

# Etrasimod: A promising therapeutic candidate against Multiple Sclerosis

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Multiple sclerosis (MS) is central nervous system (CNS) based disease. It is a chronic inflammatory demyelinating disease [1]. The main causes for MS are genetic and environmental factors. It is a disease of young people (median age of onset is around 28 years) but is lifetime and is often disabling; 50% of patients need a cane to walk 15 years after disease onset; and Worldwide more than 2.5 Million persons are affected. The pathology of MS is characterized by demyelination, inflammation, neuroaxonal damage and reactive gliosis. The exact pathophysiology of MS is not understood till now [2]. These lesions are markers of the disorder, because of the infiltration of peripheral immune cells into the brain and spinal cord. Premature lesions illustrate invading peripheral immune cells and escapes in the blood-brain barrier (BBB) [3]. Macrophages influence the infiltrate, followed by T cells+CD8, whereas lower numbers of T cells+CD4, plasma cells and B cells may also be observed. Even though the T-cell composition of infiltrates does not alter as the disease forms, the proportion of B and plasma cells raises. Macrophages and Microglia keep the chronic state of activation during the disease, forming plaques that engage loss of oligodendrocytes and myelin sheaths [4].

Since, CNS is moderately divided from the lymphatic organs and immune system, this is considered an argument for peripheral initiation of adaptive immune responses against CNS antigens, with ensuing CNS barrier infiltration. However, even in a healthy CNS, memory T cells traffic through cerebrospinal fluid (CSF), indicating a capacity for intrinsic CNS immune surveillance [5]. Commonly, CSP is considered to be a rare complication of cesarean section. The exact cause and pathology are still unknown. Nonetheless, up to 72% of cesarean scar pregnancies occur in women who have had 2 or more cesarean deliveries [8,9]. Cesarean scar pregnancies can appear at any time, from implantation to termination, but it has been reported to occur more often in the first trimester [5]. The clinical presentation of CSP is non-specific, with the most common symptom being vaginal bleeding [1,10-12]. However, it also can be an incidental finding in asymptomatic women. As Kaluarachchi et al. [13] reported, the patient had no abdominal pain, vaginal bleeding or any other obvious complaints. In the majority of cases, it can be found that the serum  $\beta$ -hCG levels are markedly increased to varying degrees.

## Pathophysiology of MS

Plaques, inflammation, destruction of myelin sheath, injury to axons and destruction of axons majorly in CNS region are extremely involved in multiple sclerosis [6]. In brain and spinal cord, plaques are observed mainly around white matter, optic nerves, corpus callosum, cerebellar peduncles, long tract regions and minimally in grey matter also. Plaques are observed in every stage of MS. In early stages, destruction of neurons, loss of axons and reactive gliosis is also observed. In many patients, inflammatory plaques consisting of demyelinated axons, less oligodendrocytes, proliferation of astrocytes with gliosis and lymphocytic as well as macrophagic parenchymal infiltrates are also seen. Grey and white matter atrophy along with inflammation and activation of microglial cells at the plaque borders is also observed. This disease is associated with T- cell mediated immune response with increased number of CD8+ cells [7].

Etrasimod (APD334) acts as a modulator of selective Sphingosine-1-phosphate (S1P) receptor in

Receptor	Pharmacological action	Reference
S1P1	Lymphocyte trafficking is regulated	[14]
S1P2	Oppose action of S1P1 receptor	
S1P3	Acts on pro-fibrotic pathways	
S1P4	Reduce the secretion and proliferation of cytokines and increase the secretion of Interleukin-10	
S1P5	Works majorly on endothelial cells within the blood brain barrier. So, helps to maintain the integrity of Blood brain barrier	

**Table 1:** Various Classes of Selective sphingosine 1- phosphate receptors.

Drug	Receptor	Pharmacological Action	References
Etrasimod	S1P1	A full agonist	[16]
	S1P2	NO activity	
	S1P3	NO activity	
	S1P4	A partial agonist	
	S1P5	A partial agonist	

**Table 2:** Impact of Etrasimod activity on various S1P receptors.

inflammatory disorders that are majorly immune mediated [8]. S1P receptor Sphingosine-1-phosphate-1 (S1P1) belongs to GPCR class-A molecules which are usually evidenced on lymphocytes, nerve cells as well as endothelial cells. There are five major classes of S1P1 and are involved in plethora of bodily functions (Table 1). Moreover, they are majorly involved in maintenance of vascular development and lymphocyte trafficking [9]. S1P is a lysophospholipid signaling molecule that is majorly derived from membrane and acts in the regulation of bodily processes that are majorly mediated through GPCR [10]. These molecules have different expressions according to the locations. S1P1, S1P2 and S1P3 are found everywhere in the body while S1P4 and S1P5 are limited to immune system and CNS [11], where S1P4 has a role in maintenance of dendritic cells, S1P5 is involved in regulating natural killer cells [12,13].

In immune mediated inflammatory disorders, Etrasimod acts as a S1P receptor modulator [15]. It majorly acts on S1P1 receptor, which is one of the five types of S1P receptor [16]. According to Hussien and his research group [9], in  $\beta$ -arrestin recruitment assay Etrasimod shows activity as a full agonist of S1P1 that can produce lymphocyte reduction even at very low plasma concentration and it agonizes S1P4 and S1P5 partially. However, on human recombinant S1P2 or S1P3 receptors, no such activity was noticed. After comparison of all these activities, it is observed that S1P1 activity is about 24 times more as compared to S1P4 while it is times more in comparison with S1P5. However, it is 1000 times more in comparison with S1P2 and S1P3 (Table 2).

Experimental autoimmune encephalomyelitis (EAE) model and collagen induced arthritis (CIA) model are the two major methods employed by Buzard and group [17]. In EAE model, MS was induced using myelin/oligodendrocyte glycoprotein (MOG35–55) as an autoantigen, which leads to demyelination as an autoimmune response. After 20 days of treatment with etrasimod, prevention of spread of disease was observed. Furthermore, histological examination

of spinal cord and brain on 37th day marked reduction in the number of lymphocytes was observed.

In CIA model, collagen was administered orally and a marked decrease in diameter of ankles was observed. After 17 days of treatment with etrasimod, regain of weight as well as refinement in histological observations of knees and ankles in affected animals were noted. Possible mechanism behind the same is considered to be inhibition of entry of lymphocytes into the joint. Table 2 depicts the activity of Etrasimod with receptor to the various S1P classes.

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