LEADING ARTICLE

Targeting Sphingosine-1-Phosphate Signaling in Immune-Mediated Diseases: Beyond Multiple Sclerosis

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Abstract

Sphingosine-1-phosphate (S1P) is a bioactive lipid metabolite that exerts its actions by engaging 5 G-protein-coupled receptors (S1PR1-S1PR5). S1P receptors are involved in several cellular and physiological events, including lymphocyte/hematopoietic cell trafficking. An S1P gradient (low in tissues, high in blood), maintained by synthetic and degradative enzymes, regulates lymphocyte trafficking. Because lymphocytes live long (which is critical for adaptive immunity) and recirculate thousands of times, the S1P-S1PR pathway is involved in the pathogenesis of immune-mediated diseases. The S1PR1 modulators lead to receptor internalization, subsequent ubiquitination, and proteasome degradation, which renders lymphocytes incapable of following the S1P gradient and prevents their access to inflammation sites. These drugs might also block lymphocyte egress from lymph nodes by inhibiting transendothelial migration. Targeting S1PRs as a therapeutic strategy was first employed for multiple sclerosis (MS), and four S1P modulators (fingolimod, siponimod, ozanimod, and ponesimod) are currently approved for its treatment. New S1PR modulators are under clinical development for MS, and their uses are being evaluated to treat other immune-mediated diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis. A clinical trial in patients with COVID-19 treated with ozanimod is ongoing. Ozanimod and etrasimod have shown promising results in IBD; while in phase 2 clinical trials, ponesimod has shown improvement in 77% of the patients with psoriasis. Cenerimod and amiselimod have been tested in SLE patients. Fingolimod, etrasimod, and IMMH001 have shown efficacy in RA preclinical studies. Concerns relating to S1PR modulators are leukopenia, anemia, transaminase elevation, macular edema, teratogenicity, pulmonary disorders, infections, and cardiovascular events. Furthermore, S1PR modulators exhibit different pharmacokinetics; a well-established first-dose event associated with S1PR modulators can be mitigated by gradual up-titration. In conclusion, S1P modulators represent a novel and promising therapeutic strategy for immune-mediated diseases.

1 Introduction

Sphingosine-1-phosphate (S1P) is a multifunctional bioactive lipid involved in multiple physiological and pathophysiological processes. S1P signals through S1P receptors (S1PR1–S1PR5) [1, 2], and is relevant for the regulation of the immune, cardiovascular, and nervous systems [3]. Thus,

Key Points

S1PR modulators are immunomodulatory drugs that modulate lymphocyte egress from lymphoid organs, and four S1PR modulators are now approved to treat multiple sclerosis.

S1P and its receptors are involved in multiple immune functions, and therapies targeting S1P signaling have been used and tested to treat immune-mediated diseases other than MS, including IBD, RA, SLE, and psoriasis, with promising results.

More selective S1PR modulators with potentially superior drug efficacy and better side-effect profiles are in the development pipeline. Ozanimod and etrasimod have shown positive results in IBD, whereas cenerimod might provide therapeutic benefits for SLE.

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it is not surprising that the S1P pathway has been implicated in the pathophysiology of immune-mediated diseases and cancer. S1PR agonists/modulators or targeting the S1P axis via inhibitors that target S1P generation, transport, and degradation may represent additional "druggable" approaches for the treatment of immune-mediated diseases [1]. Research on the S1P pathway has led to approval of safe and effective

S1PR modulators to treat MS, such as ponesimod, ozanimod, siponimod, and fingolimod [4]. Several other agents are in clinical development for MS, including amiselimod, cerafilimod, etrasimod, and GSK2018682 [4]. Beyond MS, therapies targeting S1P pathways have expanded to treat other inflammatory conditions. Currently various clinical trials have been completed while others are still ongoing
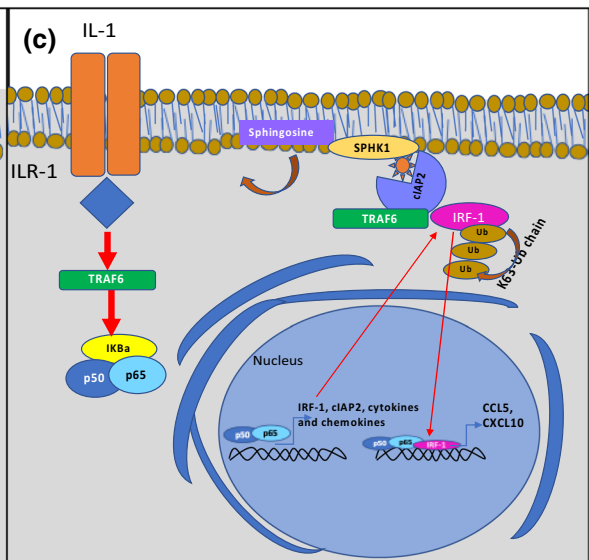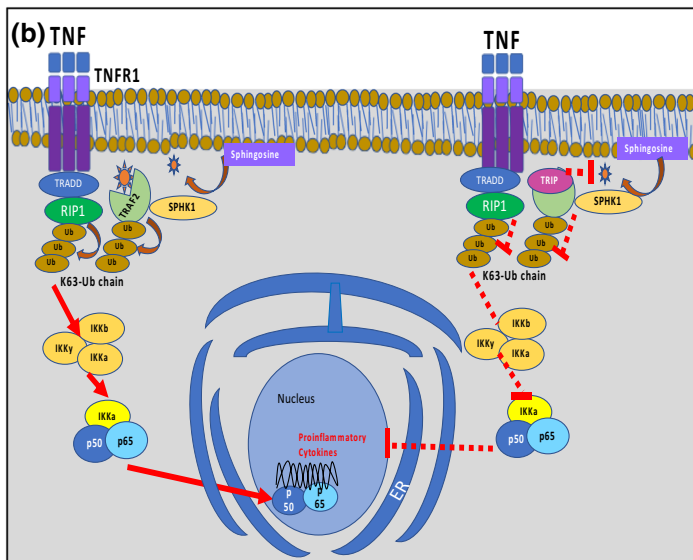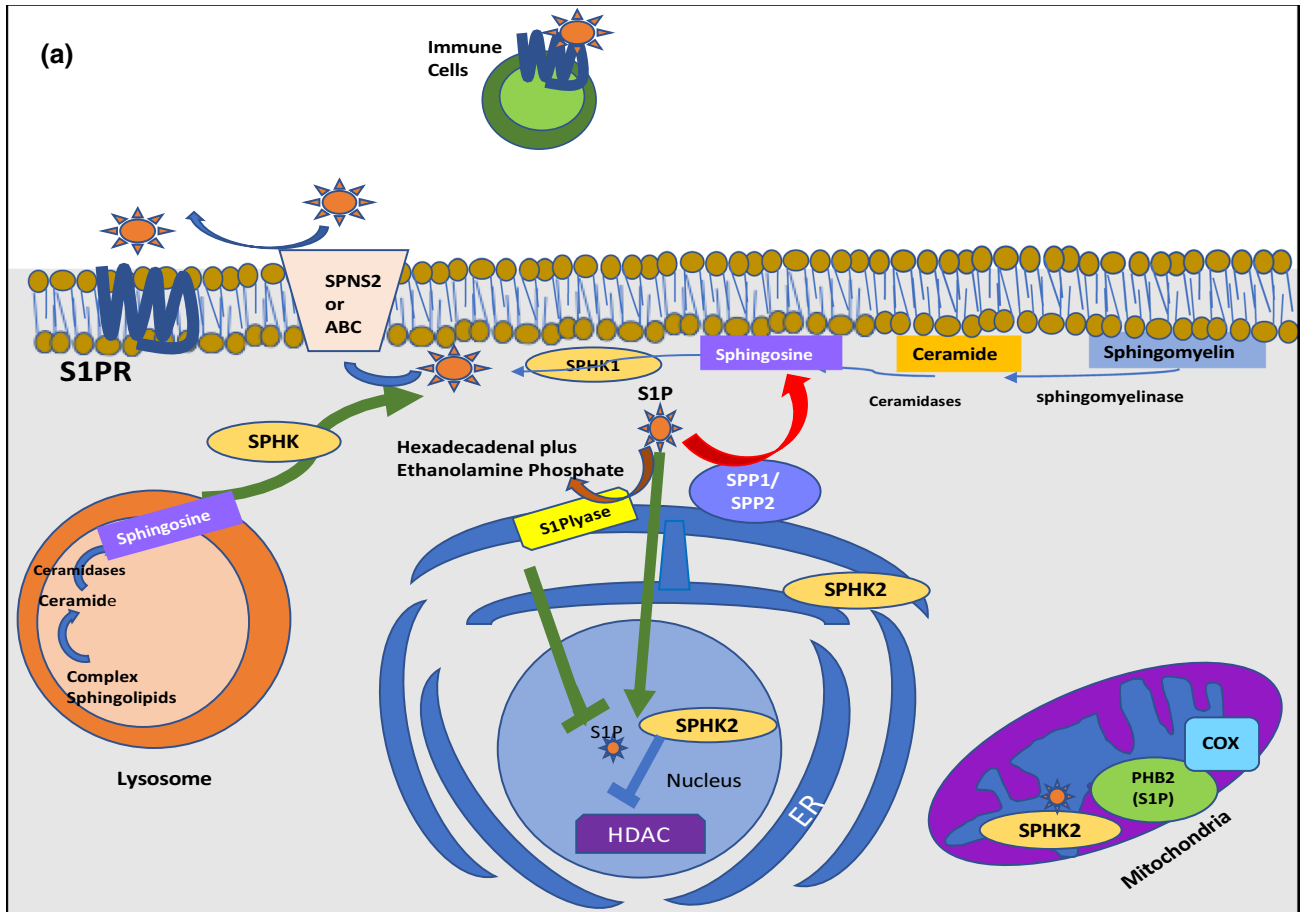
◄**Fig. 1** S1P synthesis, degradation, export, and intracellular signaling [1, 13–16]. (**a**) Ceramide is broken down by ceramidases into sphingosine, which is phosphorylated by two sphingosine kinases (SphK1, SphK2), generating S1P within lysosomes and the endoplasmic reticulum (ER). SphK1 is mainly cytosolic and is translocated to the plasma membrane upon activation. SPHK2 is located within the mitochondria, nucleus, and ER. At the ER, S1P might be dephosphorylated by S1P phosphatase (SPP1,2) to sphingosine, which can be used for ceramide synthesis or irreversibly degraded by S1P lyases. S1P is also produced in the mitochondria and nucleus by SPHK2 with intracellular targets such as prohibitin 2 (PHB2) and histone deacetylases (HDACs) [1]. PHB2 stabilizes cytochrome c oxidases (COX), whereas HDACs remove acetyl groups from histones, altering gene transcription. S1P is transported out of the cell by specific ATP-binding cassette transporters like ABCA1, ABCC1, ABCG2, and Spinter Homolog 2 (SPNS2) protein [1]. Extracellular S1P can act in a paracrine or autocrine fashion binding to S1PRs and initiating downstream signaling. (**b**) S1P generated by SPHK1 in response to TNF binds to the TNF-receptor-associated factor 2 (TRAF2), an E3 ubiquitin ligase, enhancing its activity and leading to lysine-63-linked polyubiquitination of the receptor-interacting protein 1 (RIP1) and activating the nuclear factor "kappa-light-chain-enhancer" within the NF-κB pathway, favoring transcription of proinflammatory cytokines [14, 21]. TRAF2 may alternatively bind to TRAF-interacting protein (TRIP), blocking S1P binding to TRAF2 and suppressing downstream signaling. (**c**) In response to IL-1, SPHK1 and the cellular inhibitor of apoptosis 2 (cIAP2) form a complex with interferon-regulatory factor 1 (IRF1) leading to its polyubiquitination and activation. Consequently, IRF1 enhances the expression of the chemokine CXCL10 and CCL5, which are important for mononuclear cell recruitment to sites of inflammation [15, 16]

in settings such as renal transplantation, chronic inflammatory demyelinating polyradiculoneuropathy, stroke, amyotrophic lateral sclerosis, schizophrenia, Rett syndrome, chronic plaque psoriasis, IBD, SLE, primary biliary cholangitis, pyoderma gangrenosum, transplant rejection, macular degeneration, interstitial cystitis, endometriosis, asthma, pneumonia, and glioblastoma [5–7]. Trials evaluating the effects of S1PR modulators on uveitis, acute demyelinating optic neuritis, polymyositis, dermatomyositis, graft versus host disease and renal cell carcinoma were, however, terminated before completion [6]. Here, we review strategies that target S1P-S1PRs signaling under clinical development as therapeutics for immune-mediated diseases, with an emphasis on IBD.

2 Sphingosine-1-phosphate (S1P) Signaling in Health and Disease

S1P is a signaling molecule involved in physiological processes such as cellular chemotaxis, migration, growth, and proliferation. It also participates in neurogenesis, angiogenesis, heart chronotropism, and inotropism, endothelial permeability, and blood vessel integrity and tone [8]. S1P enhances the intestinal epithelial barrier by increasing vascular endothelial (VE)-cadherin [9] and has a role in pathological

conditions such as inflammation and cancer, where immune surveillance plays a role [8]. S1P is secreted by erythrocytes, vascular, and lymphatic endothelial cells [10, 11]. Platelets and mast cells secrete and produce S1P when stimulated, but do not contribute to basal S1P levels [10, 11].

S1P is a metabolite of ceramide (the basic unit of sphingolipids) and consists of a long-chain fatty acyl group attached to sphingosine via its amino group [12]. Sphingosine and ceramide are associated with apoptosis and cellular growth arrest, whereas S1P is associated with apoptosis suppression and cellular survival [12]. Several steps are required to maintain homeostatic S1P levels such as phosphorylation, transport, and degradation [9]. Ceramide is broken down by ceramidases into sphingosine, which is phosphorylated by two sphingosine-kinases (SphK), SphK1 and SphK2, generating S1P. S1P could be reversibly dephosphorylated by S1P-phosphatase (SPP1 and SPP2), or irreversibly degraded by the S1P-lyase to hexadecanal and phosphoethanolamine (Fig. 1a, [1, 13–16]). This enzymatic pathway is responsible for the regulation of S1P levels, maintaining a lower concentration at tissues, lymphoid organs, and thymus, and a higher concentration in blood, where it can be bound to albumin or apolipoprotein M (ApoM) [17]. Free S1P or albumin-bound S1P is more susceptible to degradation than S1P bound to lipoproteins [10].

2.1 Intracellular Targets of S1P

S1P also acts directly on several intracellular targets without engagement of S1PRs [1]. It directly binds to and inhibits histone deacetylases (HDAC) 1 and 2, preventing the removal of acetyl groups from lysine residues within histone tails, and influencing the contextual chromatin states that impact gene transcription [18, 19]. The consequences of HDAC 1 and 2 inhibition by S1P are incompletely understood but its effects might be associated with SphK2, which significantly increases S1P nuclear levels inducing p21 expression [18]. P21, a potent cyclin-dependent kinase inhibitor, regulates the cell cycle progression, and probably influences the balance between cytostasis and apoptosis of malignant cells (Fig. 1a) [18]. Other intracellular S1P targets include TNF receptor associated factor 2 (TRAF-2) and the apoptosis inhibitor cIAP2 [20]. TRAF2 is an E3 ubiquitin ligase that is a key component of the nuclear factor-κB (NF-κB) activation triggered by TNF. Engagement of the TNF receptor results from the assembly of receptor-associated signaling complexes by adaptors (TRAF-2, TNFR1-associated death domain (TRADD), and the receptor-interacting protein 1 (RIP1)). TRAF-2 and S1P produced by SphK1 are needed for the lysine-63-linked polyubiquitination RIP1 that works as a scaffold for the recruitment and stimulation of IkB kinase complex. The complex includes two homologous subunits IKKα and IKKβ and a regulatory subunit

IKKγ. The IKKα phosphorylation by IKK complex leads to its lysine 48 polyubiquitination and subsequent proteasomal degradation, liberating the NFκB dimer (containing the p50 and p65 subunits) that enters the nucleus and regulates proinflammatory cytokine gene transcription [14]. On the other hand, binding of the TRAF-interacting protein (TRIP) to TRAF-2 blocks S1P binding, inhibiting TNF-induced NF-κB activation and the transcription of TNFα, interleukin-6 (IL-6), and IL-1, along with antiapoptotic proteins (Fig. 1b) [14, 21]. Intracellular interaction between the apoptosis inhibitor cIAP2 and S1P is crucial for K63-linked polyubiquitination of the interferon regulatory factor 1 (IRF-1), leading to IL-1 induced expression of chemokines CCL5 and CXCL10, which recruit mononuclear cells, essential for sterile inflammation [15, 16]. Upon IL-1R activation, IL-1R recruits the interleukin-1 receptor-associated kinase-4 (IRAK-4), IRAK-1, mitogen-activated protein kinase kinase kinase 3 (MEKK-3), TRAF-6, and the MyD88 adapter, producing the recruitment of signaling molecules and activation of mitogen-activated protein kinases (MAPKs), followed by nuclear translocation of NF-kB to induce the expression of genes encoding IRF-1, cIAP2, and a variety of cytokines. In response to IL-1, SphK1 generates S1P, mediating the recruitment and polyubiquitination of cIAP2 to TRAF-6 and the K63 polyubiquitination of IRF1 [15, 16]. Then, IRF-1 translocates to the nucleus activating the expression of IRF1 as CXCL10 and CCL5 (Fig. 1c) [15, 16].

2.2 S1P Receptors

S1P acts predominantly through activation of different subtypes of G protein-coupled receptors (S1PR). The physiological roles of S1PRs are shown in Table 1 [3, 6, 22]. S1PRs are differentially expressed in the immune system [10]. S1PR1 and S1PR4 are expressed by T cells, while B cells express S1PR1, S1PR2, S1PR3, and S1PR4. S1PR1 and S1PR2 are additionally found on macrophages and mast cells, whereas S1PR1 and S1PR5 are expressed by dendritic (DC) and natural killer (NK) cells [10, 13]. Interestingly, immune cells do not necessarily express all the S1PRs simultaneously, as there is differential expression during diverse stages of cell activation and maturation [17].

2.2.1 S1PR1

S1P signaling participates in immune cell traffic to lymphoid organs and exits to lymph and blood [10]. S1PR1 plays an essential role in the control of lymphocyte egress from the thymus, secondary lymphoid organs, and bone marrow [23, 24]. S1P-S1PR1-dependent chemotaxis requires an S1P concentration gradient, maintained by the degradative action of tissue S1P-lyase, which is absent in peripheral blood. This creates a gradient from tissues to blood/lymph, where

S1P concentrations are highest [23]. The high S1P levels in the blood induce S1PR1 internalization (desensitization) in naïve T cells, whereas in lymph node and tissues, S1PR1 is re-expressed for several hours as CD69 forms a complex with S1PR1. Once S1PR1 is re-expressed, T cells then egress from the lymph node or tissue by sensing the higher S1P levels in blood [23, 24].

During inflammation, S1P-S1PR1 may play a role in lymphocyte retention within inflamed tissue [12]. S1PR1 and S1PR4 expression on T cells is induced by CXCL9 and CXCL11 chemokines, present on the endothelium, which engage CXCR3 on T cells [12]. Interaction of integrins with their ligands (lymphocyte function-associated antigen 1 (LFA-1)/intercellular adhesion molecule (ICAM-1), very late antigen-4 (VLA-4)/vascular cell adhesion molecule-1 (VCAM-1) enables T cells to arrest and extravasate into inflamed tissue. Finally, the heterotrimeric guanine-nucleotide-binding-coupled receptor-kinase2 (GRK2) downregulates S1PR1, retaining T cells within inflamed tissue [12]. S1PR1 participates in other immune regulatory functions such as inhibiting Foxp3+Treg differentiation, while promoting Th1 development and potentially Th17 polarization [25, 26].

The S1PR1/S1P axis participates in naïve B cell trafficking from bone marrow to blood, egress from secondary lymphoid organs [12], and marginal B cell localization in spleen [27]. S1PR1 also has a role in DC migration [28]. Furthermore, S1PR1 mediates suppression of sprouting angiogenesis and enhances cell-to-cell adhesion by controlling VE-cadherin at endothelial junctions, regulating lymphatic and vascular permeability. S1PR1 also participates in astrocyte proliferation, neural protection, heart rate, endothelial integrity, and ischemic reperfusion injury [28].

2.2.2 S1PR2 and S1PR3

S1PR2 receptors might have opposite functions to S1PR1 and a pro-inflammatory role has been described [29]. S1PR2 and S1PR3 mediate vascular, intestinal, bronchial, and bladder smooth muscle vasoconstriction [9]. Indeed, hypertension and ischemia-reperfusion renal injury have been reported with the use of non-selective S1PRs, likely due to S1PR2-S1PR3 modulation. S1PR3 agonism is linked to heart-rate effects and the risk for type I and type II atrioventricular block [4]. However, despite the lower affinity of new S1P modulators, there are still first-dose cardiac effects, suggesting that S1PR1 plays a role [4]. In addition, S1PR2 and S1PR3 have been implicated in pathophysiological processes including inflammation, fibrosis, cancer cell growth, and angiogenesis [9]. S1PR2 contributes to activated B-cell localization in follicles, promoting their local confinement within germinal centers [30, 31].

Table 1 Characteristics and physiological functions of G protein-coupled S1P receptor subtypes (SPR1-5) and modulator drugs under evaluation [3, 6, 22]

	S1PR1	S1PR2	S1PR3	S1PR4	S1PR5
Expression	B, T, and dendritic cells, heart tissue, neurons, endothelium	Endothelium, heart tissue, smooth muscle vessels, tumoral cells, lung fibroblasts	Smooth muscle vessels, endothelium, heart tissue, lung fibroblasts	T cells, dendritic cells; tumoral cells	Natural killer, endothelial cells, oligodendrocytes
Signaling	Akt, ERK, Rac	Akt, NFkB Rho/ROCK	NFkB	ERK	Akt, Rho/ROCK
Clinical relevance	Immune modulation, bradycardia, tumor maintenance, theoretical breast cancer prognosis	Kidney injury, tumor maintenance, fibroblast contraction	Hypertension, tumor maintenance	Immune modulation	Immune modulation, myelination
Vascular system	Endothelial barrier integrity, heart rate control, angiogenesis	Regulates vascular tone and endothelial barrier	Modulates endothelial barrier, vasoconstriction, heart rate control. Might induces vasorelaxation	Vasoconstriction	
Immune system	Lymphocyte and dendritic cell migration. Might induce suppression of T Reg cells, promoting Th1 development and Th17 polarization	B cell migration in the follicle promoting the local confinement of germinal center B cells	Location of immature B cells and progenitors within the bone marrow	Regulation of DC function and Th17 differentiation Neutrophil trafficking Inhibition of effector cytokines, secretion of IL-10	Natural killer trafficking
Nervous system	Neural and oligodendrocyte function		Neural migration and cell function		Blood brain integrity, oligodendrocyte function
Other outcomes	Nociception, proliferation	Fibrosis, inhibition of B-cell survival, proliferation	Fibrosis, proliferation		
S1PR agonists	AMG 369, amiselimod, ASP0028, ASP4058, AUY954, cenerimod. ceralifimod, CS-077, CS-2100, CYM544, etrasimod, fingolimod, GSK1842799, GSK2018682, mocravimod, ozanimod, Ponesimod, RP-001, SEW2871, siponimod, ST-968, ST-1071, Syl948, TC-G 1006, TC-SP14, amgen 8,14		Fingolimod, ST-968, ST-1071	Amiselimod, etrasimod, fingolimod	A-971432, AMG 369, amiselimod, ASP0028, ASP4058, cerafimod, etrasimod, fingolimod, GSK2018682, ozanimod, siponimod
S1PRs antagonists	AD2900, Ex26, NIBR-0213, TASP0277308, VPC23019, W146	AB1, AD2900, JTE-013	7H9, AD2900, CAY10444, SPM-354, TY-52156, VPC23019	AD2900	AD2900

ERK extracellular signal-regulated kinases, *Akt* protein kinase B, *Rac* subfamily of the Rho family of GTPases, *Rho/ROCK* Rho-associated kinase is an effector of the small GTPase, *NFkB* nuclear factor kappa light-chain enhancer of activated B cells, *Treg* regulatory T cell, *Th* T helper cell, *STAT-3* signal transducer and activator of transcription 3, *IL-10* interleukin 10

2.2.3 S1PR4

S1PR4 plays a role in immune cell migration and on the differentiation of certain immune cells. Immunosuppressive effects are mediated by inhibition of proliferation and secretion of effector cytokines, while enhancing IL-10 [12, 32]. S1PR4 expression on DC is involved in Th17 regulation and IL-27 production, which allows T-reg to suppress cytotoxic CD8+T cells [1, 13]. S1PR4 also enhances neutrophil trafficking from inflamed tissues to the draining lymph node [13].

2.2.4 S1PR5

NK cells employ S1PR5 [33] for trafficking from bone marrow and lymph nodes into tissues. It also controls brain endothelial barrier function, tight junctions, and permeability [34], and decreases NFκB activation on brain endothelial cells by lowering expression of adhesion molecules, inflammatory chemokines, and cytokines [34]. Oligodendrocytes, the myelin-forming cells of the CNS, express S1PR5, suggesting a role in myelination [35].

3 S1PR Agonists/Modulators in Immunological Disorders

Over the past few years, the S1P/S1PRs axis has been identified as a potential therapeutic target for immune-mediated diseases, and the safety and efficacy of several S1PRs modulators have been explored in MS, RA, SLE, psoriasis, atopic dermatitis (AD), ulcerative colitis (UC), and Crohn's disease (CD) [23, 36]. S1PR1 agonists render lymphocytes incapable of sensing the S1P gradient and exiting lymph nodes, preventing their access to circulation and sites of inflammation. More than one mode of action has been proposed, acting as functional antagonists (binding internalizes receptors, desensitizing cells with a net effect of depressing S1PR-mediated signaling) and as traditional agonists (increasing activity through these pathways) [2, 4, 23]. Many S1PR modulators are prodrugs (e.g., fingolimod, amiselimod), which require conversion into their bioactive form by phosphorylation via sphingosine kinases (SphKs), whereas others are direct acting (e.g., ponesimod, siponimod, ozanimod) [37, 38]. The S1PR1 modulator/agonist-receptor complex is internalized, ubiquitinated, and degraded by the proteasome, leading to sustained desensitization, lymphocyte retention at lymph nodes, and peripheral lymphopenia [2, 23]. By contrast, native S1P induces S1PR internalization followed by recycling back to the cell surface, producing a transitory lymphopenia [2, 23]. These drugs also might block lymphocyte egress from lymph nodes by tightening the lymphatic endothelial barrier and inhibiting

transendothelial passage from lymph nodes to blood [23]. S1PR1 participates in immune cell recruitment during both acute and chronic inflammation and a significant number of preclinical and clinical studies support their use in treating immune-mediated conditions [39]. Fingolimod/FTY720 was initially tested for the prevention of acute allograft rejection [40]. However, absence of efficacy in clinical trials led to its testing for other indications [41], eventually leading to its approval as the first oral non-selective S1PRs modulator for the treatment of relapsing-remitting MS [42, 43]. Fingolimod is a prodrug that requires phosphorylation by SphK2 to form the active metabolite fingolimod-P, a non-selective agonist of all S1PRs excluding S1PR2 [6]. Fingolimod-P regulates chemotactic responses and lymphocyte migration by inducing S1PR internalization/degradation, suppressing lymphocyte egress from thymus and secondary lymphoid organs (SLO). Its action on S1PR3, S1PR4 and S1PR5 may account for some adverse effects (hypertension, bradycardia, macular edema, reduced pulmonary function, hepatic adverse effects, and neoplasm), of which cardiovascular effects are the most common [44, 45]. Selective modulators continued to be developed to improve their safety profile [44, 45].

3.1 Inflammatory Bowel Diseases

IBD is a chronic immune-mediated inflammatory disease of the gastrointestinal tract with heterogeneous behavior and prognosis [46, 47]. Our understanding of leukocyte traffic orchestrating gut inflammation has led to the use of novel biologic agents directed against intestinal T-cell traffic, such as vedolizumab, an anti-integrin monoclonal antibody. However, all available agents in use today require parenteral administration. Small molecules that could be orally administered such as S1PR1 agonist/modulators could be a valuable addition. Fingolimod has not been tested in IBD despite its efficacy in colitic animal models, with more selective S1PR modulators tested instead [48–53].

3.1.1 Mocravimod

Mocravimod/KRP-203 is a prodrug agonist of S1PR1, S1PR4, and S1PR5 and partial agonist of S1PR3. Despite attenuating colitis in mouse models [2, 54], it was minimally effective in patients with UC (NCT01375179) [55]. A multicenter, double-blind, placebo-controlled, parallel-group study evaluated the efficacy, safety, and tolerability of KRP203 in moderately active UC refractory to 5-aminosalicylates over 8 weeks [55]. The primary endpoint was clinical remission defined as a partial Mayo Clinic Score (MCS) [56] of 0–1 and modified Baron Score [57] of 0–1 with a rectal bleeding subscore of 0 [55]. Clinical remission was achieved in 2/14 patients (14%) receiving KRP203

compared with none in the placebo group. This study did not meet the minimum clinically relevant threshold for efficacy [55] and was terminated (NCT01375179); however, its small sample size was a major limitation. Overall, KRP203 was well tolerated and safe, and no adverse cardiac events were reported [55].

3.1.2 Ozanimod

Ozanimod/RPC1063/Zeposia is an oral S1PR modulator that selectively binds to S1PR1 and S1PR5 [58, 59], reducing concerns around S1PR3 engagement. Ozanimod induces S1PR1 internalization and degradation. Its effects are highest on lymphocytes that express the chemokine receptor 7 (CCR7+), (naïve and central memory lymph node-homing cells) with less or no effect on effector memory cells, thus maintaining some circulating protective immunity [58, 59]. Ozanimod is metabolized to two major metabolites (CC-112273 and CC1084037) and other minor active metabolites (RP101988 and RP101075) [58, 59]. Ozanimod decreases inflammation in animal models of immune-mediated diseases such as 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis, CD4+CD45RBhi T-cell adoptive transfer colitis, and experimental autoimmune encephalitis (EAE) [60]. These findings served as the foundation for clinical trials leading to its approval for the treatment of relapsing MS in the USA, based on the results of the RADIANCE (NCT02047734) and SUNBEAM (NCT02294058) trials [58, 61]. The TOUCHSTONE trial (NCT01647516) evaluated ozanimod's efficacy and safety in moderate-to-severe UC [62]. 197 patients were randomized to receive ozanimod 0.5 mg or 1 mg or placebo orally for 32 weeks. The primary outcome defined as clinical remission at week 8 (MCS $\leq$ 2 with no subscore > 1) was achieved by the 1 mg dose versus placebo (16% vs. 6%; $p = 0.048$) [62]. The secondary outcomes at week 8, such as clinical response (decrease in MCS of $\geq$ 3 points and $\geq$ 30% decrease in MCS with $\geq$ 1-point decrease in rectal bleeding subscore or a subscore $\leq$ 1) were reached in 57%, 54%, and 37% for the 1 mg, 0.5 mg, and placebo groups, respectively. Mucosal improvement/healing was achieved in nearly 30% of the treated patients in comparison with 12% in the placebo group [62]. On follow-up (week 32), clinical remission rates were achieved in 21%, 26%, and 6% and clinical response rates of 51%, 35%, and 20% for 1 mg, 0.5 mg, and placebo, respectively. The most frequent adverse events were anemia and headache [62]. The open-label extension (OLE) of the TOUCHSTONE trial ($n = 170$) demonstrated that 1 mg ozanimod has a rapid onset, durable efficacy, and is well tolerated through 104 weeks [63]. The results from True North, a phase 3 placebo-controlled trial evaluating ozanimod as an induction and maintenance therapy in moderate to severe UC, were presented at the American Gastroenterology Association

(ACG) 2020 [64]. Patients were randomized to receive ozanimod 1 mg ($n = 429$) or placebo ($n = 216$) in the induction period [64]. After induction, patients with clinical response were re-randomized to double-blind maintenance treatment with ozanimod or placebo through 52 weeks [64]. The primary aim for both periods was the proportion of patients in clinical remission per three-component MCS. This study met both primary endpoints, showing clinically and statistically significant results compared with placebo; clinical remission at induction 18.4% versus 6% ($p < 0.0001$) [64]. In the maintenance period 457 patients were re-randomized to ozanimod ($n = 230$) or placebo ($n = 227$), and obtained 37% versus 18.5% ($p < 0.0001$) clinical remission at week 52. Interestingly, in patients with prior anti-TNF exposure, the proportion with clinical remission was higher, but not statistically superior versus placebo at week 10 [64]. However, at maintenance, clinical remission and response showed a significant improvement regardless of anti-TNF exposure. Ozanimod demonstrated significant benefits on clinical, endoscopic, histologic, and mucosal healing endpoints for up to 52 weeks in moderate to severe UC [64]. The most common adverse events were anemia, nasopharyngitis, headache, and increased serum alanine aminotransferase or gamma-glutamyl transferase [64]. These results suggest that ozanimod could be appropriate for patients who fail anti-TNF, but the onset of action is slower. The full report of the True North trial is awaited. Currently, there are three active clinical trials for moderate-severe UC: NCT02531126, NCT01647516, NCT03915769, three of which are in phase 3. STEPSTONE, a phase 2, uncontrolled multicenter trial, recruited 69 patients with moderate to severe Crohn's disease (CD), to examine endoscopic and clinical outcomes following treatment with ozanimod for 12 weeks [65]. All patients started with a 7-day dose-escalation treatment (days 1–4 on ozanimod 0.25 mg daily, followed by 3 days at 0.5 mg daily). Then, for the additional 11 weeks, patients received ozanimod 1 mg. The primary endpoint was the change in Simple Endoscopic Score for Crohn's Disease (SES-CD) [66] from baseline to week 12, and the proportion of patients with an endoscopic response ($\geq$ 50% decrease in SES-CD) and endoscopic remission (SES-CD $\leq$ 4 points and SES-CD decrease $\geq$ 2 points with no SES-CD subscore > 1 point) were also assessed at week 12. Secondary endpoints were changes in Crohn's Disease Activity Index (CDAI) [67] from baseline to week 12, and the proportion of patients with clinical remission (CDAI score of < 150) and clinical response (CDAI reduction from baseline of $\geq$ 100 points) were also assessed at week 12. Patient-reported outcomes (PRO2) [68] were evaluated as the change from baseline to week 12 and changes in the histology activity using Geboes Histology Activity Score (GHAS) [69] and Robart's Histopathology Index (RHI) [70]. The mean change from baseline at week 12 in SES-CD was -2.2 (standard deviation (SD)

= 6); 16/69 (23.2%) obtained endoscopic response whereas 7/69 (10.1%) achieved endoscopic remission. A reduction from baseline CDAI also was observed (mean change − 130.4, SD = 103.9). Clinical response was achieved in 39/69 (56.5%), and clinical remission in 27/69 (39.1%). The mean change from baseline in PRO2 score was − 66.1 (SD = 65.4). The mean change from baseline in GHAS was − 5.9 (SD = 11) and in RHI − 10.6 (SD = 25.1). CD flare was the most frequent adverse event 18/69 (26%), followed by abdominal pain 10/69 (15%), lymphopenia 9/69(13%), arthralgia 9/10 (13%), and nausea 8/69 (12%). Although in seven patients liver enzymes increased three or more times, none discontinued the study drug. No clinically significant changes in heart rate were observed following the first dose of ozanimod. Treatment-emergent adverse events reported were two cases of herpes zoster infection (mild severity) and one case of severe sepsis. In summary, clinical, endoscopic, and histological improvement were observed in this trial [65]. Currently four phase 3 ozanimod clinical trials in CD are ongoing: NCT03467958, NCT03440385, NCT03440372, and NCT03464097.

3.1.3 Etrasimod

Etrasimod/APD334, an oral selective modulator of S1PR1, S1PR4, and S1PR5, has shown efficacy in the CD4+CD45RBhi T-cell transfer mouse model of colitis [71]. Recently, the results from a phase 2, double-blind, parallel-group study in patients with moderate to severe UC (*n* = 156) have been published (NCT02447302) [72]. Patients were randomly assigned to receive once-daily etrasimod 1 mg (*n* = 52), etrasimod 2 mg (*n* = 50), or placebo (*n* = 54) groups for 12 weeks. The primary endpoint was mean improvement in modified MCS at week 12, whereas the secondary endpoints considered the proportion of patients with endoscopic improvement at week 12 [72]. The modified MCS, which ranged from 0 to 9 (instead of from 0 to 12), includes subscores for stool frequency, rectal bleeding, and endoscopic findings, where increasing numbers indicate higher disease activity. Both endpoints were met in the 2 mg group. A significant improvement in the modified MCS was observed for the etrasimod 2 mg group compared with placebo with a least-square mean difference of 0.99 (CI 0.30–1.68; *p* = 0.009) at week 12. Further, a significantly higher proportion, 41.8% versus 17%, in the group receiving etrasimod 2 mg versus placebo (CI 9.8–39.0%; *p* = 0.003) achieved endoscopic improvement. Histologic improvement was reported in 32% of patients receiving 2 mg versus 10% in those receiving placebo (*p* = 0.006). Histologic remission occurred in 20% of those treated with 2 mg compared with 6% of placebo recipients (*p* = 0.03). Adverse events were mild to moderate. Three patients had a transient, asymptomatic, low-grade atrioventricular (AV)

block (second-degree AV type 1 in one patient, and first-degree AV in two patients) [72]. However, these patients had experienced AV block before etrasimod was initiated [72]. AV block represents a disturbance or delay in the electrical conduction from the atria to ventricles. This disruption could be transitory or permanent. There are three types of AV nodal block: first degree, second degree (type 1 or 2), and third degree. The first degree and second degree type 1 have a benign course with a better prognosis than second degree type 2 or third degree [73].

Currently, Arena Pharma is evaluating etrasimod's use in other trials such as a phase 3 extension study for the treatment of moderate to severely active UC (ELEVATE OLE UC; NCT03950232) and a phase 2b trial evaluating etrasimod in moderately to severely active CD (CULTIVATE; NCT04173273). Etrasimod has also been evaluated in other conditions such as Primary Biliary Cholangitis (PBC) (NCT03155932) and Pyoderma gangrenosum (NCT03072953).

3.1.4 Amiselimod

Amiselimod/MT-1303 is an oral prodrug that is converted to its active metabolite (MT-1303-P) by sphingosine kinases (SphKs); it has been evaluated for various immune-mediated diseases such as MS, SLE, IBD, and psoriasis [37, 74–77]. Amiselimod has a higher affinity for S1PR1 than for S1PR2–5, obtaining a more favorable cardiac safety profile than non-selective S1PRs modulators [78]. In a prospective, randomized, placebo-controlled clinical trial in active CD patients with elevated inflammatory markers (*n* = 180), the primary endpoint (clinical response defined as a drop in the CDAI of 100 points at week 12) was not achieved (48.7% for amiselimod vs. 54.1% on placebo) [78]. The high placebo response rate and weak peripheral lymphocyte reduction observed might explain the unmet endpoints [78]. Its clinical development was discontinued by Biogen in 2016, and subsequently its rights were returned to Mitsubishi Tanabe Pharma [79]. Amiselimod shows a favorable safety profile in CD and might be promising for the treatment of other autoimmune/immune-mediated diseases, including UC [80]. In Japan, a phase 2 clinical trial in CD is ongoing [81]. Results from a randomized, double-blind, multiple-dose, placebo-controlled phase 1 study (*n* = 190) were recently presented at the 2021 Crohn's and Colitis Congress [82]. Healthy individuals were randomized 2:1:1 to receive a single placebo dose followed by oral amiselimod in upwardly titrated doses to achieve 0.4 mg and 0.8 mg steady-state doses, moxifloxacin 400 mg followed by placebo, or placebo followed by moxifloxacin 400 mg single dose. The study aimed to evaluate the amiselimod safety profile.

The discontinuation rate was 8% ($n = 8$) in the amiselimod group versus 4% (n=4) in the moxifloxacin group. Three patients discontinued amiselimod because of low lymphocyte counts, and one patient had atrial fibrillation requiring hospitalization and cardioversion, which led to discontinuation. All other adverse events were mild to moderate in severity. The authors conclude that upwardly titrated amiselimod was well tolerated in healthy individuals [82].

3.2 Psoriasis

Psoriasis is a chronic immune-mediated skin condition characterized by abnormal keratinocyte proliferation and lymphocyte infiltration of the dermis and epidermis [83]. Thus, drugs that induce lymphopenia and prevent lymphocyte migration might be effective.

3.2.1 Ponesimod

Ponesimod/ACT-128800, a selective modulator of S1PR1, S1PR4, and S1PR5 was evaluated in a phase 2 study (NST0128090), leading to a 75% reduction in area of involvement and severity index in 77% of patients [84, 85]. The most frequent adverse events were dyspnea, elevated liver enzymes, headache, nasopharyngitis, dizziness, bradycardia, pruritus, and cough [85]. Interestingly, liver enzyme abnormalities were significantly higher in the drug group, and these frequencies were higher than those seen in the phase 2 MS study [86, 87]. Regarding heart rate and conduction events, in this study the effect of the first-dose effect of ponesimod on AV conduction and heart rate in cardiomyocytes might be due to vagomimetic S1PR1 activity [85]. Cardiomyocytes rapidly lose sensitivity to ponesimod, which results in resolution of effects on AV conduction and heart rate [85]. In this study all heart rate and AV conduction adverse events were dose dependent and limited by up-titration [85]. A gradual up-titration with ponesimod markedly mitigated the initial cardiodynamic effects [88]. Information available in ClinicalTrials.gov states that ponesimod has not progressed to a phase 3 clinical trials in patients with psoriasis.

3.2.2 Other S1P modulators

Amiselimod: The results of a phase 2 dose-finding study of amiselimod in chronic plaque psoriasis are not yet published (NCT01987843).

IMMH002: IMMH002, a novel orally active S1PR1 modulator, showed skin improvement and decreased T-lymphocyte infiltration at the preclinical level in a mouse model, without adverse events such as bradycardia [89].

3.3 Atopic Dermatitis

Atopic dermatitis (AD) is a chronic allergic relapsing inflammatory skin disease characterized by an impairment of epidermal barrier function, and an immune response skewed towards T-helper 2 [90]. Currently, the safety and efficacy of etrasimod in AD are being evaluated in a phase 2 placebo-controlled, dose-finding trial (ADVISE; NCT04162769).

3.4 Rheumatoid Arthritis

RA is a chronic immune-mediated joint disease characterized by joint infiltration by inflammatory cells and increased cytokine and chemokine secretion leading to joint destruction and systemic inflammatory burden [91]. S1P demonstrated a role in RA by increasing TNF production, which in turn upregulates S1PRs and increases inflammatory infiltration [92, 93]. Fingolimod decreased IL-6 and TNF in synovium in mouse models of RA. Etrasimod has also shown efficacy in a collagen-induced model of arthritis [94, 95]. Recently, IMMH001 (SYL930), a S1PR1 and S1PR4 modulator, inhibited arthritis progression in Sprague-Dawley rats, improving hind paw swelling and arthritis index, diminishing pro-inflammatory cytokines and chemokines in damaged joints. Despite these encouraging results, there are no ongoing clinical studies in RA [96].

3.5 Systemic Lupus Erythematosus

SLE is an autoimmune disease characterized by aberrant B- and T-cell activation, leading to increased production of IL-1, IL-6, and autoantibodies against multiple cytoplasmic and nuclear antigens in various organ systems [97]. In preclinical studies in murine models, fingolimod, ozanimod, mocravimod, and amiselimod have shown efficacy [37, 92, 98]. Of these, mocravimod was tested in cutaneous lupus erythematosus (CLE) (NCT01294774), but the results of the trial are not yet published. No additional trials for CLE are ongoing [99].

3.5.1 Cenerimod

Cenerimod/ACT-334441, an oral S1PR1 modulator, ameliorated organ-specific and systemic autoimmunity and preserved organ function in models of SLE and Sjögren's syndrome [100]. A phase 2 (NCT02472795) clinical trial that assessed the effects of cenerimod on SLE activity and circulating lymphocytes in patients with mild to moderate SLE showed efficacy and an acceptable safety profile [101].

These findings led to an ongoing phase 2 study in patients with moderate to severe SLE (NCT03742037).

Cenerimod was tested for efficacy in a translational study with an MRL/lpr mouse SLE model and clinically in patients with SLE. The MRL/lpr mouse is an SLE model that reflects the autoimmunity and organ damage associated with SLE and was used to evaluate preclinical efficacy. Seven-week-old MRL/lpr females were treated with vehicle or cenerimod food admix. At week 11, 30% in the vehicle group died, whereas all cerenimod-treated mice survived. A significant B and T blood lymphocyte reduction was observed, along with decreased organ damage and a pronounced suppression of the inflammatory environment. Inflammatory biomarkers and lymphocyte subsets were characterized in a 12-week phase 2 clinical study (NCT02472795) in which patients were treated with multiple doses of a placebo or cenerimod. In SLE patients, cenerimod treatment reduced T and B blood lymphocytes, reduced interferon-associated biomarkers, and normalized blood antibody-secreting cell numbers [102].

3.5.2 Amiselimod

Recently, the results of a phase 1b multicenter, open-label amiselimod trial in SLE were published [103]. The primary objective was to evaluate the safety of amiselimod in SLE patients. Seventeen patients received 0.2 or 0.4 mg for 24 weeks. It was well tolerated, without serious adverse events or infections. The total SLE disease index 2000 score [104] decreased ≥ 4 points at 24 weeks in 7/17 patients. These data suggest the safety and efficacy of amiselimod in SLE [103].

Apart from the agents described above, there are multiple S1PR agonists/modulators that are being investigated for use in autoimmune/immune-mediated disorders (Table 1). These include ceralifimod (S1PR1,5; RRMS. NCT01081782, NCT01226745), CS-077 (S1PR1; MS) [105], sonepcizumab (S1PR1; macular degeneration, NCT00767949), LC51-0255 (S1PR1; UC. NCT04096573, NCT04360343), OPL-002 (S1PR1; UC/healthy subjects, NCT04451811), GSK2018682 [106] (S1PR1; healthy subjects, GSK2018682, NCT01387217, NCT01431937), and ASP4058 (S1PR1, S1PR5; healthy subjects, NCT01998646) [6].

4 Safety and Adverse Events

4.1 Infections

Since S1PRs agonist/modulators have limited effects on effector memory T-cell recirculation, patients appear to maintain immune surveillance [23]. However, upper respiratory infections and urinary tract infections have been reported. Serious infections such as herpes and disseminated

varicella zoster (VZV) are rare but have been reported with fingolimod [107]. VZV serology and administration of the recombinant zoster vaccine (Shingrix, GlaxoSmithKline) might decrease the risk of infection and associated complications [23]. Cases of progressive multifocal leukoencephalopathy (PML) have been reported with fingolimod, but the risk is 1:10,000 patients treated. A few cases of cryptococcal meningitis and disseminated cryptococcal infections have been reported with the use of fingolimod [23, 108].

4.2 Cardiovascular Events

First-degree AV block, sinus bradycardia, orthostatic hypotension, and hypertension have been reported [23, 58]. The first two aforementioned cardiac events usually occur within hours of the first dose, and are attributed to S1PR1, S1PR2, and S1PR3 agonism [72]. Initially, heart rate effects were attributed to S1PR3 agonism, because fingolimod resulted in bradycardia in wild-type but not in S1PR3 knockout mice [109]. However, subsequent research shows that S1PR1 also mediates this effect [109]. The S1PR1 activation on cardiomyocytes produces activation of G protein-coupled inwardly rectifying potassium channel, which plays a role in heart rate and cardiac conduction [72]. Then, temporary bradycardia might be explained due to myocyte hyperpolarization and transitory reduction in excitability induced by S1P receptor activation of G protein-coupled inwardly rectifying potassium channels, before S1P receptor internalization or S1P antagonism [72]. An up-titration regimen can mitigate the heart rate reduction produced by S1PR modulators exhibiting short half-lives (e.g., ponesimod, siponimod) [110]. Conversely, up-titration is not required for compounds with long half-lives (fingolimod, cerenimod) due to the less pronounced first-dose-related negative chronotropic effects, presumably due to "built-in up-titration" [4, 110]. Interestingly, an inadvertent first-dose effect is possible after a brief treatment interruption of S1PR modulators with short half-lives but without long half-life active metabolites (siponimod and ponesimod). In that situation, drug reinitiation requires a dose titration [4]. An electrocardiogram is recommended prior to initiating S1P modulators [58, 110–112]. Patients with a history of unstable angina, heart attack, stroke, transient ischemic attack, decompensated heart failure, class III or IV heart failure, Mobitz type II second-degree or third-degree AV block, sino-atrial block, or sick sinus syndrome (except patients with a pacemaker) should avoid their use [58, 110–112].

4.3 Malignancy

Cases of skin cancer (squamous cell carcinoma, melanoma, and basal cell carcinoma) have been related to fingolimod

and ozanimod [23, 58, 113]. Therefore, patients should be periodically evaluated by a dermatologist.

Other concerns related to S1PR agonist/modulators are leukopenia (reversible with drug discontinuation), teratogenicity, pulmonary disorders, transaminase elevation, anemia, macular edema, headache, and human papillomavirus infections [12, 58, 113, 114].

The identification of new S1PR agonist/modulators with a shorter half-life is desirable yet challenging. Recovery of peripheral lymphocyte counts following fingolimod requires > 5 weeks, which could complicate treatment of opportunistic infections [95]. Teratogenicity has been observed in rodents treated with fingolimod, and the long half-life in humans (8 days) requires contraception for 2 months after stopping treatment, if pregnancy is planned [58, 95]. Ozanimod has a 17- to 21-h half-life while long-acting active metabolites have half-lives of approximately 10 days, thus it must be discontinued for 3 months before conception [58]. The promising results of NCT02447302 showed etrasimod's rapid onset and offset, rapid depletion of circulating lymphocytes (approximately 53% depletion at day 3), and rapid recovery to 5% of baseline within a week of treatment cessation [72]. However, the clinical significance of receptor specificity between the drugs needs to be assessed by head-to-head comparisons in large trials [72]. Finally, enhanced selectivity and a short half-life are desirable traits for the new S1PR agonist/modulators under development as lymphocyte counts will rebound rapidly upon cessation in case of adverse events, particularly infections.

5 Future Directions for S1P Pathway Targeting

Dysregulation of the S1P pathway is observed in the intestine of IBD patients. Sphingosine kinases (SphK1) and phosphatases (SPP) are upregulated, whereas SP1-lyase is downregulated, resulting in higher S1P levels [54]. Thus, modulation of pathways involved in synthesis, degradation, and transport of S1P might represent novel druggable targets. In addition, SphK1 upregulation has been implicated in colitis-associated cancer and other cancers (diffused B-cell lymphoma, breast cancer, colorectal cancer, esophageal cancer, gastric cancer, and prostate cancer) [115–117].

5.1 Sphingosine Kinase Inhibitors

SphKs catalyze the phosphorylation of sphingosine to S1P [118]. SphKs may represent additional therapeutic targets, and preclinical studies have shown promising results [118]. SphK1 is ubiquitously expressed and has been reported to be involved in RA, asthma, and IBD [119]. Proinflammatory cytokines such as TNF activate SphK1, and this enzyme induces COX2 expression, increasing prostaglandin E2 production [119]. LCL351, a SphK1 inhibitor, induced a reduction in TNF, CXCL1, CXCL2 expression, and neutrophil infiltration in the DSS-induced model of colitis [119]. Other SphK1 inhibitors (ABC747080 and ABC294640) also modified TNF-mediated inflammation and colitis severity [117, 119]. Furthermore, in a mast cell-dependent mouse model of allergic asthma treatment with SphK1 inhibitor (SK1-I) attenuated mast cell-dependent allergic inflammation and airway hyper-responsiveness, supporting the potential use of SphK1 inhibitors for the treatment of allergic airway inflammation [120]. SphK2 inhibition ameliorated inflammation by blocking Th17 differentiation of CD4 naïve cells in a mouse model of psoriasis [121].

5.2 Sphingosine Phosphatases

The S1P phosphatases (SPP1 and SPP2) catalyze the dephosphorylation of S1P to sphingosine, participating in the regulation of S1P levels. SPP2 is found in the gastrointestinal tract, and its expression is elevated in patients with UC [122]. Moreover, in the DSS-induced colitis model, deficiency of SPP2 improved mucosal barrier integrity, suggesting that inhibition of SPP2 may be further explored in IBD [122].

5.3 S1P-lyase

This enzyme is abundant in tissue and degrades S1P irreversibly, maintaining an S1P gradient and promoting lymphocyte recirculation from tissues to blood. In a TNF-overproducing model of Crohn-like ileitis (TNFΔARE), S1P-lyase inhibitors altered the S1P gradient and attenuated ileitis [24]. In addition, an S1P-lyase inhibitor ameliorated DSS-induced colitis [123]. However, other studies in mice show that a deficit of intestinal S1P-lyase worsened disease [124]. Additional studies are needed to clarify the potential role of S1P-lyase inhibition in IBD. In preclinical models of RA, LX3305 (an S1P-lyase inhibitor) induced a reduction in the inflammatory response. Safety, tolerability, and efficacy were evaluated in a phase 2 trial (NCT00903383) in patients with active RA and showed potential clinical benefit and a favorable safety profile [125].

5.4 Spinster Homolog 2 (SPNS2)

This carrier exports S1P out of the cell, and its deletion attenuates inflammation in mouse models, such as airway inflammation, hypersensitivity, DSS- and oxazolone-induced colitis, experimental autoimmune encephalitis, and collagen-induced arthritis [126].

5.5 S1P Agonists for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Coronavirus disease-2019 (COVID-19) is currently a global pandemic [127]. Severe COVID-19 cases have been reported with the use of fingolimod in MS [128]. On the other hand, S1PR agonists (e.g., fingolimod) have been proposed as a strategy to dampen cytokine and chemokine releases in those patients displaying excessive immune responses. A phase 2 clinical trial is evaluating ozanimod efficacy on COVID-19 (NCT04405102), whereas a fingolimod trial (NCT04280588) was discontinued. Further studies are needed to evaluate their safety and efficacy in patients with COVID-19 [129].

6 Positioning S1P Modulators in IBD: Pros and Cons

New orally administered small molecules such as S1P modulators offer a viable alternative to the current therapeutic arsenal for many immune-mediated diseases, especially in IBD where to date most second-tier drugs require parenteral administration. In contrast to these biological therapies used in immune-mediated and autoimmune diseases, these drugs have the advantage of their lack of immunogenicity, oral administration, safety profile, low manufacturing cost, and shorter half-life [39]. S1P modulators are well tolerated but might have first-dose effects on heart rate and immune and pulmonary systems [88]. Importantly, S1P modulators have different pharmacokinetic properties despite their similar pharmacodynamic effects [39]. Those with short half-lives (ponesimod, siponimod) have a rapid elimination with rapid reversibility of their pharmacodynamic effects, but require up-titration initially [39]. In comparison, the S1P modulators with a long half-life (e.g., fingolimod) have a built-in up-titration [39]. Although ozanimod has a relatively short half-life, its metabolites lead to a sustained effect on cell count [39]. Short half-lives have the advantages of faster clearance in case of infections, pregnancy, or any other adverse events.

Selective S1P modulators such as ozanimod, siponimod, and ponesimod have demonstrated an improved safety profile in comparison with non-selective S1P modulators [130]. Adverse effects such as macular edema, dysregulated lung function and hypertension are attributed to non-specific S1PR1-5 activity [71]. S1PR2 and S1PR3 have been implicated in processes such as fibrosis and vasoconstriction, along with S1PR3 in cardiac conduction [71]. Regarding infections, research reveals that only specific subsets are affected, such as T (CD3) and B (CD20) lymphocytes [131, 132], whereas natural killer, NKT, granulocyte, and monocyte counts should be not affected, maintaining immune surveillance against cancer and viral infections [39, 134, 135]. Table 2 compares features of S1PR modulators mentioned in this review [4, 39, 58, 72, 74, 101, 130, 133–138].

Between 30 and 50% of patients with IBD show a primary non-response to biologics and many more lose response every year. In general, response to a second biologic is lower in patients previously treated with anti-TNF compared with biologic-naïve patients [139, 140]. S1P modulators might be promising in this group of IBD patients. Recent data from the ozanimod North Study showed efficacy in both anti-TNF naïve and anti-TNF non-naïve patients. Head-to-head trials that compare similar drugs such as etrasimod and ozanimod will be needed to address superiority. If S1P modulators are eventually approved for IBD, they could be particularly useful in anti-TNF refractory patients, those with conditions such as arthritis, psoriasis, multiple sclerosis, and in cases where the use of anti-TNF agents is contraindicated, such as demyelinating disease, psoriasis induced by anti-TNF, hypersensitivity reactions, and/or immunogenicity to anti-TNF agents.

JAK inhibitors could be seen as alternative orally administered small molecules as they have shown efficacy in patients refractory to anti-TNF. However, adverse events such as infections and thrombosis are important considerations. Drugs with better safety profiles and distinct mechanisms of action are needed. S1PR modulators might represent a viable alternative to widely used parenteral biologics.

7 Conclusions

S1P and its receptors are involved in many physiologic and pathologic processes, having a critical role in the immune response by regulating immune cell migration, driving the differentiation of immune cells, and changing their functional phenotype. S1P and SphKs may additionally participate in inflammatory cytokine signaling. Thus, modulation of S1P-S1PR signaling is a promising area for drug development. Encouraging preclinical data show the potential of targeting SphKs, SPPs, S1P-lyase, and transporters. The quest for novel efficacious oral S1PR agonist/modulators with improved selectivity, higher potency, and favorable pharmacokinetic properties and safety profile may expand the current therapeutic arsenal against IBD and other immune-mediated diseases.

Table 2 Pharmacokinetics and pharmacodynamic of selected S1P modulators [4, 39, 58, 72, 74, 82, 101, 111, 112, 133, 136–142]

	Fingolimod	Siponimod	Amiselimod	Ozanimod	Etrasimod	Ponesimod	Cenerimod
Doses (oral)	0.5 mg once daily	CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2 requires 5-day titration (0.25 mg once daily progressing until 1 mg daily). Maintenance dose: 2 mg once daily starting on day 6. Genotypes *1/*3 or *2/*3 initiate with a 4-day titration (0.25 mg once daily until 0.75 mg daily); Day 5 starts with 1 mg once daily	It still is unapproved by FDA. A Phase 1 study in healthy used upwardly titrated in doses ranging from 0.4 to 1.6 mg to achieve 0.4 mg and 0.8 mg steady-state exposure	Starts ozanimod 0.23 mg once daily on days 1 through 4; then 0.46 mg daily on days 5 through 7; maintenance dose: 0.92 mg once daily starting on day 8	It still is unapproved by FDA. Currently, 2 mg once daily dose is used in IBD Phase 3 trials.	14-day dose titration (2 mg once daily progressing until 15 mg daily); on day 15, the maintenance dosage is 20 mg daily.	It still is unapproved by FDA.4 mg once daily in a double-blind, randomized, placebo-controlled, proof-of-concept study in SLE had an improve of the disease score activity and antibody production
S1P receptor selectivity	1, 2, 3, 4, 5	1, 5	1, 5, 4 and minimal 2, 3	1, 5	1, 4, 5	1	1
Pro-drug (requires phosphorylation)	Yes	No	Yes	No	No	No	No
Metabolites actives	Yes	No	Yes	Yes	No	No	Cytochrome P450 (CYP) enzyme-independent metabolism and no major metabolites in plasma.
Half life	6–9 days	30 h	380–420 h	19–22 h	26.2–33.3 h	21.7–33.5h	Single dose 170–199 h. Multiple doses 283–539 h
Disease evaluated	MS	MS	CD, MS, SLE	IBD, MS	IBD, AD, RA	MS, Psoriasis	SLE
Development stage	Approved for MS	Approved for MS	Clinical Trials	Approved for MS	Clinical Trials	Approved for MS	Clinical Trials
Time to steady state	8 weeks	6 days	10 weeks	7 weeks	7 days	5 days	4 weeks
Time to lymphocyte count reduction (h)	4–6	4–6	No data	6–12	1–3	1–6	Dose dependent
Lymphocyte decrease from baseline (%)	70	33–76	60–66	34–68	39–53	50–70	70
T_{max} (h)	12–16	3–4.5	12–16	10	8	2–5	4–6

Table 2 (continued)

	Fingolimod	Siponimod	Amiselimod	Ozanimod	Etrasimod	Ponesimod	Cenerimod
Drugs-drugs interaction	Potent Inhibitor CYP3A (ketoconazole)	Drug-drug interactions with agents that induce or inhibit CYP 2C9 and 3A4 are likely to occur Contraindicated in CYP2C9*2*3 and *3*3 genotypes		BRCP inhibitors, CYP2C8 inhibitors, MAO inhibitors			No metabolic pathways have been identified that contribute to extent to the overall elimination
Excretion	Fecal major route whereas urinary is minor	Biliary excretion	Urine (minor) and feces	Urine (minor) and feces	Feces	Feces and urine (minor)	Feces

T_{max} time to maximum plasma concentration, *MS* multiple sclerosis, *CD* Crohn's disease, *SLE* systemic lupus erythematous, *IBD* inflammatory bowel disease, *AD* atopic dermatitis, *RA* rheumatoid arthritis, *BRCP* breast cancer resistance protein.

Declarations

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