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The Sphingosine 1 phosphate / Sphingosine 1 phosphate receptor axis: a unique therapeutic target in inflammatory bowel disease

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Structured summary

Background: Ozanimod, a high selective sphingosine 1 phosphate (S1P) receptor (S1PR) 1/5 modulator was approved by the Food and Drug Administration for the treatment of adult patients with moderately to severely active ulcerative colitis. Additional S1PR modulators are being tested in clinical development programs for both ulcerative colitis and Crohn's disease.

Aim: To provide an overview of advances in understanding S1PRs biology and summarize preclinical and clinical investigations of S1P receptor modulators in chronic inflammatory disease with special emphasis on inflammatory bowel diseases (IBD).

Methods: We performed a narrative review using PubMed and ClinicalTrials.gov.

Results: Through S1PRs, S1P regulates multiple cellular processes, including proliferation, migration, survival, and vascular barrier integrity. The S1PRs function of regulating lymphocyte trafficking is well known, but new functions of S1PRs expand our knowledge of S1PRs biology. Several S1PR modulators are in clinical development for both ulcerative colitis and Crohn's disease and have shown promise in phase II and III studies with Ozanimod now being approved for ulcerative colitis.

Conclusions: S1P receptor modulators constitute a novel, promising, safe, and convenient strategy for the treatment of IBD.

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Keywords

Inflammatory bowel diseases; S1P / S1PR axis; S1PRs modulators; preclinical studies; clinical trials

Sphingosine 1 phosphate (S1P) is a bioactive lipid mediator involved in the regulation of multiple cellular processes, including proliferation, migration, survival, and vascular barrier integrity. S1P signals through its receptors known as S1P receptors (S1PRs) belonging to the G protein-coupled receptor family. Several S1PRs modulators have been under clinical investigation for the treatment of chronic inflammatory and autoimmune diseases. This review will provide a brief summary of current and emerging evidence of the role of the S1P/S1PR axis in chronic inflammation with a special emphasis on inflammatory bowel disease (IBD) and discusses the therapeutic potential of S1P modulators.

Sphingosine 1-phosphate

Sphingosine 1-phosphate (2S-amino-1-(dihydrogen phosphate)-4E-octadecene-1,3R-diol, S1P) is a multifunctional, bioactive lipid molecule derived from the metabolism of membrane sphingolipids [1]. Sphingolipid metabolites include ceramide, sphingosine, and S1P. As shown in Figure 1, intracellular S1P synthesis occurs through sphingosine phosphorylation, catalyzed by two sphingosine kinase isoenzymes, sphingosine kinases (SPHK)1 and SPHK2, which maintain a metabolic balance of sphingosine and control the levels of S1P [2]. Once generated, S1P is excreted by an adenosine triphosphate-binding cassette transporter into the extracellular space, where it binds to its receptors and exerts biological functions [3]. Concentrations of S1P are high in blood and lymph fluid, but they are low in interstitial fluids, thus creating an S1P gradient between the blood and tissues [4]. Increased levels of S1P have been observed at sites of inflammation, inducing the recruitment of immune cells and soluble mediators and the exacerbation of inflammation [5]. In the blood, S1P is derived mainly from hematopoietic cells, particularly red blood cells, whereas lymphatic endothelial cells are the major source of S1P in lymphatic fluid [6]. S1P degrading enzymes, such as S1P lyase (SPL) and S1P phosphatase (S1PP), play an important role in maintaining low tissue levels of S1P and together with SPHK and S1P transporters, create the S1P gradient[7,8]. SPL inactivates S1P irreversibly by cleaving its acyl chain, whereas S1PP removes phosphate from S1P to produce sphingosine (Figure 1). Importantly, the S1P concentration gradient directs immune cell trafficking, such as that of lymphocytes, out of the lymph node into the circulation, and plays a role in many inflammatory conditions [9].

Advances in the understanding of S1PRs biology in cellular processes

S1P signals primarily through five specific G protein-coupled receptor subtypes, named S1PR1-5, with S1PR1 being the most extensively studied (Figure 1) [10]. The expression patterns of S1PR1-5 vary significantly among tissues, which may be related to specific roles in various organ systems, including the vascular, immune, nervous system, and others [11]. S1PR1, S1PR2, and S1PR3 are ubiquitously expressed, whereas S1PR4 and S1PR5 have a narrower expression pattern restricted to distinct cell types [5]. Although the S1PRs

function of regulating vascular barrier function and lymphocyte trafficking is well known, recent research on S1PRs biology in several human diseases, such as chronic inflammatory pathologies, autoimmunity, and cancer, together with new functions of S1PRs, such as a pro-fibrotic function in some organs, expanded our knowledge of S1PRs in cellular process and increased the interest to use them as therapeutic targets [11]. Table 1 provides an overview of the S1PR functions in health and disease.

S1PR1

S1PR1 is expressed in most mammalian cell types and is functional in many biological processes, including cell migration, proliferation, cell differentiation, vascular barrier function, and others [12]. Upon the activation by S1P, S1PR1 exclusively couples with the Gi/o alpha subunit of heterotrimeric G proteins, and then signals mainly via phospholipase C, phosphoinositide 3-kinase/Akt or Rac, Ras guanosine triphosphatase/extracellular-signal-regulated kinase and adenylyl cyclase [13]. An elevated concentration of S1P is usually coupled with an up-regulation of S1PR1 expression within the inflamed tissue of many diseases, such as chronic inflammatory pathologies, autoimmunity, and cancer [12]. In addition to inflammation, S1PR1 has been linked to fibrosis [14–17]. The role of S1PR1 in angiogenesis has also been studied, but with controversial results. It has been reported that S1PR1-deficient mice show a denser vascular network, while S1PR1-overexpressing mice have a sparser network, suggesting S1PR1 signaling acts as a vascular-intrinsic stabilization mechanism, protecting developing blood vessels against aberrant angiogenic responses [18]. Conversly, it has been suggested that S1PR1 is involved in the development of angiogenesis [19]. Downregulation of S1PR1 or functional inhibition of S1PR1 by fingolimod leads to suppression of tumor angiogenesis [20,21]. These findings suggest S1PR1 has an important role in inflammation, but further investigation of its exact role in angiogenesis and endothelial barrier function is needed.

S1PR2

S1PR2 often exerts cellular functions that are opposed to those of S1PR1, such as preventing recruitment rather than attracting cells in response to S1P [22]. However, the function and mechanisms of S1PR2 are complex and vary in different cells types with contrasting results [23]. For example, S1PR2 can both activate and inhibit Akt [24], an important signaling pathway for many cellular processes such as survival, migration, and proliferation. Furthermore, its inhibitory role in fibroblasts and endothelial cells is dependent on Rho-dependent activation of the phosphoinositide phosphatase and tensin homolog deleted on chromosome 10 (PTEN), whereas in macrophages S1PR2-mediated inhibition of Akt and migration were independent of PTEN [24]. Recent research suggests the involvement of S1PR2 in organ fibrosis [25–27] . Consistent with other S1PRs, S1PR2 also exerts influence on endothelial cells. S1PR2 regulated lymphatic endothelial cells layer structure, permeability, and expression of the junction molecules through the extracellular-signal-regulated kinase pathway, and facilitated T cell transcellular migration through vascular cell adhesion molecule-1 expression and recruitment of T cells to lymphatic endothelial cells migration sites [28]. So, while S1PR2 is involved in several cellular processes, its exact role in specific physiological and pathological courses requires further research.

S1PR3

Initially, S1PR3 has been studied mainly in immune cells and its multifactorial role in the immune system is well documented, including effects on dendritic cell maturation, macrophage chemotaxis and killing, neutrophil and eosinophil recruitment, leukocyte rolling on endothelial cells, and other effects [22]. Recent research indicates that S1PR3 is also involved in pro-fibrotic pathways [29,30] .In rheumatoid arthritis, S1PR3 is associated with the development of autoimmune arthritis and the pathogenic function of synoviocytes via increased interleukin (IL)-6 production [31].

S1PR4

Expression of S1PR4 is primarily restricted to hematopoietic and lymphoid tissue [32], but there is a limited investigation about its role in other cellular functions. In T cells, the S1P/S1PR4 axis does not affect migration, but suppresses T cell proliferation, inhibits the generation of trophic and effector cytokines, such as IL-2 and IL-4, interferon (IFN)-γ, and enhances the production of IL-10 [33]. On the contrary, T cells from S1PR4-deficient mice show no difference in proliferation and cytokine secretion compared to that from wild-type mice [34]. Instead, dendritic cell migration and cytokine secretion are profoundly affected by S1PR4 deficiency, leading to reduced differentiation towards T-helper (Th)17 cells [34]. In a recent study, the S1PR4-mediated suppression of the 5-lipoxygenase enzyme contributes to the S1P-induced anti-inflammatory effects in vitro and in vivo [35]. S1PR4 deficiency also impacts anaphylaxis, resulting in exacerbation of IgE-mediated systemic anaphylaxis, and S1PR4 has a role in the negative regulation of innate mast cell degranulation in response to co-stimulation with IgE/Ag and IL-33 [36]. In human platelets, S1PR4 mediates the inhibitory role of S1P on collagen-induced activation [37]. High S1PR4 expression is associated with shorter disease-free and disease-specific survival in estrogen receptor-negative breast cancer [38]. Interestingly, in dextran sodium sulfate (DSS)-induced colitis, S1PR4 deficiency increases mucosal IgA levels under inflammatory conditions and alleviates DSS-induced colitis [34], indicating that S1PR4 functional antagonism may have a potential role in the treatment of IBD, via the effects on dendritic cell migration, cytokine secretion, and Th17-cell differentiation.

S1PR5

S1PR5 expression was previously thought to be restricted to oligodendrocytes, but recent research indicates S1PR5 can be expressed and is important also for natural killer cells and monocytes. The activation of S1PR5 modulates oligodendrocyte progenitor migration, oligodendrocyte myelination survival, and process retraction [39,40]. S1PR5-deficient mice exhibit decreased numbers of natural killer cells in the peripheral circulation and increased numbers in the lymph nodes and bone marrow [41]. Monocytes require S1PR5 to egress from the bone marrow and enter the systemic circulation [42]. In human brain endothelial cells, S1PR5 contributes to optimal barrier formation and maintains barrier integrity [43]. In a mouse model of systemic sclerosis, S1PR5 modulates early-stage processes of fibrogenesis, potentially promoting the pathogenesis of the disease [44]. In a recent study, S1PR5 signaling promotes chromosome segregation and mitotic progression, indicating potential therapeutic

targets to inhibit the proliferation of cancer cells [45]. In all, accumulating evidence suggests an important role of S1PR5 in cell migration, proliferation, and barrier integrity.

The S1P/S1PRs axis in IBD

The pathogenesis of IBD is incompletely understood but believed to involve an interplay between genetic and environmental factors which may lead to the impairment of intestinal barrier function. This subsequently promotes the translocation of luminal microbes into the bowel wall, where they and their products are recognized by dendritic cells and macrophages [46]. These innate immune cells become activated and produce cytokines and chemokines resulting in the recruitment of additional immune cells and initiation of adaptive immune responses [47,48]. Excessive or uncontrolled innate and adaptive immune pro-inflammatory responses lead to the development of chronic intestinal inflammation and further impairment of barrier function, culminating in gut tissue damage [49].

IBD is characterized by altered immune cell circuits and trafficking [49]. Increased infiltration of T lymphocytes, a crucial component of the intestinal immune system, correlated with endoscopic activity in patients with IBD [50]. Mucosal lymphocytes originate from the bone marrow and enter secondary lymphoid tissues such as peripheral lymph nodes, spleen, and gut-associated lymphoid tissue, where they are primed via antigen-presenting cells [51]. Primed T cells are then released from lymph nodes back into the peripheral circulation, entering inflamed tissue by extravasation [5]. In the context of IBD, altered immune cell trafficking leads to the accumulation of T lymphocytes in the gut and drives inflammation, together with local immune cells such as macrophages, dendritic cells, and innate lymphoid cells [52]. Anti-integrins were the first group of medications to selectively block immune cell trafficking to the gut. Vedolizumab, an α4β7 integrin blocker is currently the only anti-integrin approved for both ulcerative colitis and Crohn's disease in clinical practice [53]. However, since the response is not universal and due to their invasive route of administration (i.e. intravenous or subcutaneous), there is a need for new drugs, specifically small molecules that are given orally. The fact that the S1P/ S1PR1 axis acts as a key regulator for lymphocyte migration from lymph nodes has sparked great interest in the role of the S1P/S1PRs axis as a therapeutic target for IBD [2].

Enzymes that control tissue S1P levels in human and experimental IBD are dysregulated, favoring synthesis over degradation [2,10]. Upon deletion of SPHK1, which is responsible for S1P generation, lower S1P concentrations and reduced severity of DSS-induced colitis have been observed [54]. However, SPHK2 deletion was shown to aggravate DSS-induced colitis and colitis-associated cancer [55]. The underlying mechanism remains unclear. In conditional gut-specific SPL-deficient mice, which show an 8-fold increase in S1P levels in tissues of the lower gastrointestinal tract including the colon, IBD symptoms of diarrhea, blood in stool, and weight loss are more severe than wild type mice [56]. However, inhibition of SPL by 4-deoxypyridoxine hydrochloride and 2-acetyl-4 (tetrahydroxybutyl) imidazole markedly increases local intestinal S1P levels, induces peripheral lymphopenia, downregulated pro-inflammatory cytokines, and attenuates Crohn's disease-like TNFΔARE chronic murine ileitis [57]. These seemingly contradictory observations might be caused by the diverse function of S1P in several biological processes. This suggests that SPHKs and SPL are

involved in IBD, but more selective strategies are needed for a therapeutic application. The development of S1P receptor-selective modulators has expanded our understanding of how to selectively target the diverse S1P function and this will be discussed in the next section. In addition, cell types involved in IBD pathogenesis, including T cells, B cells, dendritic cells, and endothelial cells, have a higher S1PR1 expression in response to chronic but not acute inflammatory signals [58]. Higher S1PR1 expression levels are observed in the colonic mucosa of patients with ulcerative colitis and is associated with increased vascular density in the inflamed mucosa [59]. S1PR1-deficient mice exhibit increased colonic vascular permeability under basal conditions and increased bleeding in experimental colitis [59].

S1PRs modulators and their roles in preclinical studies or clinical trials in IBD

The fact that S1P signaling modulates lymphocyte egress from the thymus or secondary lymphoid organs into the circulatory system makes S1P signaling a possible target for inflammatory and autoimmune diseases [60]. Treatment with an S1PR1 modulator, which induces downregulation and attenuates signaling through this receptor, blocks lymphocyte trafficking without reducing global immune function (Figure 2) [60]. This selective mechanism proved to be therapeutically effective in the treatment of multiple sclerosis [61]. S1P receptor modulators are used in two major therapeutic ways. One is as pro-drugs, such as in the case of fingolimod, which can be converted to an active metabolite by SPHKs; the other is to use them as directly acting drugs, such as ponesimod, siponimod and ozanimod [62]. *In vitro* S1P receptor modulators act as potent selective S1P receptor agonists, binding with highly selective affinity at their target S1P receptor (Table 2), whereas *in vivo* they are functional antagonists, resulting in marked and long-lasting internalization of the targeted S1P receptors, especially S1PR1. Preclinical studies employing various mouse models of colitis suggest that S1PR modulators may also be effective in the treatment of IBD [63,64]. The promising phase II & III results of the S1PR1 modulator Ozanimod led to its approval by Food and Drug Administration for ulcerative colitis and several other S1PR modulators are undergoing clinical trials of both ulcerative colitis and Crohn's disease (Table 3) [23]. Here we will discuss the S1PR modulators that have been proven to be effective in preclinical studies or clinical trials in IBD.

Ozanimod (RPC-1063)

Ozanimod (RPC-1063), (S)-5-(3-(1-((2-hydroxyethyl) amino)-2, 3-dihydro-1H-inden-4-yl)-1, 2, 4-oxadiazol-5-yl)-2-isopropoxybenzonitrile hydrochloride [65], is being developed for the treatment of multiple sclerosis, ulcerative colitis and Crohn's disease [66]. It was approved in the USA for use in the treatment of relapsing forms of adult multiple sclerosis, including relapsing–remitting disease and active secondary progressive disease [66]. Meanwhile, in the European union, ozanimod received a positive Committee for Medicinal Products for Human Use (CHMP) opinion recommending approval for the treatment of adult patients with relapsing–remitting multiple sclerosis with active disease defined by clinical or imaging features [67]. In 2021, ozanimod was approved by Food and Drug Administration for the treatment of adult patients with moderately to severely active ulcerative colitis.

Ozanimod is a potent agonist of the S1PR1 and S1PR5 receptors with 27-fold selectivity for S1PR1 over S1PR5 receptors and > 10,000-fold selectivity for S1PR1 over S1PR2, 3, 4 receptors [68]. Stimulation with ozanimod induces a sustained internalization and degradation of S1PR1 receptors. The downregulation of S1PR1 receptors on lymphocytes prevents their egress from peripheral lymphoid organs, thus reducing circulating lymphocytes and their trafficking to sites of inflammation [68]. Therapeutic administration of ozanimod in the 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in Sprague Dawley rats reduces weight loss in a dose-dependent manner, and inhibits clinical and histological disease scores, with a reduction of circulating lymphocytes [68]. Similar results are observed in a T cell adoptive transfer colitis model, indicating ozanimod is a potential candidate for the treatment of IBD [68].

Results from the first-in-human study with ozanimod in 88 healthy volunteers using a range of single and multiple doses (7 and 28 days) and a dose-escalation regimen demonstrated that ozanimod was generally well tolerated up to a maximum single dose of 3 mg and multiple doses of 2 mg/d, with no severe adverse events and no dose-limiting toxicities, only with a dose-dependent negative cardiac chronotropic effect following the first dose[69]. The treatment of ozanimod induced a robust dose-dependent reduction in total peripheral lymphocytes, with a selective effect on lymphocyte subtypes. Ozanimod caused marked decreases in cells expressing C-C motif chemokine receptor 7 and variable decreases in subsets lacking C-C motif chemokine receptor 7. After the promising results from a randomized, placebo-controlled, phase II trial of ozanimod in relapsing multiple sclerosis (RADIANCE) were released [70,71], the efficacy and safety of ozanimod for adults with relapsing multiple sclerosis was further evaluated in the randomized, double-blind, double-dummy, and multinational phase III SUNBEAM and RADIANCE [72,73]. SUNBEAM was a minimum 12-month phase III trial done at 1346 participants who were randomly assigned to ozanimod 1.0 mg (n=447), ozanimod 0.5 mg (n=451), or IFNβ-1a (n=448) [73]. The results indicated, in relapsing multiple sclerosis patients treated for at least 12 months, that ozanimod was well tolerated and demonstrated a significantly lower relapse rate than IFNβ-1a [73]. RADIANCE was a 24-month phase III trial done at 1320 participants who were randomly assigned to ozanimod 1.0 mg (n=433), ozanimod 0.5 mg (n=439), or IFNβ-1a (n=441) [72].

The efficacy and safety of ozanimod have also been evaluated in ulcerative colitis and Crohn’s disease patients. In a double-blind, placebo-controlled phase II trial of ozanimod of 197 adults with moderate-to-severe ulcerative colitis, patients were randomly assigned to ozanimod at a dose of 0.5 mg or 1 mg or placebo daily for up to 32 weeks [74]. At weeks 8 and 32, more patients receiving ozanimod 1 mg achieved clinical remission compared to placebo [74]. Clinical response was achieved by 54% and 57% of ozanimod 0.5 mg and 1 mg recipients at week 8 and 35% and 51% at week 32 [74]. At week 8, absolute lymphocyte counts declined in the group that received ozanimod [74]. The most common adverse events overall were anemia and headache [74]. In 2020, the results from the TOUCHSTONE open-label extension were released, including efficacy data with up to 4 years of follow-up and safety through the end of openlabel extension [75]. The findings indicated durable efficacy by clinical, endoscopic, histologic, and biomarker measures with ozanimod, with no new safety risk, identified [75]. In 2020, a single-arm, phase II, prospective

observer-blinded endpoint study of ozanimod induction therapy for patients with moderate to severe Crohn's disease was published [76]. All patients began treatment with a 7-day dose escalation (4 days on ozanimod 0.25 mg daily followed by 3 days at 0.5 mg daily), and then received ozanimod 1.0 mg oral capsule daily for a further 11 weeks, for a total of 12-week induction period, followed by a 100-week extension [76]. Of the 69 patients, at week 12, 16 patients experienced endoscopic response [76]. A reduction from baseline in Crohn's disease Activity Index (CDAI) score also was observed, with clinical remission (CDAI <150 points) in 27 patients and clinical response (CDAI decrease from baseline ≥100) in 39 patients [76]. In addition, ozanimod treatment reduced circulating lymphocytes counts, including total T cells, Th cells, cytotoxic T cells cells, and B cells, but not natural killer cells and monocytes [77]. The T cell subsets were not completely inhibited by ozanimod, with CD8+ TEMRA cells largely unaffected [77]. These findings suggest ozanimod treatment does not significantly reduce immune surveillance, indicating a low risk of infection or malignancy [77]. In 2020, a phase III, randomized, double-blind, placebo-controlled study on ozanimod as induction therapy was reported in moderate-to-severe ulcerative colitis [78,79]. 645 patients received ozanimod 1.0 mg (n=429) or placebo (n=216) once-daily for 10 weeks [78,79]. Statistically significant differences between ozanimod and placebo-treated patients were reported in clinical remission at week 10 and clinical response, including Mayo rectal bleeding score, endoscopic improvement and mucosal healing [78,79]. Then 457 patients who had a clinical response to ozanimod 1.0 mg were given ozanimod 1.0 mg or placebo during the maintenance of the study, and at week 52, more patients receiving ozanimod 1 mg than placebo achieved clinical remission [78,79].

Given the experience with non-selective S1PR modulators, such as fingolimod, special emphasis was given to exploring the safety profile of ozanimod. The most commonly observed adverse events overall were anemia, nasopharyngitis, alanine aminotransferase increase, and headache[79]. The overall safety signals and adverse events are described in Table 4. The safety concerns led to a thorough recommendation for a pre-treatment assessment of Ozanimod that can be found in Table 5. Currently, ozanimod is undergoing phase III evaluation in moderate to severe Crohn's disease in various countries ((NCT03467958, NCT03440385, NCT03440372, NCT03464097).).

Etrasimod (APD-334)

Etrasimod is a synthetic, next-generation, oral S1P receptor modulator in clinical development for the treatment of immune-mediated inflammatory disorders [80]. Etrasimod is a full agonist of human S1PR1 and a partial agonist of S1PR4 and S1PR5 in a β-arrestin recruitment assay, whereas neither agonist nor antagonist activity was observed on either the human recombinant S1PR2 or S1PR3 receptors [80,81]. In the adoptive transfer of CD4+CD45RB^{high} T cells mouse colitis model, treatment with etrasimod results in significant reductions in mucosal thickness, and lower histopathology scores with fewer inflammatory infiltrates [81]. In the colons of CD4+CD45RB^{high} severe combined immunodeficient (SCID) mice, treatment with etrasimod significantly reduces the expression of T cell and monocyte markers, such as CD4 (T cells, natural killer and dendritic cells), CD3γ (T lymphocytes), CD11b (monocytes, natural killer and dendritic cells), and Ly6G (neutrophils, and granulocytes), suggesting that etrasimod treatment decreases

infiltration and expansion of these cell populations [81]. Consistently, T-cell and/or monocyte-derived pro-inflammatory cytokines Tumor necrosis factor-α, IL-1β, IL-6, and IL-17A are also significantly lower in CD4+CD45RB^{high} SCID mice treated with etrasimod, whereas the anti-inflammatory cytokine IL-10 is induced by etrasimod treatment [81].

The result of etrasimod in phase II, proof of concept, double-blind, parallel-group, randomized trial of patients with moderately to severely active ulcerative colitis was published in 2019 [62]. Adult outpatients with modified Mayo clinic scores (stool frequency, rectal bleeding, and endoscopy findings) of 4-9, endoscopic subscores of 2 or more, and rectal bleeding subscores of 1 or more were randomly assigned to groups given once-daily etrasimod 1 mg (n=52), etrasimod 2 mg (n=50), or placebo (n=54) for 12 weeks at 87 centers in 17 countries [62]. At week 12, etrasimod 2 mg led to a significantly greater mean improvement in modified Mayo clinic scores from baseline than placebo, and endoscopic improvement occurred in 41.8% of patients receiving etrasimod 2 mg vs 17.8% receiving placebo [62]. These results indicated the efficacy of etrasimod in the treatment of moderate to severe ulcerative colitis. Current safety data show a favorable safety profile but are limited by a relatively small number of participants [82]. Currently, there are several ongoing phase III studies in severely active ulcerative colitis (NCT04706793, NCT03950232, NCT03996369, NCT04176588, and NCT03945188) and moderate to severe Crohn's disease (NCT04173273).

Amiselimod (MT-1303)

Amiselimod (MT-1303), 2-amino-2-{2-[4-(heptyloxy)-3-(trifluoromethyl) phenyl] ethyl} propan-1, 3-diol hydrochloride, a structural analogue of fingolimod, was designed as a prodrug lacking S1PR3 agonism for the treatment of autoimmune disease. Amiselimod is converted to its active metabolite, (S)-amiselimod phosphate (amiselimod-P), by SPHKs *in vivo* [83,84]. Amiselimod-P shows high selectivity for S1PR1 and S1PR5, minimal agonist activity for S1PR4, and no distinct agonist activity for S1PR2 or S1PR3 [83]. The conversion of amiselimod into its active metabolite is slower than fingolimod [85]. In both preclinical and phase I studies, amiselimod shows a favorable cardiac safety profile with approximately 5-fold weaker G protein-gated inwardly rectifying potassium (GIRK) activation than fingolimod-phosphate (fingolimod-P) [83,86]. In a phase I study, no clinically significant bradycardia was observed after administration of amiselimod up to 0.75mg [83].

A randomized, double-blinded, placebo-controlled phase II trial in relapsing multiple sclerosis reported 0.2 mg and 0.4 mg amiselimod significantly reduced the total number of gadolinium-enhanced T1-weighted lesions with no serious adverse events in any group and no clinically significant heart rate reduction at any dose [87]. These findings were confirmed in a phase II extension study of oral amiselimod in relapsing multiple sclerosis, showing that amiselimod was well tolerated and dose-dependently effective in controlling disease activity for up to 2 years of treatment [88]. The effects of amiselimod were evaluated in murine systemic lupus erythematosus models and preclinical results suggested that it inhibits the progression of lupus nephritis by reducing the infiltration of autoreactive T cells into the kidneys [89]. Two clinical phases II trials in systemic lupus erythematosus (NCT02307643) and psoriasis (NCT01987843) have been completed without released reports [90,91] .

In the intestine, the effects of amiselimod were evaluated in chronic colitis of immune-deficient SCID mice by adoptive transfer of $CD4^{+}CD45RB^{high}$ T cells. The results demonstrated that amiselimod regulates lymphocyte trafficking, limits infiltration of colitogenic Th1 and Th17 cells into the colon, and inhibits the development of chronic colitis [92]. The investigation of the effects of amiselimod in moderate-to-severe, active Crohn's disease in a 14-week, randomized, placebo-controlled, phase II trial [93] with an open-label extension of ≥22 weeks [94] has been completed. However, amiselimod 0.4 mg/day for 12 weeks did not show a significant effect on clinical or biochemical disease activity in refractory Crohn's disease [95]. The effects of amiselimod in ulcerative colitis patients may be further evaluated [89].

KRP-203

KRP-203, 2-amino2-propanediol hydrochloride, an S1P receptor agonist with some similarities in molecular structure to fingolimod, has been developed for immunomodulation in autoimmune diseases and organ transplantation [5,96,97]. KRP-203, which is supposed to be selective for S1PR1, prolonges graft survival and attenuates chronic rejection in rat allograft models, indicating that KRP-203 might regulate both T cell trafficking and B cell response [98]. KRP-203 administration substantially reduced atherosclerotic lesion formation and induced lymphopenia in LDL-$R^{-/-}$ mice, with reduced numbers of total (CD4+, CD8+) and activated (CD69+/CD8+, CD69+/CD4+) T cells in peripheral lymphoid organs, and lower levels of cytokine and chemokine (tumor necrosis factor-α, regulated and normal T cell expressed and secreted) levels in plasma and aortas [99]. In IL-10 gene-deficient mice, KRP-203 significantly inhibits ongoing colitis in part through decreasing the infiltration of lymphocytes at inflammatory sites and by blocking T-helper 1 cytokine production in the colonic mucosa [100].

In 2011, a clinical trial evaluated the efficacy and safety of KRP-203 in moderately active refractory ulcerative colitis patients, with approximately 72 randomized subjects [101]. The trial has been terminated, but results have not been published yet [101].

Other S1PRs modulators as potential future inflammatory therapies

Fingolimod (FTY720), Siponimod (BAF312), Ponesimod (ACT-128800), and Cenerimod (ACT-334441) have been investigated in preclinical studies or clinical trials of several diseases but have yet to be tested in IBD.

Fingolimod was characterized as a non-selective agonist of all of the S1P receptors (S1PR), except for S1PR2, and in addition, as a selective S1PR1 functional antagonist of S1PR1 [102]. Fingolimod exhibits clear efficacy in reducing the frequency of relapses and disability progression on long-term follow-up of patients with multiple sclerosis compared to placebo, in phase III trials (FREEDOMS, FREEDOMS II, and TRANSFORMS) and was the first approved oral treatment for relapsing-remitting multiple sclerosis, licensed by the Food and Drug Administration in 2010 and by the European Medicines Agency in 2011 [103]. Treatment with fingolimod decreases the clinical and histopathologic severity of oxazolone-induced colitis[104], TNBS colitis mouse model[105], and DSS colitis model[106]. Despite the clinical efficacy of fingolimod in the treatment of multiple sclerosis and the promising preclinical

results of fingolimod in the treatment of other diseases, the occurrence of adverse events raised concerns about the safety profile of fingolimod [102]. Infections, bradyarrhythmias and atrioventricular blocks, increased blood pressure, respiratory adverse effects, liver injury, and basal cell carcinoma were observed, perhaps related to the nonselective mechanism of action of fingolimod [102], suggesting that more selective S1PR1 modulators may be needed.

Siponimod (BAF312), targeting S1PR1 and S1PR5, is the second S1P receptor modulator to enter clinical trials for multiple sclerosis [107]. It was designed using fingolimod as the lead structure, and optimizing it for potency at S1PR1, with limiting effects on S1PR3 (for risk of side effects), and pharmacokinetics (allowing for once a day oral dosing, but also for rapid recovery of peripheral lymphocyte counts following discontinuation) [108]. According to the data of a phase I study, siponimod induces profound but rapidly reversible inhibition of lymphocyte trafficking [109]. However, although siponimod lacks affinity with S1PR3, which was associated with bradycardia in mice and it induces rapid but transient bradycardia in humans [109]. In a phase II study and its extension study of siponimod in patients with relapsing-remitting multiple sclerosis, promising results are observed with siponimod on MRI lesion activity in model-based analyses and its tolerability in relapsing-remitting multiple sclerosis [110,111]. In a subsequent phase III study in secondary progressive multiple sclerosis, siponimod reduced the risk of disability progression with a safety profile similar to that of other S1P modulators [112].

Ponesimod, is a reversible, orally active, selective S1PR1 modulator with at least 10-fold more activation potency on the S1PR1 than on any other S1P receptor subtype[113]. A double-blind, placebo-controlled, dose-finding phase II study evaluated the efficacy and safety for the treatment of patients with relapsing–remitting multiple sclerosis showed that ponesimod was generally well tolerated and significantly reduced the number of new lesions, showing a beneficial effect on clinical endpoints [114]. In the meantime, a double-blind, randomised, placebo-controlled, parallel-group, multicentre phase II study of oral ponesimod to assess efficacy, safety, and tolerability in patients with moderate to severe chronic plaque psoriasis indicated more patients in the ponesimod groups than the placebo group experienced improvements at week 16 [115]. However, ponesimod was associated with dyspnea, elevated liver enzymes, and dizziness [116].

Cenerimod, is a selective S1PR1 modulator with a 16-fold higher activation potency on the S1PR1 compared to the natural ligand S1P, whereas displaying no detectable agonist activity on the S1PR2, at least 2000-fold less active at the S1PR3 than S1P, 30- to 35-fold lower potency at the S1PR4 than S1P, but two-fold more potent on the S1PR5 receptor than S1P [115]. A phase I study in healthy participants showed that cenerimod is well tolerated with no significant safety concerns [117]. A double-blind, randomized, placebo-controlled, proof-of-concept study showed that cenerimod has the potential to treat patients with systemic lupus erythematosus with an acceptable safety profile [118]. Cenerimod caused a statistically significant dose-dependent reduction in total lymphocyte count from baseline to end of treatment [118]. Compared with placebo, cenerimod 4 mg showed a clinical and biological improvement on change from baseline in systemic lupus erythematosus disease activity index-2000 score, and on biomarker anti-dsDNA antibodies [118].

Summary and future perspective

Most IBD patients show either a primary non-response or lose responsiveness during the long-term maintenance treatment with current therapies, including anti-Tumor necrosis factor, anti-integrin, anti-IL-23 monoclonal antibodies and JAK inhibitors. This justifies the need for alternate, efficient, and well-tolerated new medical therapies [10]. S1P receptor modulators have been investigated in several preclinical and clinical trials related to chronic inflammatory disorders, such as relapsing-remitting multiple sclerosis, systemic lupus erythematosus, psoriasis, and IBD [119] showing efficacy in several of those diseases. Solid information on the biology of the different S1P receptors, their cellular function, and their clinical relevance is emerging, mostly confirming the role of S1PR1 in inflammation. One advantage of the S1P receptor modulators is that all of them can be conveniently administered by the oral route [120]. Furthermore, the second generation of S1P receptor modulators, such as siponimod, amiselimod, and ozanimod, are more selective and might offer better safety and tolerability with fewer cardiac side-effects [119]. The promising phase II and III data of ozanimod in the treatment of ulcerative colitis and Crohn's disease patients and of etrasimod in ulcerative colitis suggest S1P receptor modulators targeting S1P signaling may constitute a novel, promising, safe, and convenient strategy for the alleviation of the symptoms of IBD [62,74,121]. What remains to be clarified in this therapeutic area? The distinct and exact mechanisms of different modes of action of the highly selective S1P receptor modulators, which will help to find the best combination therapeutic strategies for optimal clinical efficacy and safety with limited side effects. This is particularly true as there appears to be a partial disconnect between peripheral lymphocyte numbers and inflammation at the level of the mucosa, suggesting direct anti-inflammatory efficacy independent of a reduction of lymphocytes in the peripheral circulation. The exact profile of lymphocyte subpopulations in the mucosa influenced by S1P modulation is still unclear, and defining it would help better understand the immunomodulatory function of these novel drugs. Finally, long-term safety data collected post-approval of this novel class of medications will shed light on safety and tolerability, critical factors for therapeutic success. S1P modulators are here to stay, and future work will determine their place in the treatment algorithms for Crohn's disease and ulcerative colitis.

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Abbreviations:

CDAI	Crohn's disease Activity Index

DSS	dextran sodium sulfate
IBD	Inflammatory bowel diseases
IFN	interferon
IL	interleukin
PTEN	phosphatase and tensin homolog
S1P	sphingosine 1 phosphate
S1PR	sphingosine 1 phosphate reptor
SCID	severe combined immunodeficient
SPHK	sphingosine kinases
SPL	S1P lyase
S1PP	S1P phosphatase
Th	T-helper
TNBS	2,4,6-trinitrobenzene sulfonic acid

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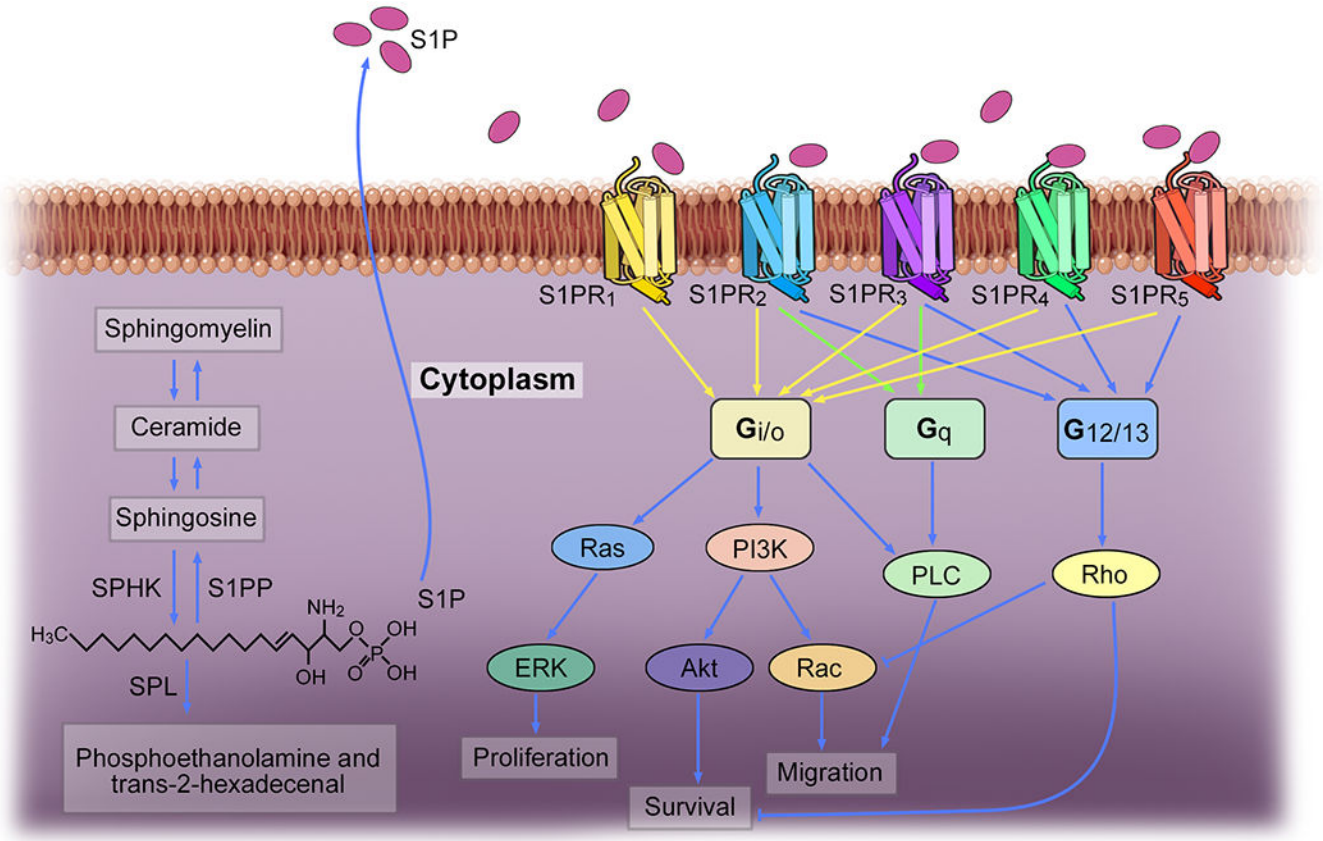

Figure 1. S1P/S1PRs signaling pathways.

Intracellular S1P synthesis is catalyzed by SPHK1 and SPHK2. The degradation of S1P is catalyzed by S1PP and SPL. S1P signals primarily through five G protein-coupled receptor subtypes named S1PR1-5.

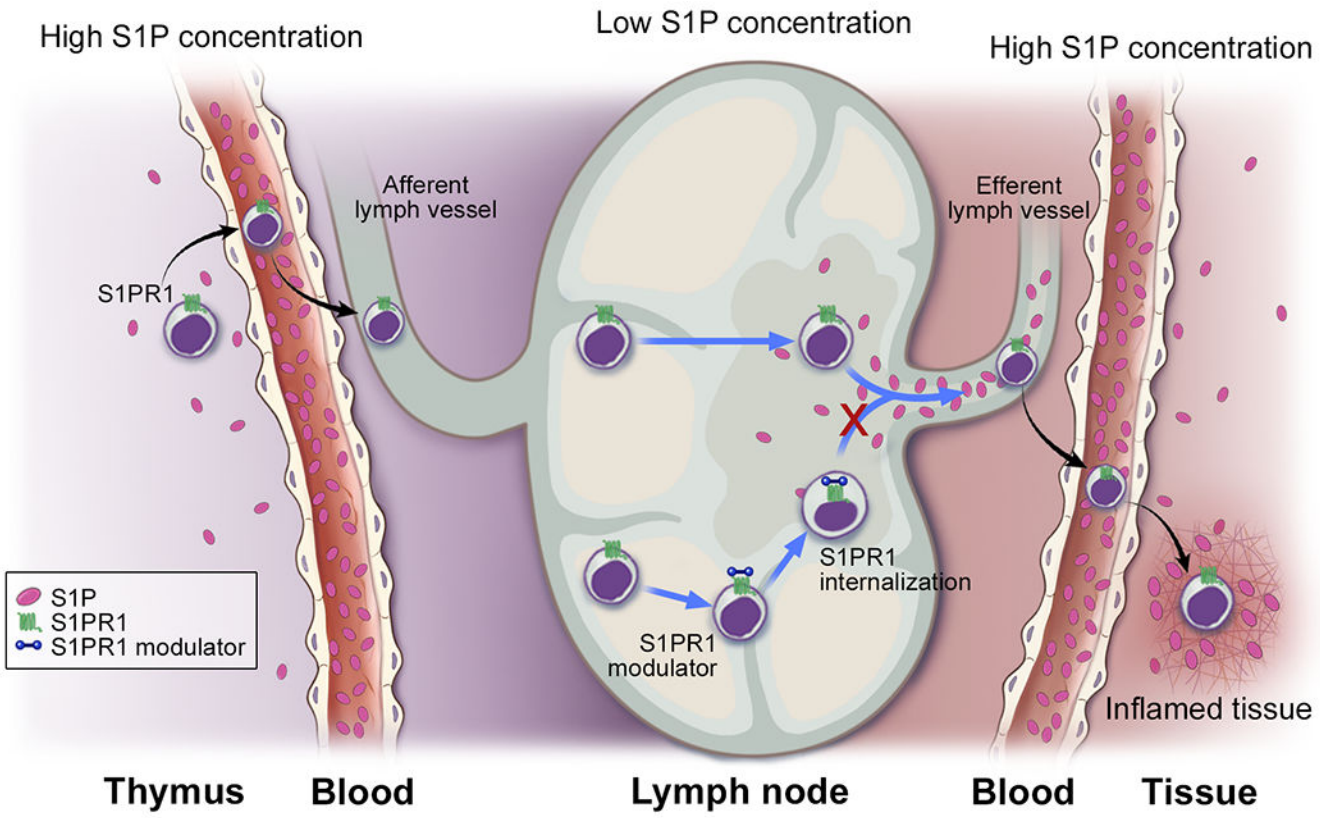

Figure 2. S1PR modulators regulate sequestration of T lymphocytes.

Treatment with an S1PR1 modulator, which induces downregulation and attenuates signaling through this receptor, blocks lymphocyte trafficking.

Table 1

Main functions of S1PRs

Name	Main functions
S1PR1	1) Cell growth and proliferation 2) Cell migration 3) Cell differentiation 4) Vascular integrity 5) Angiogenesis 6) Lymphocyte egress 7) Fibrosis 8) Chemotaxis
S1PR2	1) Cell growth and proliferation 2) Cell migration 3) Endothelial barrier function 4) Fibrosis
S1PR3	1) Dendritic cell maturation 2) Macrophage chemotaxis and killing 3) Neutrophil and eosinophil recruitment 4) Leukocyte rolling on endothelial cells 5) Fibrosis 6) Cytokine production
S1PR4	1) Cell migration 2) Cytokine secretion 3) Cell differentiation
S1PR5	1) NK cells egress 2) Monocytes egress 3) Cell proliferation 4) endothelial barrier integrity

Table 2

Characterization and preclinical investigations of S1PR modulators

Name	Synonym	Formula	Affinity to S1PRs	Animal colitis models investigated	REF
Ozanimod	RPC-1063	$C_{23}H_{24}N_4O_3$	S1PR1 and 5	TNBS-induced colitis in Sprague Dawley rats, Colitis in SCID mice by adoptive transfer of CD4+CD45RB^{high} T cells	65,68
Etrasimod	APD-334	$C_{26}H_{26}F_3NO_3$	S1PR1, 4 and 5	Colitis in SCID mice by adoptive transfer of CD4+CD45RB^{high} T cells	80,81
Amiselimod	MT-1303	$C_{19}H_{30}F_3NO_3$	S1PR1, 4 and 5	Colitis in SCID mice by adoptive transfer of CD4+CD45RB^{high} T cells	83–86,92
KRP-203	KRP 203	$C_{24}H_{26}ClNO3S$	S1PR1	Colitis in IL-10$^{-/-}$ mice	96–100
Fingolimod	FTY720	$C_{19}H_{34}ClNO_2$	S1PR1,3,4 and 5	Colitis in IL-10$^{-/-}$ mice, oxazolone-induced colitis, TNBS-induced colitis, DSS-induced colitis	102,104–106,122–124
Siponimod	BAF312	$C_{29}H_{35}F_3N_2O_3$	S1PR1 and 5	None	107,108
Ponesimod	ACT-128800	$C_{23}H_{25}ClN_2O_4S$	S1PR1	None	116
Cenerimod	ACT-334441	$C_{25}H_{31}N_3O_5$	Mainly S1PR1 and 5	None	115,125

Table 3

Clinical trials of S1PR modulators

Name	Clinical trials			FDA Approvals	REF (ClinicalTrials.gov number)
	UC	CD	Non-IBD		
Ozanimod	Phase III, completed	Phase III, recruiting	Phase III in MS, completed	MS, 2020; UC, 2021	NCT02294058, NCT01628393, NCT02047734, NCT02435992, NCT03467958, NCT03440385, NCT03440372, NCT03464097, and others.
Etrasimod	Phase III, recruiting; Phase III, active	Phase II and III, recruiting	Phase II in Eosinophilic Esophagitis, recruiting; Phase II in Atopic Dermatitis, active	None	NCT04706793, NCT04176588, NCT03945188, NCT04173273, NCT04682639, NCT04162769, and others
Amiselimod	None	Phase II, completed	Phase II in Plaque Psoriasis, completed; Phase II in SLE, completed	None	NCT02378688, NCT02389790, NCT01987843, NCT02307643
KRP-203	Phase II, Terminated	None	Phase II in Subacute Cutaneous Lupus Erythematosus, completed	None	NCT01375179, NCT01294774
Fingolimod	None	None	Phase III in MS, completed	RRMS, 2010	NCT00289978
Siponimod	None	None	Phase III in SPMS, completed; Phase III in MS, recruiting; Phase II in Active Dermatomyositis.	None	NCT01665144, NCT03623243, NCT02029274
Ponesimod	None	None	Phase III in MS, completed; Phase II in Psoriasis, completed	None	NCT02425644, NCT01208090
Cenerimod	None	None	Phase II in SLE, completed	None	NCT02472795

CD, Crohn's disease; FDA, Food and Drug Administration; MS, multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SLE, systemic lupus erythematosus; UC, ulcerative colitis

Table 4

Ozanimod safety signals and adverse events

System	Specific adverse reaction	Patients at risk	Timing of reaction	Preventive measures	Follow-up measures	Ref.
CVS	Bradycardia/ transient AV conduction delays/AV blocks	Preexisting ischemic heart disease, heart failure, bradyarrythmias and conduction blocks	During induction	Contraindicated in high risk populations, including ischemic heart disease, heart failure, bradyarrythmias and conduction blocks	Assess when clinically indicated	126,127
	Orthostatic hypotension		During induction, usually transient			126,127
	Hypertension		During maintenance, usually persistent	Avoidance of tyramine-containing foods and contraindicated with MAO inhibitors	Monitor blood-pressure during treatment and manage appropriately if clinically significant	127
Respiratory	Decline in pulmonary function		~3 months after treatment initiation		Spirometric evaluation of respiratory function during therapy only when clinically indicated	128
Hematologic	Lymphopenia, rarely severe (<0.2 × 109/L)		During induction		Continue treatment unless severe lymphopenia develops. Resolves after treatment discontinuation	69,128
Ophthalmic	Macular edema	History of uveitis or diabetes mellitus	Two weeks to 1 year from first dose	Patients at risk should undergo an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation	Patients at risk should undergo regular ophthalmic follow-up examinations and in any case of new change in vision	128
GI	Liver injury	History of significant liver disease	Any time throughout course of treatment, mostly transient	Measure baseline liver function test	Assess if clinically indicated. Discontinue treatment if significant liver injury is confirmed	70
Immune defense	Oral Herpes and Herpes zoster		Any time throughout course of treatment		Discontinue treatment in case of serious infection	70,128
	Nasopharyngitis and upper respiratory tract infection		Any time throughout course of treatment		Discontinue treatment in case of serious infection	70,128
	Urinary tract infection		Any time throughout course of treatment		Assess if clinically indicated	70,128

CVS, cardiovascular system; AV, atrioventricular; MAO, monoamine oxidase; GI, gastrointestinal

Table 5

Recommended Ozanimod pre-treatment assessment

Baseline Assessment	Test	Advice
Cardiac Evaluation[&]	ECG to exclude baseline bradyarrythmias or conduction blocks, blood pressure, check drug history for medications that may slow heart rate or AV conduction	Cardiac contraindications: MMI, unstable angina, class III or IV heart failure, type 2 second degree or type 3 degree AV block, sick sinus syndrome, significant QTc prolongation
Complete Blood Count	Including lymphocyte count	Patients with counts $<0.2 \times 10^9$/L were excluded from trial programs, a mean 50% reduction in total lymphocyte count is expected
Liver Function Tests	Transaminases and bilirubin level	5% develop transaminitis > 3x ULN
Ophthalmic Assessment	Fundoscopy	Patients with a history of diabetes, uveitis or macular edema
Virology and TB	Hep B, VZV serology and TB IGRA	Consider VZV vaccination if VZV IgG negative (live vaccines require administration 3 months prior to initiation). Herpes zoster is the most common opportunistic infection
Other contraindications	Patient history	TIA or stroke < 6 months, severe untreated sleep apnea
Review current or prior medications	Patient history	Anti-neoplastic, immunosuppressive, or immune-modulating therapies may lead to unintended additive immunosuppression. Monoaminooxidase inhibitors are contraindicated
Dose titration at start	Titrate once daily dose to maintenance dose at one week: 0.25mg days 1–4, 0.5mg days 5–7, then 1mg QD	

[&]Request cardiologist consultation in patients with a preexisting cardiac condition.AV, atrioventricular; ECG, electrocardiogram; VZV, varicella-zoster virus; MI, myocardial infarction; QTc, QT Interval; ULN, upper limit of norm; TB, tuberculosis; IGRA, interferon-gamma release assays; Hep B, hepatitis B virus; TIA, transient ischemic attack; QD, every day.