients will have to decide for themselves how this data is to be interpreted.

From a practical standpoint, siponimod is approved for relapsing forms of MS and appears to have reduced adverse

cardiac effects, mitigating the need for first-dose observation except in the setting of certain pre-existing cardiac diseases. Analysis of liver enzyme CYP2CP genotype is required before starting siponimod to assess for potential effects on siponimod metabolism that may contraindicate use or mandate a reduced dose.

Ozanimod

Like siponimod, ozanimod is a more selective S1PR modulator with affinity for S1PR1 and S1PR5 (Figure 1). Treatment with 0.5 mg ozanimod vs placebo reduced the mean number of gadolinium-enhancing lesions (1.5±3.7 vs 11.1±29.9; odds ratio 0.16, 95% CI .08-.30; *P*<.0001).[29] Treatment with 0.5 mg ozanimod vs intramuscular interferon β-1a for 24 months reduced ARR by 21% (*P*=.001).[30] Treatment-emergent adverse effects were higher in those treated with interferon β-1a, including treatment-emergent adverse events that led to discontinuation. In another trial 0.5 mg ozanimod vs intramuscular interferon β-1a reduced ARR by 31% (*P*=0.0013).[31] No first-dose clinically significant bradycardia or second-degree or third-degree atrioventricular block was reported. In both trials comparing ozanimod to interferon β-1a, ozanimod reduced volume loss in the whole brain, cortical gray matter, and the thalamus.[32] Among those for whom cognitive processing speed was measured, ozanimod treatment resulted in sustained improvement compared with interferon β-1a at 6 and 18 months.[33] The significance of these subset analyses will need to be confirmed by additional long-term studies.

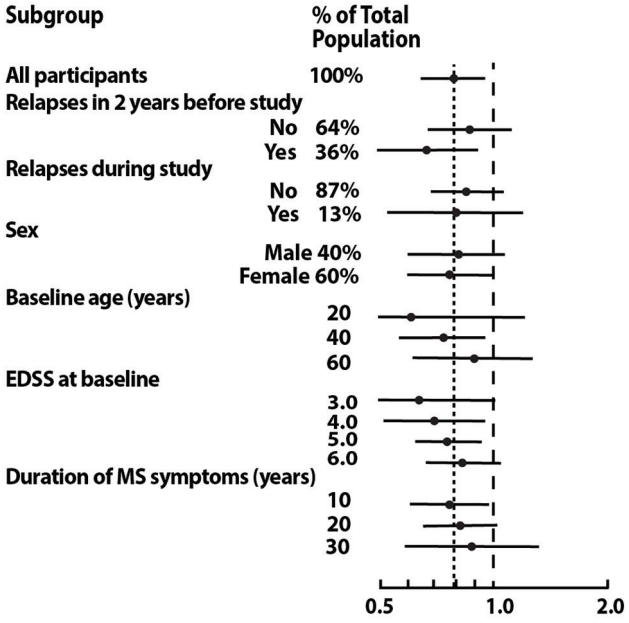

Figure 2. Hazard ratio for progression to disability of participant subgroups compared with total population in siponimod pivotal trial. Authors of the Center for Drug Evaluation and Research summary review[25] noted those who had relapses in the 2 years prior to the study (36% of participants) had a relative risk reduction of 33% compared with 13% for those who did not. From this, they concluded that a minority of participants with more active disease drove the overall treatment effect. Differences between subgroups with lower age, shorter disease duration, relapse during the study, and baseline lower Expanded Disability Status Scale (EDSS) scores were also noted. From Lee P, Bastings E, Dunn B, Unger E, Center for Drug Evaluation and Research. Application Number 209884Orig1s000 summary review. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209884Orig1s000SumR.pdf.

Ponesimod

Ponesimod is an S1PR modulator, highly selective for the S1PR1 subtype. In a large head-to-head superiority study of ponesimod (20 mg) vs teriflunomide (14 mg) for relapsing MS, ponesimod significantly reduced ARR by 30.5% over 108 weeks (0.202 vs 0.290; *P*=0.0003).[34] Those treated with ponesimod also had significant reductions in fatigue compared with those treated with teriflunomide, as measured by the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS), a validated disease-specific fatigue measure (mean FSIQ-RMS score -3.57; *P* = .0019). Treatment with ponesimod also reduced combined active lesions (new Gd^+ T1 plus new or enlarging T2 lesions) by 56% compared with teriflunomide (1.4 vs 3.16; *P*<.0001).

Summary

The S1PR modulators represent a unique class of oral therapies for MS. By limiting the lymphocyte circulation, these agents exert significant anti-inflammatory effects; through direct CNS effects they may provide additional therapeutic benefits. Whether a direct CNS therapeutic benefit of S1PR modulation exists is yet to be decided authoritatively. The clinical significance of limiting disease progression, volume loss, and cognitive decline is of utmost importance; any agent with such properties may provide meaningful long-term benefit in addition to reducing inflammation. Knowing that cognitive impairment, volume loss, and the substrates of progression occur early in MS suggest it may be beneficial to use such agents early in the course of MS rather than waiting until progression is clinically evident. The more selective S1PR modulators appear to have fewer short-term adverse effects, particularly on cardiac conduction. The long-term adverse effects of the newer agents are yet to be determined. ■

1. Coelho RP, Saini HS, Sato-Bigbee C. Sphingosine-1-phosphate and oligodendrocytes: from cell development to the treatment of multiple sclerosis. *Prostaglandins Other Lipid Mediat*. 2010;91(3-4):139-144.
2. Edsall LC, Spiegel S. Enzymatic measurement of sphingosine-1-phosphate. *Anal Biochem*. 1999;272(1):80-86.
3. Bryan L, Kordula T, Spiegel S, Milstien S. Regulation and functions of sphingosine kinases in the brain. *Biochem Biophys Acta*. 2008;1781(9):459-466.
4. Karunakaran I, van Echten-Deckert G. Sphingosine 1-phosphate – a double edged sword in the brain. *Biochim Biophys Acta Biomembr*. 2017;1859(9 Pt B):1573-1582.
5. Dukala DE, Soliven B. S1P1 deletion in oligodendroglial lineage cells: effect on differentiation and myelination. *Glia*. 2016;64(4):570-582.

6. Qin J, Berdyshev E, Goya J, Natarajan V, Dawson G. Neurons and oligodendrocytes recycle sphingosine-1-phosphate to ceramide. *J Biol Chem*. 2010;285(19):14134-14143.
7. Novgorodov AS, El-Awani M, Bielawski J, Obeid LM, Gudz TI. *Activation of sphingosine-1-phosphate receptor S1P5 inhibits oligodendrocyte progenitor migration*. FASEB. 2007;21(7):1503-1514.
8. Kempf A, Tews B, Arzt ME, et al. The sphingolipid receptor S1PR2 is a receptor for Nogo-a repressing synaptic plasticity [published correction appears in PLoS Biol. 2014. Feb;12(2):e1001818]. PLoS Biol. 2014;12(1):e1001763.
9. Pattingre S, Bauvy C, Carpentier S, Levade T, Levine B, Codogno P. Role of JNK1-dependent Bcl-2 phosphorylation in ceramide-induced macroautophagy. *J Biol Chem*. 2009;284(5):2719-2728.
10. Nayak D, Huo Y, Kwang WX, et al. Sphingosine kinase 1 regulates the expression of proinflammatory cytokines and nitric oxide in activated microglia. *Neuroscience*. 2010;166(1):132-144.
11. Farez MF, Correale J. Spingosine 1-phosphate signaling in astrocytes: implications for progressive multiple sclerosis. *J Neurol Sci*. 2016;361:60-65.
12. Jalliard C, Harrison S, Stankoff B, et al. Edg8/S1P5: an oligodendroglial receptor with dual function on process retraction and cell survival. *J Neurosci*. 2005;25(6):1459-1469.
13. Kim HJ, Miron VE, Dukala D, et al. Neurobiological effects of sphingosine 1-phosphate receptor modulation in the cuprizone model. *FASEB J*. 2011;25(5):1509-1518.
14. Noda H, Takeuchi H, Mizuno T, Suzumura A. Fingolimod phosphate promotes the neuroprotective effects of microglia. *J Neuroimmunol*. 2013;256(1-2):13-18.
15. Columbo E, Di Dario M, Capitolo E, et al. Fingolimod may support neuroprotection via blockade of astrocyte nitric oxide. *Ann Neurol*. 2014;76(3):325-337.
16. O'Sullivan C, Schubart A, Mir AK, Dev KK. The dual S1PR1/S1PR5 drug BAF312 (Siponimod) attenuates demyelination in organotypic slice cultures. *J Neuroinflammation*. 2016;13:31.
17. Taylor Meadows KR, Selkirk JV, Akhtar MW, Hutton C, Opiteck GJ, Scott FL. *Ozanimod (RPC1063) is potentially neuroprotective through direct CNS effects*. ECTRIMS Online Library. 2017;200838:P1183.
18. Kihara Y, Zhu Y, Jonnalagadda D, Liu C, Siddoway B, Chun. Differential CNS effects of siponimod vs fingolimod revealed by single-cell transcriptome analyses of primary astrocytes. *ECTRIMS Online Library*. 2019:P1008.
19. Kappos L, Radue, EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387-401.
20. Calabresi PA, Radue E-W, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomized, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13(6):545-556.
21. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):402-415.
22. Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med*. 2018;379(11):1017-1027
23. Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2016(10023);1075-1084.
24. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet*. 2018;391(10027):1263-1273.
25. Lee P, Bastings E, Dunn B, Unger E, Center for Drug Evaluation and Research. *Application Number 209884Orig1s000 summary review*. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209884Orig1s000SumR.pdf. Accessed January 7, 2020.
26. Selmaj K, Li DK, Hartung HP, et al. Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study. *Lancet Neurol*. 2013;12(8):756-767.
27. Cree B, Fox R, Giovannoni G, et al. Uncoupling the impact on relapses and disability progression: Siponimod in relapsing and non-relapsing patients with secondary progressive multiple sclerosis in the phase 3 EXPAND study. *Neurology*. 2018;90:Suppl 15, S8.005.
28. Kapoor R, Ho P-R, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open label extension. *Lancet Neurol*. 2018;17(5):405-415.
29. Cohen JA, Arnold DL, Comi G, et al. Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016;15(4):373-381..
30. Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. *Lancet Neurol*. 2019;18(11):1021-1033.
31. Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. *Lancet Neurol*. 2019;18(11):1009-1020.
32. Arnold DL, Cohen JA, Cree BAC, et al. *Reduced brain volume loss in relapsing multiple sclerosis with ozanimod versus interferon beta-1a in two phase 3 trials (SUNBEAM and RADIANCE)*. Paper presented at: 5th Congress of the European Academy of Neurology; June 29 - July 2, 2019; Oslo, Norway
33. DeLuca J, Cohen JA, Cree BAC, et al. *Sustained improvement in cognitive processing speed in multiple sclerosis patients completing 18 months of ozanimod treatment: results from the phase 3 SUNBEAM trial*. Paper presented at: The Consortium of Multiple Sclerosis Centers Annual Meeting; May 28 - June 1, 2019; Seattle, WA.
34. Kappos L, Burcklen M, Freedman MS, et al. Efficacy and safety of ponesimod compared to teriflunomide in patients with relapsing multiple sclerosis: results of the randomized, active-controlled, double-blind, parallel group phase 3 OPTIMUM study. *ECTRIMS Online Library*. 2019;279416:93.

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Disclosure

MBS has disclosures at www.practicalneurology.com