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Management of Multiple Sclerosis and Effectiveness of Ozanimod in Relapsing Multiple Sclerosis

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***Abstract*—** *Multiple Sclerosis (MS) is termed as an autoimmune disorder characterised by multiple demyelinating lesions in the central nervous system (CNS). Till date, no drug provides the complete cure for MS. All the immunotherapeutic agents and most of the receptor modulators target Relapsing Multiple Sclerosis (RMS). Thus the main challenge until recent times remained to develop a suitable therapy for Secondary progressive MS (SPMS), until the approval of the non-selective sphingosine-1-phosphate (S1P) receptor modulator Fingolimod in 2010 which led to the discovery of many such drugs over the years. The most recent FDA approved drug named Ozanimod is a selective receptor modulator of S1P which targets a receptor subtypes S1PR1 and S1PR5 thereby resulting in decreased lymphocyte migration into CNS. Like fingolimod and siponimod, it induces rapid internalisation and degradation of S1PR1 and produces a decrease in circulating B and T lymphocytes. However, when compared to Fingolimod and Siponimod, Ozanimod has quicker lymphocyte reconstitution, after discontinuation. Apart from regular action, modulation of S1PR with Ozanimod also decreases inflammatory cell infiltration of CNS leading to reduced disease activity in patients with MS. Thus, the use of ozanimod in patients with RMS may provide promising results due to its high efficacy and very low frequency of side effects.*

***Keywords*—** *Multiple Sclerosis, Demyelinating lesions, Relapsing Multiple Sclerosis, Ozanimod.*

I. INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune condition where the immune system attacks the protective myelin sheath that covers the nerves, and axons (axonopathy). [1, 4] The myelin damage results in the formation of lesions making the communication flow between nerve cells harder. [1, 2] This might result in "signal breakdown" further leading to symptoms and relapses. [1, 3] Signs and symptoms vary widely depending upon the amount of nerve damage and which nerve is affected. People with severe MS often lose the ability to walk independently or experience great difficulty in walking, paralysis, vision loss, while others experience long periods of remission without any specific symptoms or include mild symptoms, that includes blurred vision, numbness and tingling in the limbs. [5] However, MS is characterized by BBB breakdown, infiltration immune cells in CNS, demyelination, astrogliosis, and neurodegeneration. [6] MS is most common in Western countries particularly the U.S resulting in approximate 400,000 cases on per year estimates than affecting approximately 2.5 million populations worldwide. [7,8] In accordance to the National Institute for Neurological Disorders and Stroke (NINDS), 250,000–350,000 people in the United States are living with MS Also, the National Multiple Sclerosis Society has estimated that the number might soon be closer to 1 million. [9] It usually affects the younger population between 15-50 years, It has a prolonged course. It is about twice as common in women as men. [7, 9] The exact cause of MS remained unknown. However, it is believed to involve a combination of genetic factors and nongenetic trigger (eg, viral infection, low vitamin D levels) resulting in an autoimmune disorder where T cells get activated and destroy the myelin sheath leading to recurrent immune attacks on the CNS. [10, 7] Multiple areas in CNS gets demyelinated which is initiated by inflammation due to entry of activated T lymphocytes, the release of cytokines and macrophages. In later stages destruction of the axon is noted which is responsible for the progressive and persistent disability. [11] Diagnosis of MS is based on clinical presentations and various lab tests involving MRI, lumbar puncture etc. [12] MS is classified into 4 types depending upon the time of disease progression and lesion development i.e, a)Relapsing-remitting MS (RRMS) b)Secondary progressive MS (SPMS) c)Primary progressive MS (PPMS) d)Progressive-relapsing MS (PRMS). Among all the types RRMS consists of approximately 85% of cases. [13] Management of MS involves Immunomodulating therapy (IMT) and therapies to modify symptoms. Most of the FDA approved diseases modifying agents for MS (DMAMS) is used only in the relapsing forms.[14] However Sphingosine 1-phosphate (S1P) receptor modulators (eg, ozanimod, fingolimod) shows good result in actively progressing secondary diseases, thus most preferred over any other DMAMS like Interferons (eg, IFN beta-1a, IFN beta-1b), Monoclonal antibodies (eg, alemtuzumab, ocrelizumab) and Miscellaneous immunomodulators (eg, mitoxantrone, dimethyl fumarate). [15, 16] The preference of S1P receptor modulators over other DMAMS came as an advantage due to their ubiquitous presence in CNS and CVS and also less comparative side effects and adverse drug reactions than other modulators. [17] Among the S1P receptor modules, Fingolimod was the first approved drug by the FDA in 2010 because of its potential efficacy in treating relapsing multiple sclerosis (RMS). Later on, many drugs with similar efficacy were identified. [18, 14] The most recent FDA approved S1P

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receptor modulator is Ozanimod which was done based on the randomized trial, active-controlled Phase 3 SUNBEAM™ (Where safety and efficacy of Ozanimod vs INF beta-1a were compared) and RADIANCE™ (Where safety and efficacy of the selective S1P receptor modulator Ozanimod was studied). [19, 15, 16] According to FDA Ozanimod 0.92 mg, once a day, given by oral administration is the only approved S1P receptor modulator that offers RMS patients with the initiation of therapy without any genetic test. [19] Before Ozanimod approval, many comparative studies (fingolimod vs Ozanimod) were conducted which was suggestive that Ozanimod has a superior benefit-risk profile than fingolimod for the treatment of RMS. Thus Ozanimod is the most preferred drug in RMS due to its high efficacy and less frequency of side effects. [20]

II. Etiology

Around, 2.5 million individuals are affected globally. It generally affects young individuals between 20-40 years old. Women are affected by multiple sclerosis twofold as often as men. [21] The exact pathophysiology of multiple sclerosis is unclear but it autoimmune. The wide division of lesions results in clinical features for example loss of sensation, muscle weakness, visual loss, cognitive impairment, and bladder and bowel disturbance. [22] Demyelination is a characteristic of multiple sclerosis pathology. NG2-glia is oligodendrocyte precursors that can differentiate into mature oligodendrocytes and thus may contribute to remyelination in patients with multiple sclerosis. It is initiated by the demyelination of the CNS, followed by the activation of the adaptive immune response in the periphery. [23] Multiple sclerosis largely comprises three stages:

i. A preclinical stage, that includes both genetic and environmental factors causing the disease,
ii. A relapsing-remitting clinical stage, which features discrete, self-limited episodes of neurologic dysfunction.
iii. Progressive clinical-stage during which neurologic dysfunction gradually worsens, affecting the patient. [24] Relapsing-remitting multiple sclerosis is characterized by the influx of immune cells leading to inflammation; inflammation in the progression is compartmentalized behind a relatively closed blood-brain-barrier. Inflammation by macrophages and microglia is further distinct in progressive multiple sclerosis compared with relapsing-remitting multiple sclerosis. [25] In the progressive stage of multiple sclerosis, inflammation becomes trapped within the brain compartment behind a closed or repaired blood-brain barrier. Numerous vessels with perivascular inflammation in the absence of leaky endothelial cells were seen in patients with progressive multiple sclerosis. Besides, in the progressive stage of multiple sclerosis, lymph follicle-like structures are formed in the meninges and the large perivascular spaces. Those lymph-follicle-like structures are associated with rapid disease progression and profound brain damage. [26] In affected areas, the endothelial blood-brain barrier becomes leaky and allows the entry of serum proteins and cells into the CNS. Dysferlin is a protein located at the cytoplasm of cell membranes. It plays a major role in the maintenance and repair of the muscle cell membrane. Within actively demyelinating as well as inactive lesions, endothelial cells with dysferlin reactivity were frequent at the site of ongoing myelin destruction as well as in a broad zone of the periplaque white matter. Besides, improved numbers of dysferlin-positive vessels were found in the normal-appearing white matter, isolated from classic demyelinated plaques. Whereas in acute and early relapsing multiple sclerosis, no dysferlin expression was seen in areas of the normal-appearing white matter that were far-away from demyelinating lesions and devoid of pathologic alterations, dysferlin-reactive vessels were present in the normal-appearing white matter of patients with progressive multiple sclerosis, which showed diffuse inflammatory infiltrates, microglial activation, and diffuse axonal injury. [27] Multiple sclerosis belongs to a group of inflammatory demyelinating diseases of the CNS, which include acute disseminated leukoencephalitis, Devic's neuromyelitis optica, and Balo's concentric sclerosis. They all occur on a condition of an inflammatory reaction, composed of lymphocytes and activated macrophages or microglia, and show demyelination, in which axons are partially preserved. It is broadly believed that an inflammatory process of putative autoimmune nature is the driving force of tissue injury in multiple sclerosis. [28]

III. Factors Leading to Multiple Sclerosis

Major factors include genetics, viral infections, gender differences, and various pathophysiological factors. [29]

A. Genetic Factors

The increased risks of occurrence within families indicate that genetic factors play an important role in multiple sclerosis. Multiple Sclerosis is more likely to hit siblings than the general population and is more likely to strike monozygotic compared to dizygotic twins. Recently, whole-genome screens have been conducted in different populations and identified different chromosomal regions potentially harboring multiple sclerosis susceptibility genes. The human leukocyte antigen (HLA) was found to control immune response genes in multiple sclerosis. The HLA-DRB1 1501 molecule explains about 50% of multiple sclerosis cases. [29]

B. Viral Infections

Current findings from a population-based investigation hold the implication of the EBV in multiple sclerosis susceptibility. Additional studies of progressive multiple sclerosis cases found the EBV present within B cells that infiltrate the meninges and white matter— strong evidence for the contribution of EBV in multiple sclerosis through B cells as triggers. Another type of virus, coronaviruses, has also been found in the brains of multiple sclerosis patients. [29]

C. Gender Differences

Sex dimorphism in multiple sclerosis is explained by the effects of sex chromosomes and sex steroid hormones on the immune system, blood-brain barrier, and parenchymal CNS

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cells. Amusingly, positive neuroprotective effects of multiple sclerosis were noted in clinical studies for elevated levels of hormones in both female and male hormones (estrogens, progesterone, and androgen), an elevation that could be related to anti-inflammatory actions on the immune system or the CNS. [29]

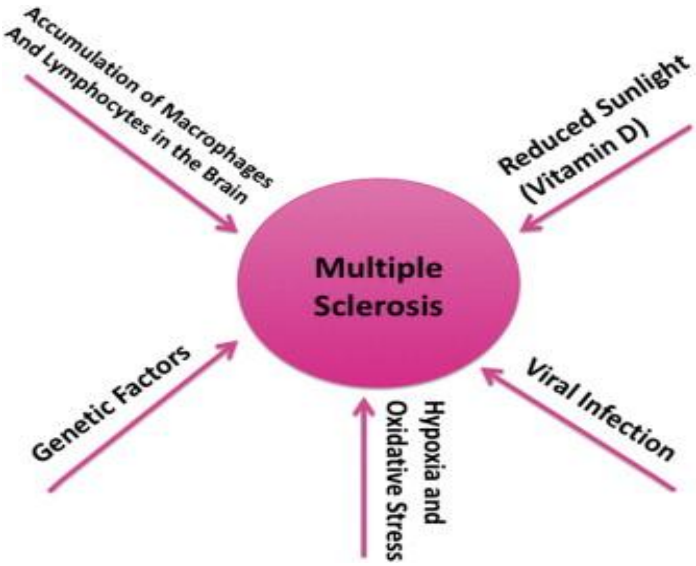

Figure 1. Factors that lead to Multiple Sclerosis

IV. MECHANISM

Multiple sclerosis is a chronic inflammatory disease of the CNS characterized by extensive inflammation, focal demyelination, and a variable degree of axonal loss. Axonal damage in multiple sclerosis lesions recently involved significant attention, because neuroimaging studies imply that it may be the major pathological correlate of permanent functional deficit. [30] There are different mechanisms by which multiple sclerosis occurs that include genetics, environmental, autoimmune, infection, progressive, and relapsing multiple sclerosis. [24]

Table 1. Mechanism of Multiple Sclerosis

Progressive multiple sclerosis	Relapsing multiple sclerosis
Progressive multiple sclerosis mechanisms include those that are immune dependent and immune independent. In immune-dependent forms, an innate immune response is recognized in the brain that involves microglia, macrophages, B cells, and lymphoid follicles. There may be chronic activation of peripheral T cells and innate cells. In immune-independent forms, mitochondrial injury and oxidative stress also occur.	Relapsing multiple sclerosis is determined by immune cells that migrate into the CNS. Numerous treatments have been shown to efficiently treat relapsing multiple sclerosis and act on the subsequent common pathways: decrease number and function of effectors cells, increase the number and function of regulatory cells.

Meningeal inflammation is a type of ectopic lymphoid-like structures has recommended playing a well-known function in the development of cerebral cortical grey matter pathology in multiple sclerosis. The incidence of B cell follicle-like structures was linked with an associated quantitative increase in diffuse meningeal inflammation that linked with the degree of microglial activation and grey matter cortical demyelination. [31]

V. IMMUNOPATHOGENESIS OF MULTIPLE SCLEROSIS

Multiple sclerosis is an immune-mediated disease that involves both the cellular and humoral immune system. The specific mechanism by which autoreactive T cells are activated remain unidentified but may occur through non-specific polyclonal activation by bacterial or viral antigens or from structural homologies between a self-protein and a pathogenic protein. T cells acquire the potential to cross the blood-brain barrier after activation. This process is driven by the expression of cell surface integrins on inflammatory cells that mediate their binding to the vascular cell adhesion molecule (VCAM-1) expressed on capillary endothelial cells. VCAM-1 expression is induced by TNF-α and IFN during inflammation. Matrix metalloproteases (MMPs) are released by T cells that facilitate their passage through the extracellular matrix. MMPs are involved in the successive degradation of myelin components. After entry into the CNS, T cells are reactivated on encountering CNS-related autoantigenic peptides in the context of class 2 molecules of the MHC expressed by local antigen-presenting cells and dendritic cells. This commits T cells towards a proinflammatory phenotype. Although Th1 cells were previously believed to be key players in multiple sclerosis immunopathogenesis, experimental multiple sclerosis models show an important role for a novel subset of inflammatory T cells, Th17 cells. Activated T cells cause myelin disruption that leads to the release of new CNS antigens. A surge of proinflammatory cytokines and the recruitment of additional inflammatory cells and specific myelin antibody-forming B cells to the site of inflammation further contribute to tissue injury. [32]

Sphingosine 1-phosphate is a phospholipid-soluble signaling molecule that interacts with G protein-coupled receptors. [34] The S1PR is concerned in several immune-mediated disorders, such as multiple sclerosis, rheumatoid arthritis, and inflammatory bowel diseases. [35] Five subtypes of S1PR were identified and demonstrated that S1PR1 has a role in lymphocyte migration and was also found in cardiovascular structures, while S1PR2 modulated cardiovascular function, bone structure, and fertility, together with S1PR3. On the whole, S1PR1–3 has been associated with cancer and metastases as they have a role in cell migration; and S1PR4 and S1PR5 were found to adapt the migration of hematopoietic cells and lymphocytes, respectively. It was found that the number of circulating lymphocytes decreased due to the Antagonism of the S1PR1. Pharmacological agents with targeted S1PR1 modulatory effects have been identified, including ozanimod, siponimod, and ponesimod. [34]

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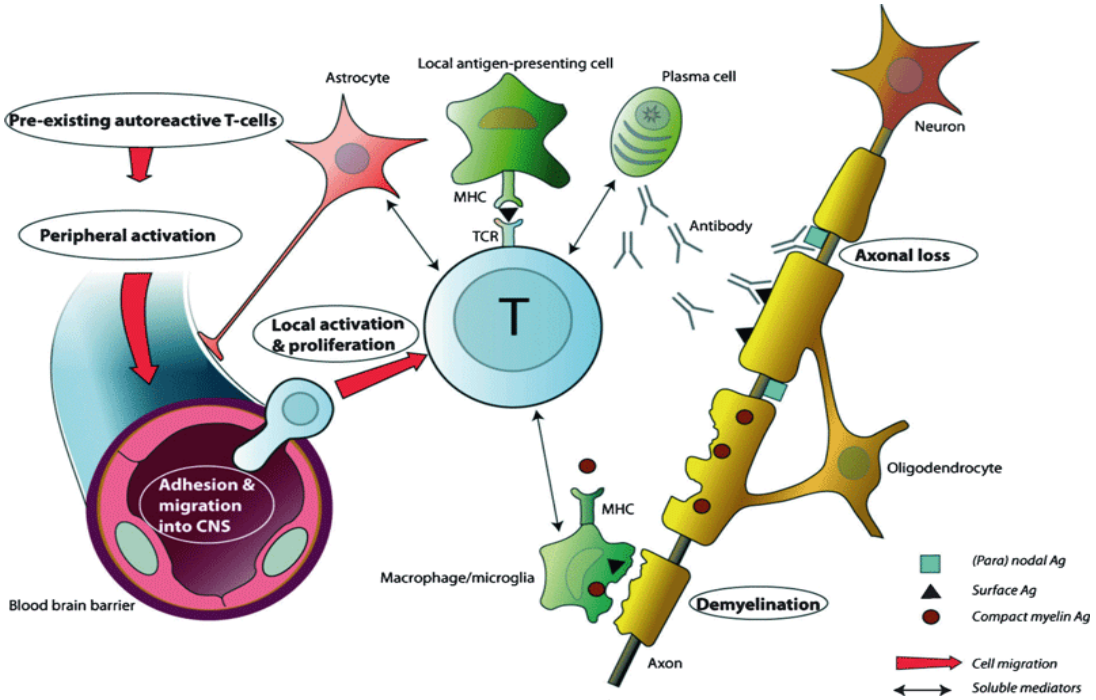

Figure 2. Immunopathogenesis of Multiple Sclerosis

VI. MANAGEMENT

Management of MS depends on the clinical presentation. However, treatment is separately addressed for relapse, a disease-modifying therapy for patients with RMS and SPMS, symptomatic therapy and complementary therapy.

i. Treatment for Relapse/Acute Attacks:

Treatment is aligned irrespective of type (RMS / SPMS) of MS, the drug of choice remains corticosteroids over the years and even today. It acts by reducing the duration of relapse and accelerating recovery, no convincing evidence is obtained on the degree of recovery. Most common regimen: 1) Methylprednisolone sodium succinate given intravenously IV, 500-1,000 mg per day for 3-5 days. (First-line therapy) 2) Methylprednisolone, 1g IV for 3 days followed by oral prednisolone, 60-80mg per day for 1 week. 3) Plasmapheresis (second-line therapy): Removing blood from the body, filtering to remove antibiotics. The clean blood is pumped back to the body. 4) Intravenous immunoglobulin (IVIG): Injected immunoglobulin helps to boost the immune system. [36, 39]

ii. Disease-modifying therapy (RMS / SPMS):

The Food and Drug Administration (FDA) has approved several drugs that modify MS. Based on dosage form they are: 1) Injectables: Medications that can be given as injectables include immunosuppressive agents like Interferon-beta-1a (Avonex, Rebif), Interferon beta-1b (Betaseron, Extavia), Glatiramer acetate (Copaxone, generic versions such as Glatopa), Pegylated interferon beta-1a (Plegridy) In 2018, injection daclizumab (Zinbryta) was withdrawn from the market due to safety concerns. 2) Infusions: Most common infusion forms include recombinant monoclonal antibodies like Alemtuzumab (Lemtrada), Mitoxantrone (Novantrone), Natalizumab (Tysabri), Ocrelizumab (Ocrevus) 3) Oral treatments: Tablet forms include Teriflunomide (Aubagio), Fingolimod (Gilenya), Dimethyl fumarate (Tecfidera), Cladribine (Mavenclad), Siponimod (Mayzent) Capsule forms include Ozanimod (Zeposia), Diroximel fumarate (Vumerity). [37, 39]

iii. Alternative therapies/ Symptomatic management:

Table 2. Alternative therapies/ Symptomatic management

Symptoms	Management
Spasticity	Inj botulinum toxin, baclofen, diazepam.
Ataxia	Isoniazid, clonazepam.
Sensory Symptoms	Carbamazepine, gabapentin, amitriptyline.
Spastic bladder	Anticholinergic like oxybutynin.
Fatigue	Amantadine.
Impotence	Sildenafil.
Depression	Imipramine, amitriptyline.

iv. Complementary therapies:

Diet Control, balanced diet, Exercises like walking, swimming etc., Physiotherapy. [38] Treatment is Initiatiated while treating a patient for the first time, either induction or escalation approach is most preferred. The treatment is initiated by first-line medications (INF, GA) if the treatment shows no to lesser response then the therapy is switched to second-line medications (Natalizumab, Alemtuzumab, Fingolimod, Ozanimod)

Table 3. Examples of drugs in different therapies

Therapy	Medications
First-line	IFNBs, GA, teriflunomide, and dimethyl fumarate
Second-line	Natalizumab, Alemtuzumab, Fingolimod, Ozanimod
Third-line (very less preferred)	Cyclophosphamide.

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Fingolimod is approved as a second-line treatment in the EU and as first-line in the United States, Canada and other countries. [41]

In first-line therapy, medications differ in terms of efficacy and tolerability. Evidence suggests that high dose IFNB 1-a 44 mcg SC 3 times a week is more effective than low dose IFNB 1-a 30 mcg IM once a week. [42] Natalizumab, fingolimod and other second-line medications can be used as initial treatment in patients with aggressive MS with an induction approach. [43] Switch therapy should be considered in patients receiving first-line medications but continue a similar relapse rate as compared to the pre-treatment phase, or showing irreversible neurological disability. The most preferred second-line drugs are Natalizumab and Fingolimod. [44]

A. Treatment Cessation: Treatment shall be stopped when 1) Serious ADR is precipitated due to drug use. 2) If the patient becomes pregnant or in lactating womens. 3) Patients with poor treatment adherence. 4) In patients with confirmed disability progression over a year in the absence of any relapse. [45]

B. Emergency Management: Often the treatment in emergency care should be selected in such a manner that it stabilizes acute life-threatening conditions as soon as possible. The most considered treatment options include IV steroids, IV immunoglobulin (IVIG) and Plasmapheresis.A study provided the understanding that plasmapheresis may be superior to IV steroids in patients with acute fulminant MS. [46] According to the American Academy of Neurology (AAN), plasmapheresis is possibly effective and may be considered in acute fulminant demyelinating CNS disease. [47]

C. New Emerging Treatment Strategies: Multipotent hematopoietic stem cell, BHT-3009, a DNA vaccine, Nanoparticles, Altered peptide ligands (APL), Cyclic Peptides, Mannan a carrier to modulate immune responses. [48]

D. Remyelination: Agents in development include Benztropine: Anticholinergic, Clemastine: Antihistamine, MD1003 (High dose biotin): Myelin Biosynthesis. [49]

E. Treatment followed in Indian hospitals

Table 4. Treatment followed in Indian hospitals

Treatment Type	Medications
Acute Relapse	Corticosteroids, Plasmapheresis
Disease-Modifying therapy	INF-beta, Glatiramer acetate
Therapy in disease progression 1)Oral therapy	Sipnoimod, Dimethyl fumarate, Teriflunomide
2)Infusion therapy	Natalizumab for primary progression Mitoxantrone for secondary progression

VII. OZANIMOD AND ITS EFFICACY

Ozanimod is an investigational oral DMT and a selective S1P receptor modulator intended to target only the receptor subtypes S1PR1 and S1PR5. The therapeutic effects of ozanimod in multiple sclerosis are unidentified but involve the decrease in lymphocyte migration into the CNS. [33] It is an orally bioavailable, small molecule that acts directly and through its metabolites to selectively activate S1PR1 and S1PR5. It acts as a functional antagonist of the S1P1R by promoting receptor internalization and degradation, resulting in a reduction of the number of circulating lymphocytes. [51] It works by acting on certain types of immune cells called lymphocytes that are centrally concerned in the autoimmune attack on the myelin sheath. It binds to receptors present on the cells' surface, keeping them from reaching the brain. Consequently, the amount of activated lymphocytes is decreased, diminishing the immune attack. [52] It blocks sources of inflammation in relapsing multiple sclerosis by acting as an S1PR1 receptor agonist. [53] It crosses the blood-brain barrier and its affinity for the S1PR-1 is comparable to fingolimod and siponimod. Like fingolimod and siponimod, it induces rapid internalization and degradation of S1PR-1 and produces a decrease in circulating B and T cell lymphocytes. Compared to fingolimod and siponimod, there is quick lymphocyte reconstitution after it is discontinued. Of note, ozanimod treatment considerably improves experimental autoimmune encephalomyelitis scores, even in the presence of restored blood lymphocyte counts, supporting a direct CNS therapeutic role. [54] It was revealed through various experiments that ozanimod was able to alter the experimental autoimmune encephalomyelitis glutamatergic synaptic alterations, through attenuation of local inflammatory response driven by activated microglia and infiltrating T cells. [55] Besides, modulation of S1PR on microglia, oligodendrocytes, astrocytes, and neurons is proposed to have straight beneficial effects. Modulation of S1P receptors with ozanimod may decrease inflammatory cell infiltration of the CNS leading to a reduction in disease activity in patients with multiple sclerosis. [56] The occurrence of cardiac adverse events complicates the beginning of treatment with fingolimod and requires cardiac monitoring. In contrast to fingolimod, ozanimod don't have a greater affinity for the S1P3R, which might indicate significant pharmacodynamic differences between these 2 compounds that impact cardiac safety and the effect on the QTc interval. [51] A RADIANCE Part B study was conducted between two doses (1 mg and 0.5 mg) of oral ozanimod compared with IFN in patients with RMS for two years. Oral ozanimod was also evaluated in two doses (1 mg and 0.5 mg) in RMS patients for at least one year in SUNBEAM study. Ozanimod demonstrated a major decline in new and enlarging T2 lesions over one year for 1 mg. The drug had the ability to inhibit brain atrophy that provided patients a long and productive life, living with relapsing, remitting multiple sclerosis without disability. [53]

A phase 2 trial of ozanimod in patients with relapsing multiple sclerosis showed a dose-dependent reduction in circulating lymphocytes that were linked with important reductions in inflammatory and neurodegenerative brain lesions. [57] A Dose-blinded extension of a randomized phase II study was conducted that demonstrated sustained efficacy in subjects continuing treatment up to 2 years and reached similar efficacy in subjects who switched from placebo; no unexpected safety signals emerged. [58] A phase 1 study established that treatment with ozanimod produced dose-dependent reductions in absolute lymphocyte count over 12 weeks in patients with relapsing multiple sclerosis. Results from the exploratory analyses demonstrated that this decrease

was due primarily to decreases in T and B cells. [59] The major focus for the treatment of multiple sclerosis must be the decline of permanent disability. It is established that permanent disability results from cumulative axon loss. [60]

VIII. Conclusion

Despite the availability of numerous treatment options for RMS, there is no accurate and effective therapy for SPMS. However (selective S1PR modulator) Ozanimod prevents migration of lymphocytes from lymphatic tissues into CNS, also decreases inflammatory cell infiltration of CNS that reduces the further disease progression in patients with MS. Use of ozanimod may provide promising results in patients with RMS potentially due to its high efficacy and very low frequency of side effects. It is also effective in many other inflammatory conditions like Rheumatoid Arthritis, Systemic Lupus Erythematosus and Diabetes Miletus.

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