Ozanimod

Subjects: Others

Contributor: Grace Lassiter , Carlie Melancon , Tyler Rooney , Anne-Marie Murat , Jessica S. Kaye , Adam M. Kaye , Rachel J. Kaye , Elyse M. Cornett , Alan D. Kaye , Rutvij J. Shah , Omar Viswanath , Ivan Urits

Multiple sclerosis (MS) is a prevalent and debilitating neurologic condition characterized by widespread neurodegeneration and the formation of focal demyelinating plaques in the central nervous system. Current therapeutic options are complex and attempt to manage acute relapse, modify disease, and manage symptoms. Such therapies often prove insufficient alone and highlight the need for more targeted MS treatments with reduced systemic side effect profiles. Ozanimod is a novel S1P (sphingosine-1-phosphate) receptor modulator used for the treatment of clinically isolated syndrome, relapsing–remitting, and secondary progressive forms of multiple sclerosis. It selectively modulates S1P1 and S1P5 receptors to prevent autoreactive lymphocytes from entering the CNS where they can promote nerve damage and inflammation. Ozanimod was approved by the US Food and Drug Administration (US FDA) for the management of multiple sclerosis in March 2020 and has been proved to be both effective and well tolerated. Of note, ozanimod is associated with the following complications: increased risk of infections, liver injury, fetal risk, increased blood pressure, respiratory effects, macular edema, and posterior reversible encephalopathy syndrome, among others. Further investigation including head-to-head clinical trials is warranted to evaluate the efficacy of ozanimod compared with other S1P1 receptor modulators.

ozanimod multiple sclerosis sphingosine-1-phosphate receptor modulator Zeposia relapsing-remitting

1. Introduction

Multiple sclerosis (MS) is one of the most prevalent and disabling neurologic conditions worldwide. It is a chronic inflammatory disease that results in widespread neurodegeneration and the formation of focal demyelinating plaques in the white and grey matter of the CNS [1][2][3]. MS globally affects approximately 2.5 million people, with the majority aged 20–40 years when symptoms present [4]. Women are affected more often than men, with a female to male prevalence ratio of almost 3:1 [5]. To date, there has not been one specific factor identified as the cause of disease; rather, MS is thought to arise in genetically susceptible individuals who are exposed to environmental and immune triggers [3]. Environmental and lifestyle factors such as Vitamin D deficiency, low sun exposure, Epstein–Barr virus, smoking, and obesity have shown to be involved in the development of MS [6].

The onset of MS symptoms is usually sudden and most commonly presents as unilateral loss of vision, sensory loss, motor and muscle weakness, or ataxia [4][7]. Diagnosis of MS is established using clinical judgment and neurologic examinations, with evidence of CNS damage disseminated in time and space. Magnetic resonance

imaging (MRI) with gadolinium is useful in identifying demyelinated lesions throughout the CNS. Cerebrospinal fluid analysis and immunoglobulin levels are also helpful in establishing diagnosis [8].

Multiple sclerosis is classified into clinically isolated syndrome (CIS), relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive relapsing MS (PRMS) based on the clinical course of disease [6]. CIS is identified as the first episode of symptoms, with MRI findings similar to MS but not meeting full diagnostic criteria. RRMS is the most common form and constitutes eighty-five percent of all MS patients, characterized by recovery periods between attacks [6][9]. Most people with RRMS will convert to the secondary-progressive course (SPMS), with continued worsening of symptoms. Primary-progressive MS (PPMS) is defined by worsening symptoms from the disease onset without periods of relapse [6].

The pathophysiology of MS has traditionally been viewed as a two-stage process, with focal inflammation and demyelination early in the course, and axonal loss and neurodegeneration more prominent over time [8]. The disease pathology begins when autoreactive T-cells cross the blood-brain barrier (BBB) and induce inflammation. These CD8+ T-cells secrete pro-inflammatory cytokines and aid in the activation and recruitment of other immune cells, including B-cells, macrophages, microglia, astrocytes, and plasma cells [6].

There is no current cure for MS, but there are several disease-modifying therapies (DMTs) used, especially for the relapsing–remitting MS [10]. Although the currently approved pharmacologic options have demonstrated efficacy in managing and slowing the disease, they are associated with greater risks and non-compliance due to side effect profiles [4]. This emphasizes the continued need for novel medications with high safety profiles, particularly those that target MS early in its course to mitigate disease progression and improve quality of life.

2. Ozanimod Drug Information

In March 2020, the FDA approved Ozanimod for the treatment of RRMS, SPMS and CIS. Ozanimod, sold under the brand name ZEPOSIA, is a sphingosine-1-phosphate receptor (S1PR) modulator. Unlike earlier drugs of its class, Ozanimod is currently the only US FDA approved S1PR modulator that does not require genetic testing or first-dose observation [11][12].

Patients should undergo a series of baseline assessments, including complete blood count, electrocardiogram, and liver function tests, before starting Ozanimod. If the patient has a history of uveitis or macular edema, they should also receive an ophthalmic examination. As the drug may increase the risk of infections due to lymphocyte depletion, varicella-zoster virus antibodies should be tested for and patients should avoid live-attenuated vaccines during treatment [11][13].

Initiation of Ozanimod within six months of a cardiovascular event is contraindicated. Patients with a history of heart block, including Mobitz type II second or third-degree atrioventricular blocks, sino-atrial block, and sick sinus syndrome, should not be treated with Ozanimod unless they have a pacemaker. Other contraindications include severe untreated sleep apnea and simultaneous treatment with a monoamine oxidase inhibitor [11][13].

Ozanimod carries a risk of infections, bradyarrhythmia and atrioventricular conduction delays, liver injury, a decline in pulmonary function, transient decrease in heart rate, increased blood pressure, fetal risk, and macular edema. Adverse reactions from pooled SUNBEAM and phase III RADIANCE data include upper respiratory infection, elevated hepatic enzymes, orthostatic hypotension, urinary tract infection, hypertension, and back pain [11][13][14][15]. Despite these possible reactions, patients with relapsing multiple sclerosis reported good tolerability during phase II and II clinical trials [11][14][15][16]. Ozanimod has a relatively short half-life and lower peak plasma concentrations when compared to Fingolimod, the first S1PR modulator approved for the treatment of RRMS. These differences allow for once-daily dosing and contribute to lower systemic side effects [17][18].

3. Ozanimod Mechanism of Action

Ozanimod (Zeposia) is an immunomodulatory drug used for the treatment of clinically isolated syndrome, relapsing–remitting, and secondary progressive forms of MS. Ozanimod is an oral agent that modifies the course of the disease by selectively modulating sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) activity [19]. S1P is phosphorylated by sphingosine kinase 1 or 2 to become an active phospholipid [19]. Once active, these phospholipids, heavily concentrated in red blood cells, the brain, spleen, and eyes, regulate numerous functions involved in immunity, heart rate, smooth muscle tone, and endothelial cell development [20].

There are four types of sphingosine phosphate receptors. Type 1, 2, and 3 receptors exist ubiquitously. Type 4 and 5 receptors are present in lymphoid tissue, and the spleen and oligodendrocytes, respectively [19]. The expression of these receptors is low in lymph nodes, and expression allows for the exit of T-cells in response to the lymph–lymph node chemotactic gradient [19]. A strong S1P gradient is created by high concentrations in the blood and lymph and low concentrations in the intracellular and interstitial fluids [21]. B-cells and T-cells can use this gradient as a signal to enter the circulation. Disruption of this gradient results in lymphopenia due to lymphocyte failure to exit from lymphoid organs [22]. In fact, mice deprived of S1P1 show an absence of circulating lymphocytes as these cells remain confined to the thymus and other secondary lymphoid tissues [23].

S1P also holds an important function in the regulation of vascular integrity as a suppressor of angiogenesis [15]. These phospholipids reinforce the adherens junctions and stimulate the development of endothelial cells [24]. S1P localization and signaling are crucial for preserving vascular homeostasis, as it has been shown that mice that lack S1P and are fed a diet high in lipids have increased formation of atherosclerotic lesions [25].

S1P is hydrophobic and requires a chaperone molecule without which it cannot freely circulate in the bloodstream. Approximately 65% of S1P circulates bound to HDL-anchored ApoM, while the remaining S1P circulates bound to albumin [26]. S1P's functions vary depending on whether it is bound to ApoM or albumin. Only S1P bound to ApoM was shown to suppress inflammatory responses induced by cytokines [25]. Of note, S1P concentration is reduced in coronary artery disease, acute myocardial infarction, type II diabetes, and chronic kidney disease [27][28][29][30][31][32]. Via the modulation of S1P1 and S1P5, Ozanimod prevents circulating autoreactive lymphocytes from entering the CNS from peripheral tissues, in addition to reducing their concentration in the bloodstream.

4. Conclusions

Our understanding of multiple sclerosis pathophysiology and its clinical implications has grown tremendously over the decades. Treating the disease has become a complex task as clinicians now have many pharmacologic treatment options for this indication. Current therapeutic options include three broad categories: management of acute relapse, disease modifying therapies (DMTs), and symptomatic management. Clinicians should also be aware of the off-label use of medications to treat MS, such as Rituximab and neuromodulation techniques. Many of the aforementioned therapies were not originally developed to target MS pathophysiology and as such prove insufficient alone, highlighting the need for targeted MS treatments with reduced systemic side effect profiles.

Ozanimod is recently FDA approved for the treatment of clinically isolated syndrome, relapsing–remitting, and secondary progressive forms of MS. It is an oral agent that selectively modulates S1P1 and S1P5 receptor activity, which prevents autoreactive lymphocytes from entering the CNS where they can promote nerve damage and inflammation. This selectivity allows for modification of the disease course and once-daily dosing, and contributes to lower systemic side effects when compared to other drugs of its class. Furthermore, Ozanimod is currently the only US FDA approved S1PR modulator that does not require first-dose observation or genetic testing. Numerous clinical studies have demonstrated that ozanimod is both effective in the treatment of multiple sclerosis and well tolerated by patients. Further studies are required to evaluate its efficacy when compared with other available therapies, and as our understanding of MS pathophysiology and disease progression continues to evolve.

References

1. Lassmann, H. Pathogenic Mechanisms Associated With Different Clinical Courses of Multiple Sclerosis. Front. Immunol. 2019, 9, 3116.
2. Lassmann, H.; Brück, W.; Lucchinetti, C.F. The Immunopathology of Multiple Sclerosis: An Overview. Brain Pathol. 2007, 17, 210–218.
3. Zephir, H. Progress in understanding the pathophysiology of multiple sclerosis. Rev. Neurol. 2018, 174, 358–363.
4. Huang, W.-J.; Chen, W.-W.; Zhang, X. Multiple sclerosis: Pathology, diagnosis and treatments. Exp. Ther. Med. 2017, 13, 3163–3166.
5. Wallin, M.T.; Culpepper, W.J.; Campbell, J.D.; Nelson, L.M.; Langer-Gould, A.; Marrie, R.A.; Cutter, G.R.; Kaye, W.E.; Wagner, L.; Tremlett, H.; et al. The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology 2019, 92, e1029–e1040.
6. Kamm, C.P.; Uitdehaag, B.M.; Polman, C.H. Multiple Sclerosis: Current Knowledge and Future Outlook. Eur. Neurol. 2014, 72, 132–141.

7. De Sa, J.C.C.; Airas, L.; Bartholome, E.; Grigoriadis, N.; Mattle, H.; Oreja-Guevara, C.; O'Riordan, J.; Sellebjerg, F.; Stankoff, B.; Vass, K.; et al. Symptomatic therapy in multiple sclerosis: A review for a multimodal approach in clinical practice. Ther. Adv. Neurol. Disord. 2011, 4, 139–168.
8. Omerhoca, S.; Akkas, S.Y.; Icen, N.K. Multiple sclerosis: Diagnosis and Differrential Diagnosis. Arch. Neuropsychiatry 2018, 55 (Suppl. S1), S1–S9.
9. Confavreux, C.; Vukusic, S. Natural history of multiple sclerosis: A unifying concept. Brain 2006, 129 Pt 3, 606–616.
10. Dobson, R.; Giovannoni, G. Multiple sclerosis—A review. Eur. J. Neurol. 2019, 26, 27–40.
11. Lamb, Y.N. Ozanimod: First Approval. Drugs 2020, 80, 841–848.
12. Bristol Myers Squibb. US Food and Drug Administration Approves Bristol Myers Squibb's ZEPOSIA® (Ozanimod); A New Oral Treatment for Relapsing Forms of Multiple Sclerosis. Available online: https://www.chemdiv.com/u-s-food-and-drug-administration-approves-bristol-myers-squibbs-zeposia-ozanimod-a-new-oral-treatment-for-relapsing-forms-of-multiple-sclerosis/ (accessed on 2 December 2020).
13. Celgene Corporation. ZEPOSIA® (Ozanimod) Capsules: US Prescribing Information; FDA: Summit, NJ, USA, 2020.
14. Comi, G.; Kappos, L.; Selmaj, K.W.; Bar-Or, A.; Arnold, D.L.; Steinman, L.; Hartung, H.-P.; Montalban, X.; Havrdová, E.K.; Cree, B.A.C.; 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, 1009–1020.
15. Cohen, J.A.; Comi, G.; Selmaj, K.W.; Bar-Or, A.; Arnold, D.L.; Steinman, L.; Hartung, H.-P.; Montalban, X.; Havrdová, E.K.; Cree, B.A.C.; 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, 1021–1033.
16. Cohen, J.A.; Comi, G.; Arnold, D.L.; Bar-Or, A.; Selmaj, K.W.; Steinman, L.; Havrdová, E.K.; Cree, B.A.C.; Montalbán, X.; Hartung, H.-P.; et al. Efficacy and safety of ozanimod in multiple sclerosis: Dose-blinded extension of a randomized phase II study. Mult. Scler. J. 2019, 25, 1255–1262.
17. Chaudhry, B.Z.; Cohen, J.A.; Conway, D.S. Sphingosine 1-Phosphate Receptor Modulators for the Treatment of Multiple Sclerosis. Neurotherapeutics 2017, 14, 859–873.
18. Meno-Tetang, G.M.L.; Li, H.; Mis, S.; Pyszczynski, N.; Heining, P.; Lowe, P.; Jusko, W.J. Physiologically Based Pharmacokinetic Modeling of FTY720 (2-Amino-2[2-(-4-octylphenyl)ethyl]propane-1,3-diol hydrochloride) in Rats After Oral and Intravenous Doses. Drug Metab. Dispos. 2006, 34, 1480–1487.

19. Subei, A.M.; Cohen, J.A. Sphingosine 1-Phosphate Receptor Modulators in Multiple Sclerosis. CNS Drugs 2015, 29, 565–575.
20. Cohen, J.A.; Chun, J. Mechanisms of fingolimod's efficacy and adverse effects in multiple sclerosis. Ann. Neurol. 2011, 69, 759–777.
21. Obinata, H.; Hla, T. Sphingosine 1-phosphate and inflammation. Int. Immunol. 2019, 31, 617–625.
22. Schwab, S.R.; Pereira, J.P.; Matloubian, M.; Xu, Y.; Huang, Y.; Cyster, J.G. Lymphocyte Sequestration Through S1P Lyase Inhibition and Disruption of S1P Gradients. Science 2005, 309, 1735–1739.
23. Matloubian, M.; Lo, C.G.; Cinamon, G.; Lesneski, M.J.; Xu, Y.; Brinkmann, V.; Allende, M.L.; Proia, R.L.; Cyster, J.G. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature 2004, 427, 355–360.
24. Eilken, H.M.; Adams, R.H. Dynamics of endothelial cell behavior in sprouting angiogenesis. Curr. Opin. Cell Biol. 2010, 22, 617–625.
25. Galvani, S.; Sanson, M.; Blaho, V.A.; Swendeman, S.L.; Obinata, H.; Conger, H.; Dahlbäck, B.; Kono, M.; Proia, R.L.; Smith, J.D.; et al. HDL-bound sphingosine 1-phosphate acts as a biased agonist for the endothelial cell receptor S1P1to limit vascular inflammation. Sci. Signal. 2015, 8, ra79.
26. Murata, N.; Sato, K.; Kon, J.; Tomura, H.; Yanagita, M.; Kuwabara, A.; Ui, M.; Okajima, F. Interaction of sphingosine 1-phosphate with plasma components, including lipoproteins, regulates the lipid receptor-mediated actions. Biochem. J. 2000, 352 Pt 3, 809–815.
27. Prüfer, N.; Kleuser, B.; Van Der Giet, M. The role of serum amyloid A and sphingosine-1-phosphate on high-density lipoprotein functionality. Biol. Chem. 2015, 396, 573–583.
28. Tong, X.; Peng, H.; Liu, D.; Ji, L.; Niu, C.; Ren, J.; Pan, B.; Hu, J.; Zheng, L.; Huang, Y. High-density lipoprotein of patients with Type 2 Diabetes Mellitus upregulates cyclooxgenase-2 expression and prostacyclin I-2 release in endothelial cells: Relationship with HDL-associated sphingosine-1-phosphate. Cardiovasc. Diabetol. 2013, 12, 27.
29. Tong, X.; Lv, P.; Mathew, A.V.; Liu, D.; Niu, C.; Wang, Y.; Ji, L.; Li, J.; Fu, Z.; Pan, B.; et al. The compensatory enrichment of sphingosine -1- phosphate harbored on glycated high-density lipoprotein restores endothelial protective function in type 2 diabetes mellitus. Cardiovasc. Diabetol. 2014, 13, 82.
30. Sattler, K.J.E.; Elbasan, S.; Keul, P.; Elter-Schulz, M.; Bode, C.; Gräler, M.H.; Bröcker-Preuss, M.; Budde, T.; Erbel, R.; Heusch, G.; et al. Sphingosine 1-phosphate levels in plasma and HDL are altered in coronary artery disease. Basic Res. Cardiol. 2010, 105, 821–832.

31. National Center for Biotechnology Information. PubChem Compound Summary for CID 52938427, Ozanimod. 2020. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Ozanimod (accessed on 2 December 2020).
32. Tran, J.Q.; Hartung, J.P.; Peach, R.J.; Boehm, M.F.; Rosen, H.; Smith, H.; Brooks, J.L.; Ms, G.A.T.; Olson, A.D.; Gujrathi, S.; et al. Results from the First-in-Human Study With Ozanimod, a Novel, Selective Sphingosine-1-Phosphate Receptor Modulator. J. Clin. Pharmacol. 2017, 57, 988–996.