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MINIREVIEWS

Unveiling the biological role of sphingosine-1-phosphate receptor modulators in inflammatory bowel diseases

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Abstract

Inflammatory bowel disease (IBD) is chronic inflammation of the gastrointestinal tract that has a high epidemiological prevalence worldwide. The increasing disease burden worldwide, lack of response to current biologic therapeutics, and treatment-related immunogenicity have led to major concerns regarding the clinical management of IBD patients and treatment efficacy. Understanding disease pathogenesis and disease-related molecular mechanisms is the most important goal in developing new and effective therapeutics. Sphingosine-1-phosphate (S1P) receptor (S1PR) modulators form a class of oral small molecule drugs currently in clinical development for IBD have shown promising effects on disease improvement. S1P is a sphingosine-derived phospholipid that acts by binding to its receptor S1PR and is involved in the regulation of several biological processes including cell survival, differentiation, migration, proliferation, immune response, and lymphocyte trafficking. T lymphocytes play an important role in regulating inflammatory responses. In inflamed IBD tissue, an imbalance between T helper (Th) and regulatory T lymphocytes and Th cytokine levels was found. The S1P/S1PR signaling axis and metabolism have been linked to inflammatory responses in IBD. S1P modulators targeting S1PRs and S1P metabolism have been developed and shown to regulate inflammatory responses by affecting lymphocyte trafficking, lymphocyte number, lymphocyte activity, cytokine production, and contributing to gut barrier function.

Key Words: Inflammatory bowel disease; Sphingosine-1-phosphate; Intestinal inflammation; T helper 1/T helper 17; Sphingosine 1 phosphate; Modulators; Immune responses

Core Tip: Recent literature has highlighted the use of novel oral small molecules, so-called sphingosine-1-phosphate (S1P) receptor modulators, in the therapeutic treatment of inflammatory bowel disease (IBD). Reviews and clinical trials have reported the safety profile and role of S1P modulators in alleviating IBD, but little information is available on their biological function. This is a comprehensive mini-review describing key biological mechanisms beyond the activity of S1P modulators reported in preclinical and clinical studies. The data from this study will contribute to the research field of developing therapeutic strategies in IBD based on the pathogenic biological background.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammation of the gastrointestinal tract that includes two main forms: ulcerative colitis (UC) and Crohn's disease (CD). IBD is thought to be mediated by dysregulation of the immune system, and its high epidemiological prevalence worldwide has led to great concern regarding the treatment and therapeutic management of patients[1]. Although current therapeutic agents have led to significant improvements in IBD in recent years, there is still a large percentage of patients who do not respond to these agents[2], and high immunogenicity has also been associated with monoclonal antibodies[3]. Sphingosine-1-phosphate (S1P) receptor modulators are novel oral small molecule drugs that have better prospects in terms of route of administration, pharmacokinetic properties, immunogenicity, manufacturing and cost compared to other biologic agents in IBD [4]. S1P is a highly bioactive molecule that regulates important biological processes such as inflammation, immune cell transport, and cell growth and transformation[5]. S1P level creates a gradient between blood and tissues, which contributes to the recruitment of immune cells and inflammatory mediators in tissues. S1P exerts its biological function by activating specific S1P receptors expressed by different cell types, initiating a signaling cascade that modulates lymphocyte migration, endothelial permeability, angiogenesis, cell proliferation, cell survival, apoptosis, and differentiation[6]. The components of S1P metabolism and S1P signaling have been associated with the regulation of immune responses and inflammation-related pathologies in the gastrointestinal tract. A number of agents targeting the inflammatory activity of sphingosine kinases (SphK1, SphK2) and S1P receptors are currently being tested in preclinical and clinical studies[5]. Amiselimod (MT-1303), etrasimod (APD-334), ozanimod (RPC-1063), and KRP-203 (2-amino-2-1,3-propanediol hydrochloride) belong to the class of S1P modulators currently in clinical development for IBD, and they help prevent lymphocyte migration into the gut[3]. Gut T lymphocyte colonization is a critical factor in chronic gut inflammation, considering the role they play in inflammatory immune responses and immune cell interactions. Overexpression of SphK kinases and the SphK/S1P axis are associated with the regulation of inflammation in the tumor microenvironment and mediate the development of gastric and colon cancer[7]. S1P receptor modulators (FTY720, ozanimod, etrasimod) have been proposed as therapeutics for gastrointestinal cancer due to their potential anti-inflammatory effects[8]. Elucidating the different mechanisms of action of therapeutics for IBD could be an important factor in selecting the right drug for the right patient.

In this brief review, we describe the main biological mechanisms of S1P receptor modulators in IBD and how these mechanisms might influence disease progression according to current experimental and clinical data.

ROLE OF T LYMPHOCYTES AND CYTOKINES IN INFLAMED IBD TISSUE

T helper (Th) lymphocytes play a key role in modulating immune responses in the intestinal mucosa by secreting cytokines and influencing the activity and function of other immune cells[9]. In the context of immune homeostasis, the intestinal mucosa has inflammatory immune responses under control, which are regulated by a delicate balance of Th1, Th2, Th3, Th9, Th17, and regulatory T cells (Tregs)[10-12]. Naive T cells circulate through secondary lymphoid organs until they interact with antigen-presenting cells (APCs) (*e.g.*, dendritic cells, macrophages, B cells) in the gut-associated lymphoid tissue, where they encounter their cognate antigen presented by APCs. This interaction leads to the activation and proliferation of T cells, which are also imprinted into a gut homing phenotype. Imprinted T cells express specific integrins and chemokine receptors to either settle in the small intestine or migrate to the colon [13-15]. The extravasation process of T cell homing begins with the binding and rolling of T cells across

the endothelium, which is mediated by the binding of selectins and integrins on T cells to their ligands on endothelial cells. This binding slows down T cells and activates them through tissue-activated chemokines [C-X-C motif chemokine ligand 10 (CXCL10), chemokine ligand 25 (CCL25)]. Conformational changes of integrins during the interaction between T cells and endothelium lead to the arrest of activated T cells, followed by transmigration through the endothelium into the intestinal tissue (Figure 1).

The development of IBD has been linked to the synergistic effects of Th cell activity, cytokines, antimicrobial peptides, and endoplasmic reticulum (ER) stress[16-18], which initiate signaling cascades leading to the activation of key pro-inflammatory transcription factors, including nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3), which further amplify and integrate signals from various stimuli[19].

In IBD, an imbalance has been observed between pro- and anti-inflammatory cytokines, which are released by the intestinal mucosa and influence the duration and intensity of inflammatory responses [20]. An accumulation of Th1 cells has been observed in IBD[21]. The proliferation and differentiation of Th1 cells is induced by interleukin 12 (IL-12)-secreting APCs[22]. Th1 cells produce interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) cytokines, which can exacerbate chronic epithelial damage of the intestinal mucosa, as they are thought to control beta-catenin signaling of intestinal epithelial cells and limit their differentiation and proliferation during intestinal inflammation[23]. IFN-γ production in colitis has been shown to induce other cells of the innate immune system to secrete inflammatory cytokines, thereby increasing chronic inflammation[24]. A specific IFN-γ+ cytotoxic CD4+ T cell subset directly promotes apoptosis of intestinal epithelial cells and intestinal enteroids in an *in vivo* colitis model[25].

In UC, both IL-10 and IL-13 cytokines are significantly increased, but the anti-inflammatory activity of IL-10 is not sufficient to reduce the activity of IL-13. The latter is restricted to the inflamed areas of the intestinal mucosa and is associated with epithelial barrier damage, cell apoptosis, decreased mucosal repair rate, and alteration of tight junctions, which negatively affects mucosal permeability[26,27].

Th17 cells are another important player in intestinal inflammation. They produce the cytokines IL-17 and IL-22, which are associated with the initiation of colitis, as they can trigger and amplify multiple inflammatory pathways. Th17 cells can also be converted to a Th1 cell phenotype in response to inflammatory cytokines (IL-12, IL-23)[28]. A disturbed Th17/Treg balance is thought to be responsible for the development of IBD. Th17 cells enhance inflammatory responses, while Tregs suppress intestinal inflammation and autoimmunity. Treg deficiency and an increase in Th17 activity have been observed in IBD[29].

The role of Th9 cells in mucosal inflammation has also been highlighted in experimental and human UC because expression of the transcription factor PU.1, a regulator of cellular communication, and secretion of IL-9 by Th9 cells can prevent the proliferation of intestinal epithelial cells and regulate the expression of several tight junction proteins. These factors promote the translocation of certain bacterial species to the intestine, leading to subsequent immune cell activation and inflammation of the intestinal mucosa[30].

Another pro-inflammatory type of T cells recently studied in CD are γδT cells[31]. The major subtype γδ2$^+$ of γδT cells has pro-inflammatory activity after migrating into inflamed intestinal tissue, where it produces the inflammatory cytokines TNF-α and IL-17A and induces the secretion of IFN-γ from αβT cells[32].

A pathogenic mechanism mediated by CD8+ T cells in the development of IBD has also been proposed. During chronic inflammation, cytotoxic CD8+ T cells can disrupt the intestinal epithelial barrier by recognizing peptides derived from commensal bacteria on the major histocompatibility complex class I of epithelial cells and releasing the inflammatory cytokines IFN-γ and TNFα, which destroy the tight junctions of intestinal epithelial cells. When the epithelial barrier is disrupted, bacteria can invade the lamina propria and trigger an immune response mediated by innate immune cells (*e.g.*, macrophages), which induces a strong pro-inflammatory milieu that drives CD8+ T cells toward Tc1 cells or IFN+ Tregs and further exacerbates tissue damage[33]. In parallel, the decreased apoptosis of intestinal lamina propria T cells observed in IBD patients favors their pro-inflammatory effect on tissues [34] (Figure 1).

BIOLOGY OF S1P METABOLISM AND SIGNALING IN IBD

S1P is a sphingosine-derived phospholipid found in high concentration in blood and in lower concentration in other tissues. Sphingolipids contain ceramides as a structural backbone with longer, amide-linked acyl chains ranging from 14 to 36 carbon atoms in length[35]. Ceramide synthesized in the ER is hydrolyzed to sphingosine, which is then phosphorylated by SphKs (SphK1 and SphK2) to form S1P, an important regulator of inflammation[36]. S1P comprises several types of sphingolipids (S1P1-5) that act by binding to 5 G protein-coupled receptors (S1PR1-5) and by affecting key intracellular molecules that regulate gene transcription, including activation of the pro-inflammatory transcription factor NF-κB and inhibition of histone deacetylases (HDACs), which are epigenetic regulators of gene expression.

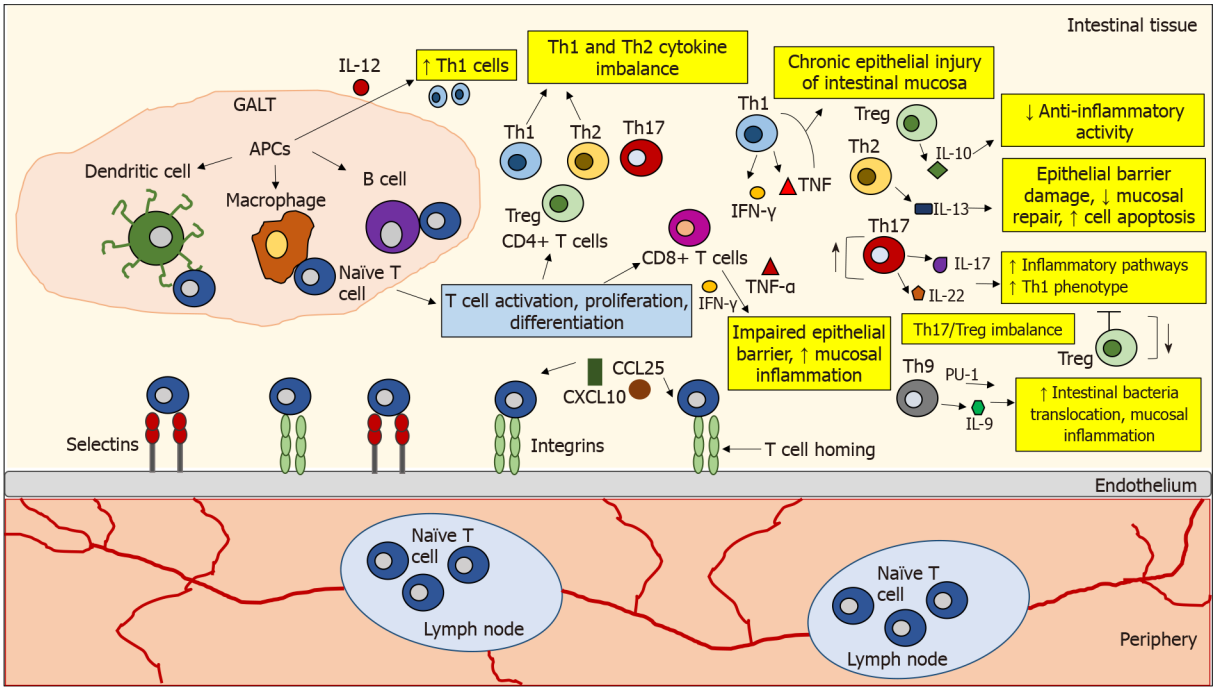

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Figure 1 The role of T lymphocytes in inflamed Inflammatory bowel disease tissue. Naive T cells circulate through secondary lymphoid organs until they interact with antigen-presenting cells (APCs) (*e.g.*, dendritic cells, macrophages, B cells) in gut-associated lymphoid tissue, where they encounter their cognate antigen presented by APCs. This interaction leads to T cell activation, proliferation, and differentiation. T cell homing begins with the binding and rolling of T cells across the endothelium, which is mediated by the binding of selectins and integrins on the T cells to their ligands expressed on the endothelial cells. This binding slows T cell activation by tissue-activated chemokines (C-X-C motif chemokine ligand 10, chemokine ligand 25). The development of inflammatory bowel disease (IBD) is associated with dysregulated activity of T helper (Th) cell subtypes. In IBD, an imbalance has been observed between pro- and anti-inflammatory cytokines released by the intestinal mucosa that influence the duration and intensity of inflammatory responses. In IBD, an accumulation of interleukin 12 (IL-12)-induced Th1 cells was observed. Th1 cells produce interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which may enhance chronic epithelial injury of the intestinal mucosa. IL-10 secreted by regulatory T cells (Tregs) is not sufficient to counteract inflammatory activity in IBD. IL-13 secreted by Th2 cells is associated with epithelial barrier damage, decreased mucosal repair, and increased cell apoptosis. Th17 cells produce IL-17 and IL-22 cytokines that trigger multiple inflammatory pathways. Th17 cells can also be converted to a Th1 cell phenotype. A disturbed Th17/Treg balance is thought to be responsible for the development of IBD. Th9 cells can promote the translocation of intestinal bacteria and inflammation of the intestinal mucosa by expressing the transcription factor PU.1 and the cytokine IL-9. CD8+ T cells can disrupt the intestinal epithelial barrier by releasing IFN-γ and TNF-α and increase mucosal inflammation. APCs: Antigen-presenting cells; CXCL10: C-X-C motif chemokine ligand 10; CCL25: Chemokine ligand 25; GALT: Gut-associated lymphoid tissue; IL: Interleukin; IFN-γ: Interferon-gamma; TNF-α: Tumor necrosis factor-alpha; Th: T helper; Treg: T regulatory cells.

Abnormal S1P signaling has been demonstrated in preclinical colitis models, suggesting that targeting S1P production or interaction with S1PRs may alleviate colitis and reduce disease severity[37-39]. Metabolomic analysis of colon biopsies from IBD patients has revealed transcriptional and metabolic changes in sphingolipid metabolism that are thought to influence inflammation and intestinal mucosal integrity[40].

The SphK/S1PR network has been associated with the induction of inflammation-related transcription factors, including NF-κB[41] and forkhead box O[42]. The SphK/S1P axis has been shown to mediate inflammatory responses, induced by various pro-inflammatory effectors such as IL-1β and TNF-α[43,44]. Immune responses mediated by monocytes and macrophages also activate SphK/S1P signaling. Human monocytes express all five S1PRs[45], which have been shown to regulate monocyte chemotaxis and apoptosis[46]. Macrophage recruitment and manifestation of their anti-inflammatory properties have been shown to be modulated by increased activity of SphK1[47] (Figure 2). Increased expression of SphK1 has been demonstrated in IBD animal models and in human colon tissue from IBD patients, where it mediated colon damage during intestinal inflammation[48]. The SphK1/S1P/S1P1 axis was suggested to be an important signaling link between NF-κB and STAT3 transcription factors in a colitis animal model, which may have a significant impact on the relationship between chronic inflammation and colitis-associated cancer[49]. A possible role of sphingosine phosphate lyase (SPL), which degrades S1P, has been highlighted in colon carcinogenesis. SPL is expressed in differentiated enterocytes, Paneth cells, and inflammatory cells[50] and has been shown to be downregulated in colon carcinomas, resulting in increased S1P levels in neoplastic intestinal tissue[51].

S1P is a second messenger involved in the regulation of various biological processes and cellular activities, including cell survival, differentiation, migration, proliferation, immune response, trafficking of T and B cells, and cancer pathogenesis[52]. S1P also has a significant impact on the barrier function of the intestinal epithelium, as it has been shown *in vitro* to increase the concentration of E-cadherin, an

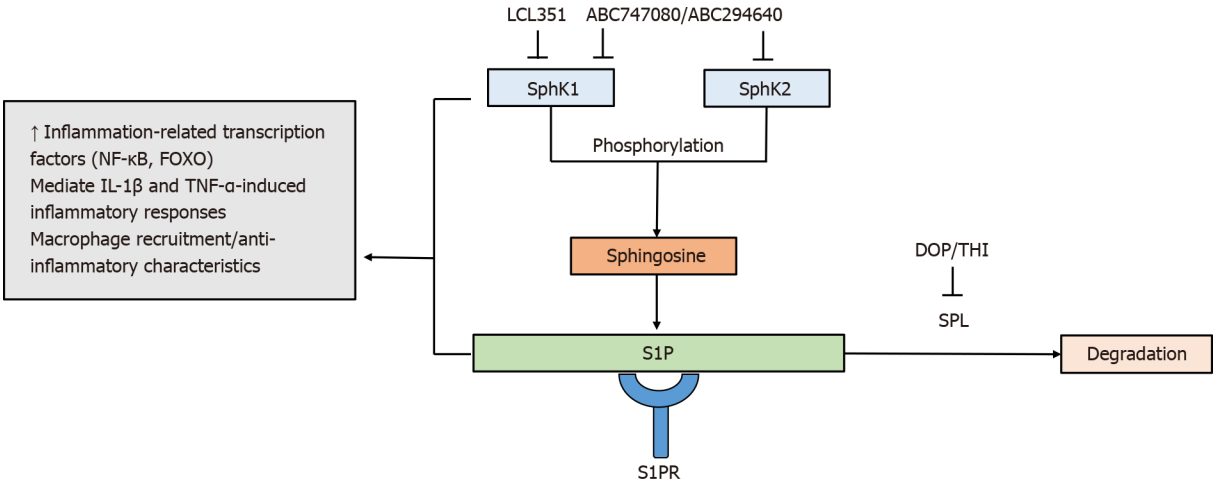

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Figure 2 Targeting sphingosine-1-phosphate metabolism by sphingosine-1-phosphate modulators. Sphingosine kinases (SphK1/SphK2) phosphorylate sphingosine to form sphingosine-1-phosphate (S1P). S1P degradation is mediated by sphingosine phosphate lyase. Components of S1P metabolism are involved in inflammatory responses. The SphK/S1P receptor network is associated with the induction of inflammation-related transcription factors, including nuclear factor-kappa B and forkhead box O. The SphK/S1P axis has been shown to mediate inflammatory responses induced by pro-inflammatory cytokines interleukin 1-beta and tumor necrosis factor-alpha. Increased activity of SphK1 modulates the recruitment of macrophages and the manifestation of their anti-inflammatory properties. S1P modulators targeting components of S1P metabolism contribute to the regulation of inflammatory immune responses. FOXO: Forkhead box O; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; NF-Kβ: Nuclear factor-kappa B; S1P: Sphingosine-1-phosphate; SPL: Sphingosine phosphate lyase.

important adherens junctions protein, thereby improving barrier integrity[53]. *In vitro* studies have also shown that S1P can improve intestinal barrier integrity by reducing TNF-α-dependent disruption[54]. S1P1 binds to S1PR1 to regulate the extravasation and migration of lymphocytes from peripheral lymphoid organs to other tissues. The controlled S1P/S1PR1-dependent mechanism is also responsible for preventing extensive trafficking of T lymphocytes into inflamed tissues after antigen-mediated T cell activation. The increased level of S1P in blood leads to the internalization of S1PR1, and the decrease in S1PR1 expression in lymph nodes and tissues allows T cells to interact with APCs[55]. The re-expression of S1PR1 on the surface of T lymphocytes after several hours causes them to migrate from the lymph node or tissue into the blood, where S1PR1 senses the increased S1P and regulates the transport of immune cells into the bloodstream[3]. Elevated S1P levels in colitis *in vivo* have been shown to activate the transcription factor STAT3 and the production of the NF-κB-regulated cytokine IL-6, initiating a signaling cascade that leads to the upregulation of S1PR1[56]. Increased levels of S1PR1 and SphK1 have been detected in the inflamed intestinal mucosa of patients with UC[57].

Small molecules acting as S1PR modulators can prevent lymphocyte invasion of inflamed tissues by the process described above. S1PR1 agonists can induce persistent lymphopenia by leading to internalization and subsequent ubiquitination and proteasome degradation of the receptor. This prevents lymphocytes from leaving the lymph node because they cannot recognize S1P levels[55,58]. S1P2 acts as a pro-inflammatory factor and, together with S1P3, mediates vascular and intestinal vasoconstriction and fibrosis[59], and S1P2-S1P3 activity has been linked to NF-κB signaling, which is involved in cytokine production, cell survival, and inflammation[60]. *In vitro* and *in vivo* experiments have shown that the S1PR2 receptor can promote proliferation of intestinal epithelial cells and increase cell permeability, possibly by regulating the expression of SphK2, HDAC1, HDAC2, and the extracellular signalregulated protein kinase 1/2 (ERK1/2) pathway. Suppression of S1PR2 in the dextran sodium sulfate-induced colitis model has been shown to ameliorate pathological damage in the colon[61]. Rodent colitis induced by deoxycholic acid (DCA) has been associated with enhanced induction of S1PR2, which together with DCA-stimulated ERK1/2 protein kinases and released lysosomal cathepsin B, mediates the activation of NLR family pyrin domain containing 3 inflammasome formation[62]. S1P/S1PRs (1-3) can induce the expression of inflammatory mediators in rat intestinal smooth muscle cells, including IL-1 and cyclooxygenase-2 (COX-2) through activation of the transcription factor early growth response protein 1 and IL-6 through activation of the transcription factor STAT3[63]. S1P4 has an immunosuppressive function by inhibiting cytokine secretion and cytokine-driven proliferation of effector T lymphocytes and promoting secretion of the anti-inflammatory cytokine IL-10[64]. Expression of S1P4R4 on dendritic cells is associated with dendritic cell migration and cytokine production[65]. Expression of S1PR4 on dendritic cells is also involved in the regulation of Th17 cells and the production of IL-27, which promotes Treg-mediated suppression of CD8+ cytotoxic T cells. Migration of neutrophils from inflamed tissues to draining lymph nodes is promoted by S1PR4[66]. S1P5 may have an impact on immune regulation, considering its expression on endothelial cells within the blood-brain barrier[52] and the link between S1P5 expression and regulation of natural killer cell number[67].

S1PRs have been highlighted as important research targets in IBD because they regulate leukocyte migration and differentiation, endothelial function, and their interaction with immune cells, contributing to the development of intestinal inflammation[68]. S1P signaling triggered by S1P binding to S1PR, has been shown to mediate and regulate pro-inflammatory responses, including the pro-inflammatory TNF-α pathway, which is currently a therapeutic target in IBD[5]. Sphingolipid-metabolizing enzymes (SphK1, SphK2) are expressed by all cells of the gastrointestinal tract as well as immune cells, and the SphK/S1P/S1PRs signaling axis mediates both normal and pathogenic inflammatory responses by influencing lymphocyte trafficking and activation of cytokine signaling. Novel agents acting as SphK inhibitors and S1PRs antagonists are being evaluated in preclinical and clinical studies for their effect in ameliorating SphK/S1P/S1PRs-mediated exacerbation of inflammation in IBD [5]. Expression of S1PR1 and SP1R4 on T cells and expression of S1PR2 on lymphatic endothelial cells (LECs) regulate the migration of T cells through LECs and into lymphatic vessels and lymph nodes. S1PR1 and S1PR4 act differently in modulating T cell motility and binding to the adhesion molecule vascular cell adhesion protein 1 (VCAM-1). Deficiency of S1PR4 has been associated with disruption of the composition of peritoneal B cell populations and decreased immunoglobulin A levels in inflammatory colitis *in vivo*[69]. S1RP2 expression is increased in vascular endothelial cells in response to microbial components and the pro-inflammatory cytokine TNF-α[70]. S1PR2 regulates the layer structure and permeability of LECs as well as the expression of adherens junction proteins *via* the ERK signaling pathway[71]. Activated S1PR3 has been shown to induce the expression of the enzyme COX-2, an inflammatory mediator, in vascular smooth muscle cells through its interaction with calcium-dependent protein kinase C and Src tyrosines[72]. Increased activation of COX-2 and high inflammatory intensity were associated with increased S1P formation in a colitis animal model[39]. The effect of SphK/S1P/S1PR signaling on linking chronic inflammation and cancer development in the gastrointestinal tract has highlighted the important role of S1PR modulators in malignancies in IBD[7]. FTY720, a SphK1 and S1PR inhibitor, was proposed as an anticancer agent in gastrointestinal cancer cells because it led to the deactivation of cancer-related downstream signaling pathways (ERK1/2, Act, c-Myc, β-catenin), which enhanced pro-apoptotic activity and tumor regression. FTY720 regulates inflammation by inducing S1PR degradation, inhibiting SphK1 activity and expression, and disrupting pro-inflammatory NF-κB/IL-6/STAT3 signaling[7]. S1PRs may be mediators of inflammatory responses in the tumor microenvironment by exerting functions on the transport and activity of innate immune system cells[8]. S1PR1 is associated with macrophage recruitment, apoptosis and anti-inflammatory responses, dendritic cell transport and inhibition of IFN-α secretion, neutrophil and eosinophil/mast cell recruitment, monocyte transport and natural killer cell egress from the lymph nodes. S1PR2 enhances antibody-mediated phagocytosis by macrophages and regulates monocyte migration. S1PR3 and S1PR4 regulate monocyte and neutrophil recruitment. S1PR3 is involved in dendritic cell-mediated maturation, promotion of Th1 response, and suppression of Tregs. S1PR5 is related to natural killer cell exit from the bone marrow and monocyte trafficking[8]. S1PR modulators tested in preclinical and clinical studies (*e.g.*, JTE013, mocravimod, amiselimod, ozanimod, etrasimod, FTY720) have shown a promising role as immunomodulators in the prevention of chronic inflammation and the treatment of inflammatory gastrointestinal cancers[8].

S1P/S1PR MODULATORS IN IBD: BIOLOGICAL MECHANISMS AND EFFECTS ON DISEASE COURSE

The development of oral small molecules targeting S1P/S1PR signaling and metabolism has shown great promise in the therapeutic area of IBD, followed by two decades of monoclonal antibodies. S1P modulators are advantageous in IBD therapy due to their low molecular weight, oral administration, low immunogenicity, rapid action, and inexpensive production. An important mechanism of action of S1P receptor modulators is that they antagonize S1P1 receptors on lymphocytes, thereby inhibiting their migration from secondary lymphoid organs to the periphery, resulting in a decrease in the number of circulating lymphocytes, including autoreactive T cells, thus causing immunomodulation[73]. Another indirect function of S1P drugs in IBD is to affect S1P metabolism by being able to inhibit the activity of components of S1P metabolism (Figure 2). Several novel selective S1P modulators are currently in development and are being evaluated for efficacy and safety profile in preclinical and clinical studies (Table 1 and Figure 3).

BIOLOGICAL FUNCTION OF S1P/S1PR MODULATORS AND PHASE OF CLINICAL DEVELOPMENT IN IBD

Amiselimod (MT-1303)

Amiselimod (MT-1303) is an oral selective modulator of the S1P1 receptor that is converted *in vivo* by

Table 1 Sphingosine-1-phosphate modulators and mechanism of action in inflammatory bowel disease

S1P modulator	Mechanism of action in IBD	Developmental phase	Ref.
Amiselimod (MT-1303)	Modulator of the S1P1 receptor→ S1P1; Internalization into lymphocytes→↓migration to the periphery; ↓Infiltration of pro-inflammatory Th1/Th17 cells into the colon; ↑Tregs in mesenteric lymph nodes	Phase IIa	[73-75]
Fingolimod (FTY720)	Specific inhibitor of S1PR1; Interferes with S1P signaling→↓lymphocyte entry into lymph nodes; ↑CD4+CD25+FOXP3+ T cells, ↑CD25, FOXP3 expression, Treg activity; ↑ Immunosuppressive cytokines IL-10 and TGF-β and CTLA-4→↑Treg-mediated immunomodulation; ↓Pro-inflammatory signaling (IL-12p70, Th1 cytokines); ↓Pro-inflammatory signals on dendritic cells→↑activity of CD4+CD25+ Tregs	Preclinical studies, not tested in humans	[76-83]
Etrasimod (APD-334)	Agonist of S1P1, partial agonist of S1P4/S1P5; Lymphopenia, ↓mucosal thickness, immune cell infiltration, expression of T-cell and monocyte markers; ↓Pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-17A, ↑anti-inflammatory IL-10	Phase II/III	NCT03996369, NCT03945188, NCT03950232, NCT04173273[84-86]
Ozanimod (RPC-1063)	Selective S1P1 and S1P5 receptor agonist; ↓T cell migration→↓peripheral lymphocytes↑S1P1 receptor internalization and degradation; ↓Circulating B and CCR7+ T lymphocytes→↓ inflammation; ↓Mononuclear cell infiltrate and mucosal thickness	Phase II/III	NCT03440385, NCT03464097, NCT03467958, NCT03440372[87-92]
KRP-203	Modulator of S1P1 receptor, partial agonist of S1PR3 receptor; Lymphopenia, ↑homing of lymphocytes to peripheral lymph nodes; ↓Infiltration of inflammatory cells in the lamina propria of the intestine; ↓CD4+ T and B220+ B cells in peripheral blood and in the lamina propria of the colon; ↓Peripheral naive and central memory CD4+ and CD8+ T cells and B cells; ↑Lymphocytes in mesenteric lymph nodes and spleen; ↓Pro-inflammatory cytokines IFN-γ, TNF-α, and IL-12 in the lamina propria of the colon	Phase II	[93-96]
LCL351	SphK1 inhibitor→↓S1P production; ↓Neutrophil infiltration into sites of inflammation, ↓ inflammatory marker TNF-α; Altered S1P levels and ↓neutrophil chemoattractants CXCL1 and CXCL2→↓leukocyte recruitment to sites of inflammation	Preclinical studies	[43,97]
ABC747080 and ABC294640	Inhibitors of SphKs→↓S1P formation, SphK activity; ↓TNF-α-induced activation of NF-Kβ; ↓ Effects of TNF-α on leukocyte recruitment and TNF-α- mediated increase in adhesion protein expression levels; ↓Pro-inflammatory cytokines (TNF-α, IL-1β, IFN-γ, IL-6) in colon tissue	Preclinical studies	[98]
DOP and THI	S1P lyase inhibitors; Peripheral lymphopenia, ↓CD4+ and CD8+ T cells; ↓Pro-inflammatory cytokines, including TNF-α, IL-6, IL-12, IFN-γ and IL-17; ↓S1PR1 expression on T lymphocytes; Depletion of late immature T cells (CD4+CD8+ double positive) and mature CD4+CD8- and CD4-CD8+ single positive cells	Preclinical studies	[99,100]
W-061	S1P receptor agonist; ↓Lymphocyte migration to the spleen and lamina propria, pro-inflammatory Th1 and Th17 cells in the lamina propria→ prevention of changes in intestinal mucosal architecture	Preclinical studies	[101]
SEW2871	S1P1 agonist; Mild inflammatory cell infiltration, ↓CD4+ T cells in the lamina propria of the colon; ↓Pro-inflammatory cytokines TNF-α and IFN-γ were significantly reduced in colonic tissues; Improved intestinal barrier function, ↑typical tight junction protein expression and distribution in the intestinal epithelium; ↓Apoptosis of intestinal epithelial cells→ restoration of colon tissue injury	Preclinical studies	[102,103]

CCR7: C-C chemokine receptor type 7; CTLA-4: Cytotoxic T-lymphocyte–associated antigen 4; CXCL: C-X-C motif chemokine ligand; FOXP3: Forkhead box P3; IBD: Inflammatory bowel disease; IFN-γ: Interferon-gamma; IL: Interleukin; NF-κB: Nuclear factor-kappa B; S1P: Sphingosine 1 phosphate; S1PR: Sphingosine 1 phosphate receptor; SphKs: Sphingosine kinases; TGF-β: Transforming growth factor-beta; Th: T helper; TNF-α: Tumor necrosis factor-alpha; Tregs: Regulatory T cells.

SphKs to its active metabolite MT-1303 phosphate (MT1303-P)[73]. The effect of MT-1303 on chronic colitis was studied in immunodeficient SCID mice induced by adoptive transfer of CD4+CD45RB^{high} T cells from BALB/c mice, an animal model for IBD. Oral administration of MT-1303 proved effective in the IBD mouse model and comparable to the effect of an anti-mTNF-α monoclonal antibody. MT-1303 significantly inhibited the infiltration of Th1 and Th17 cells into the colon by inducing the internalization of S1P1 into lymphocytes from lymph nodes and preventing their migration to the periphery. MT-1303 treatment also showed an effect on the migration of Tregs in normal mice by leading to an increased number of Tregs and an increased proportion of Tregs in mesenteric lymph nodes[74]. MT-1303 is currently enrolled and completed in a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase IIa study comparing amiselimod 0.4 mg administration to placebo over a 14-wk treatment period to evaluate safety, tolerability, and efficacy in patients with moderate-to-severe active Crohn's disease. MT-1303 treatment proved no better than placebo in eliciting a clinical response and was well tolerated, with no new safety concerns[75].

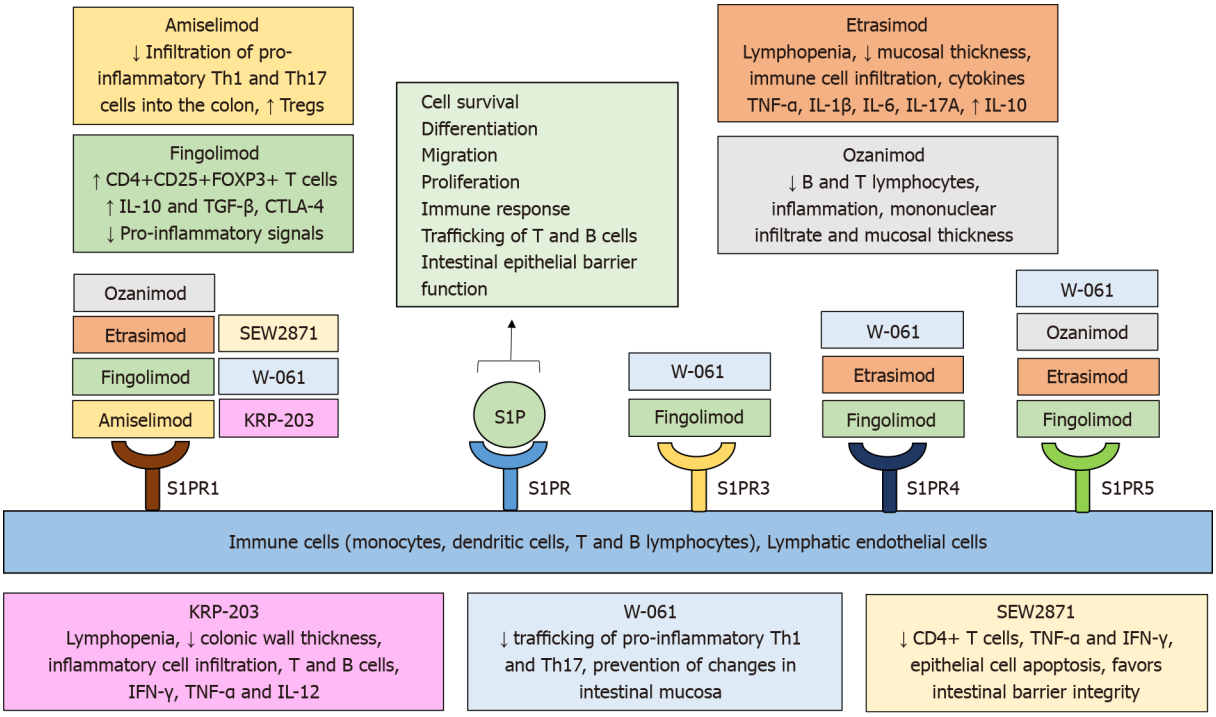

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Figure 3 Sphingosine-1-phosphate receptor modulators in preclinical and clinical studies in inflammatory bowel disease. Sphingosine-1-phosphate (S1P) receptors (S1PRs) have been highlighted as important research targets in inflammatory bowel disease (IBD). S1PRs are expressed on immune cells and lymphatic endothelial cells. Binding of S1P to S1PR regulates a variety of biological processes, including cell survival, differentiation, migration, proliferation, immune response, trafficking of T and B cells, and intestinal epithelial barrier function. Several novel, selective S1PR modulators are currently being tested in IBD and contribute to the amelioration of the inflammatory process in inflamed intestinal tissue by regulating immune cell concentration, activity, trafficking, and cytokine secretion, as well as intestinal barrier function and integrity. S1P: Sphingosine 1 phosphate; S1PR: Sphingosine 1 phosphate receptor; IBD: Inflammatory bowel disease; Th: T helper; Tregs: Regulatory T cells.

Fingolimod (FTY720)

Fingolimod (FTY720) is a specific inhibitor of S1PR1, which is a synthetic sphingosine analog (2-amino-2-2-(4-octylphenyl) ethyl-1,3-propanediol hydrochloride) of myriocin[76]. The main mechanism of action of FTY720 involves the induction of lymph node homing or sequestration of T cells. FTY720 is phosphorylated by SphK2[77] *in vivo*, and FTY720 phosphate can act as an S1P agonist that activates four of the five known G-protein-coupled S1PRs (S1P1, 3, 4, 5). S1PR1 and S1PR4 are mainly expressed on T and B lymphocytes. FTY720 interferes with S1P signaling, impeding lymphocyte entry into lymph nodes and thus delaying their subsequent return to the circulation[78]. FTY720 has not been shown to impair the activation, expansion, and differentiation of T cells to memory phenotypes, nor does it induce cell apoptosis[78-80]. FTY720 can effectively treat Th1-mediated colitis in mice by strongly affecting the activity of Tregs *in vivo*. Specifically, FTY720 administration in colitis mice was associated with increased numbers of CD4+CD25+FOXP3+ T cells and induction of CD25 and FOXP3 expression in CD4+ T cells. The immunosuppressive cytokines IL-10 and TGF-β, as well as CTLA-4, a receptor mediating the immunomodulatory function of Tregs, were also upregulated in the presence of FTY720. The therapeutic effect of FTY720 on ameliorating intestinal inflammation was associated with the downregulation of pro-inflammatory signals such as IL-12p70 and Th1 cytokines. It was suggested that FTY720-induced downregulation of pro-inflammatory signals on dendritic cells might contribute to the enhanced activity of CD4+CD25+ Tregs[81]. Although FTY720 has been approved by the Food and Drug Administration for the treatment of relapsing multiple sclerosis[82], it has not been tested in IBD patients because some adverse events (*e.g.*, elevated liver enzymes) have been noted[83].

Etrasimod (APD-334)

Etrasimod (APD-334) is a next-generation synthetic S1P receptor modulator that acts as a full agonist of human S1P1 and a partial agonist of S1P4 and S1P5[84]. Treatment with APD-334 in colitis mice resulted in dose-dependent lymphopenia, decreased mucosal thickness, and immune cell infiltration by significantly reducing the expression of T cell and monocyte markers. T cell and/or monocyte-derived proinflammatory cytokines TNF-α, IL-1β, IL-6, and IL-17A were also significantly reduced in APD-334-treated mice, and there was a dose-dependent increase in the anti-inflammatory cytokine IL-10 after APD-334 administration[85]. APD-334 has been enrolled in phase II/III clinical trials in patients with UC. In the Phase-2 OASIS study in patients with moderately-to-severely active UC with prior failure or

intolerance of conventional or biologic therapy, administration of 2 mg APD-334 resulted in significant improvement in clinical symptoms, followed by clinical remission and endoscopic improvement, with no serious life-threatening adverse events or death[86]. Moderately to severely active UC patients are currently enrolled in the ELEVATE phase III trial (NCT03996369, NCT03945188, NCT03950232). An ongoing phase II/III trial (CULTIVATE, NCT04173273) is recruiting 1265 patients with CD to evaluate the safety and efficacy of APD-334.

Ozanimod (RPC-1063)

Ozanimod (RPC-1063) is a small molecule, selective S1P1 and S1P5 receptor agonist. RPC-1063 can bind to S1P1 and S1P5 receptors, limiting the migration of T cells from peripheral lymphoid organs and reducing the number of peripheral lymphocytes[87]. The exact mechanism of action in alleviating IBD has not yet been determined. Administration of RPC-1063 in three models of autoimmune disease (experimental autoimmune encephalitis, 2,4,6-trinitrobenzenesulfonic acid colitis, and CD4+CD45RBhi T-cell adoptive transfer colitis) has shown that it induces internalization and degradation of the S1P1 receptor, leading to a reduction in circulating B and CCR7+ T lymphocytes[88], which in turn leads to a reduction in inflammation. The potential benefit of RPC-1063 for CD patients was also highlighted in a spontaneous ileitis mouse model, in which treatment with RPC-1063 resulted in a reduction in mononuclear infiltrate and mucosal thickness[89]. RPC-1063 has completed phase II/III clinical trials in patients with moderate to severe UC in which it demonstrated improved clinical, endoscopic and histologic outcomes, including reduction in rectal bleeding scores, maintenance of clinical remission, mucosal healing, histologic and durable remission. Based on the good safety profile and efficacy results, RPC-1063 was approved by regulatory authorities for the treatment of moderate to severe UC[90,91]. Histologic improvements, endoscopic remission, and a good safety profile were also reported in a phase II trial evaluating RPC-1063 in moderate-to-severe CD patients[92], and placebo-controlled phase III trials of RPC-1063 in patients with moderate-to-severe active CD are ongoing (NCT03440385, NCT03464097, NCT03467958, NCT03440372).

KRP-203 (2-amino-2-1,3-propanediol hydrochloride)

KRP-203 is a selective S1P1 modulator with a molecular structure similar to that of FTY720. Like FTY720, it induces lymphopenia by decreasing the number of lymphocytes in peripheral blood and promoting lymphocyte homing to peripheral lymph nodes[93]. KRP-203 is phosphorylated *in vivo* by SphK2. The phosphate metabolite (KRP-203 phosphate) is the active molecule that targets the S1P1 receptor and acts as a partial agonist for the human S1P3 receptor[94]. The treatment efficacy of KRP-203 in chronic colitis was investigated using a IL-10 gene-deficient (IL-$10^{-/-}$) mouse model. Mice treated with KRP-203 showed significantly reduced severity of colitis, reduced thickness of the colonic wall, reduced expansion of glandular crypts, and reduced infiltration of inflammatory cells in the lamina propria of the intestine. Administration of KRP-203 to colitis mice significantly decreased the number of CD4+T and B220+B cells in the peripheral blood and lamina propria of the colon and increased the number of lymphocytes in the mesenteric lymph nodes and spleen. After treatment with KRP-203 in colitis mice, the production of the pro-inflammatory cytokines IFN-γ, TNF-α, and IL-12 by lymphocytes in the lamina propria of the colon was significantly reduced[95]. KRP-203 was tested for its safety, tolerability, and efficacy in patients with moderately active 5-aminosalicylate-refractory UC, where it resulted in significant reductions in peripheral naive and central memory CD4+ and CD8+ T cells and B cells. KRP-203 was also found to be safe and well tolerated and resulted in clinical remission (NCT01375179)[96].

LCL351 (L-erythro-2-N-(1'-carboxamidino)-sphingosine hydrochloride)

LCL351 is a selective inhibitor of SphK1, which plays a role in S1P production. SphK1 can be activated in response to TNF-α and induce the expression of COX-2 and the production of prostaglandin E2[43]. SphK inhibitors, including LCL351, act *via* a two-way mechanism. They can either cause competitive inhibition of kinase activity or lead to proteolysis of SphK1. LCL351 showed efficacy in reducing inflammation in DSS-induced colitis in mice. LCL351 had a longer residence time in colon tissue than in blood without causing cell death. Treatment of colitis mice with LC351 blocked the infiltration of neutrophils into inflammatory sites and slightly attenuated the induction of TNF-α. The altered S1P levels mediated by LCL351, together with the reduction of neutrophil chemoattractants CXCL1 and CXCL2, may help prevent leukocyte recruitment to sites of inflammation and keep immune cells in the circulation[97].

ABC747080 (4-2-4-(4-chlorophenyl)thiazol-2-ylcarbamoyl-vinyl-2-methoxy-phenyl ester) and ABC294640 (3-(4-chlorophenyl)-adamantane-1-carboxylic acid (pyridin-4-ylmethyl)amide)

ABC747080 and ABC294640 are small molecules that act as selective inhibitors of SphKs and have been studied in mouse models of UC. These SphK inhibitors decreased cellular S1P formation in human endothelial cells and rat intestinal epithelial cells *in vitro* and caused a dose-dependent suppression of the activity of SphK. Treatment of fibroblasts with ABC294640 resulted in inhibition of TNF-α- induced NF-κB activation. Treatment with the SphK inhibitors ABC747080 or ABC294640 SphK *in vitro* was associated with attenuation of the effects of TNF-α on leukocyte recruitment, including TNF-α- mediated increases in adhesion protein (ICAM-1, VCAM-1) expression levels. Addition of ABC747080 or

ABC294640 to TNF-α-treated rat intestinal epithelial cells and human endothelial cell lines inhibited TNF-α-mediated induction of COX-2 activity, measured as production of PGE2. ABC294640 was also associated with decreased levels of pro-inflammatory cytokines (TNF-α, IL-1β, IFN-γ, IL-6) in colonic tissue of mice with colitis. The favorable modulation of inflammatory mediators, including S1P, NF-κB, TNF-α, VCAM-1, ICAM-1, COX-2, IL-1β, IFN-γ, and IL-6 by SphK targeting, suggests that the anti-IBD activity of SphK modulators is associated with SphK inhibition and decreased S1P synthesis[98].

DOP (4-deoxypyridoxine hydrochloride) and THI (2-acetyl-4-(tetrahydroxybutyl)imidazole) SPL inhibitors

DOP (4-deoxypyridoxine hydrochloride) and THI (2-acetyl-4-(tetrahydroxybutyl)imidazole) are small molecules that target S1P lyase (SPL), an enzyme that, together with phosphatases, tightly regulates S1P levels and keeps them low in tissues[99]. The potential anti-inflammatory effects of these SPL inhibitors on IBD were investigated in a TNF-driven mouse model of chronic ileitis with CD features. Mice treated with SPL inhibitors DOP and THI showed peripheral lymphopenia characterized by decreased numbers of CD4+ and CD8+ T cells. DOP treatment was also associated with a reduction in ileal mRNA transcripts of pro-inflammatory cytokines, including TNF, IL-6, IL-12, IFN-γ, and IL-17, resulting in attenuation of active (granulocytic) inflammation, chronic (lymphocytic/monocytic) inflammation, and overall inflammatory indices. DOP SPL inhibitor treatment resulted in downregulated S1PR1 surface expression on lymphocytes. DOP treatment was associated with promotion of thymic atrophy, depletion of late immature T cells (CD4+CD8+ double-positive) and mature CD4+CD8- and CD4-CD8+ single positive cells. It has therefore been suggested that the impairment of T cell maturation and thymic activity mediated by SPL inhibitors may significantly impair the anti-inflammatory effects of SPL inhibitors in IBD[100].

W-061

W-061 is an S1P receptor agonist that has been shown to bind all human S1P receptors except S1PR2. The therapeutic effect of W-061 on IBD was tested in a mouse model of DSS-induced colitis. Administration of W-061 to colitis mice suppressed the migration of lymphocytes to the spleen and lamina propria and induced their homing to secondary lymphoid tissues (mesenteric lymph nodes, Peyer's patches). Specifically, W-061 inhibited the migration of pro-inflammatory Th1 and Th17 cells into the lamina propria, prevented changes in intestinal mucosal architecture, and ameliorated the acute exacerbation of colitis[101].

SEW2871

SEW2871, a selective S1P1 agonist, was administered to IL10$^{-/-}$ colitis mice to investigate its function in alleviating chronic inflammation in IBD, as its protective effect on the development of colitis was demonstrated[102]. Treatment with SEW2871 resulted in mild infiltration of inflammatory cells, a reduced inflammatory score, and a decrease in CD4+ T cells in the lamina propria of the colon. The levels of pro-inflammatory cytokines TNF-α and IFN-γ were significantly reduced in the colon tissue of SEW2871-treated mice. A beneficial effect of SEW2871 on gut barrier function was also highlighted in this study. SEW2871 treatment prevented colonic permeability in IL-10$^{-/-}$ mice and promoted the typical expression and distribution of tight junction proteins in the intestinal epithelium. A possible beneficial effect of SEW2871 on the healing of colon tissue injury was observed, as SEW2871 reduced apoptosis of intestinal epithelial cells[103].

CONCLUSION

The development of IBD is mediated by dysregulated immune responses that initiate and maintain a vicious cycle of chronic inflammation. Understanding the immunopathogenesis of IBD is of great clinical importance for the development of effective therapeutics targeting these immunological pathogenic mechanisms. S1P modulators are orally administered small molecules that show promise in alleviating chronic inflammation and clinical symptoms in IBD patients. Their therapeutic efficacy is based on the fact that they regulate immune cell trafficking at sites of inflammation and are involved in immune cell interaction, cytokine production and pro-inflammatory signaling, as well as contributing to gut barrier function. The S1P receptor agonists etrasimod and ozanimod have shown favorable efficacy and safety profiles in UC and CD, patients respectively, and have significantly improved the clinical and endoscopic characteristics of IBD patients[104]. Ozanimod is being studied in ongoing phase III trials for CD (NCT03440372, NCT03440385, and NCT03464097) and UC (NCT02435992 and NCT02531126). Phase III trials (NCT03996369, NCT03945188, NCT03950232) are currently ongoing to evaluate etrasimod in patients with UC and a phase II-III trial (NCT04173273) is ongoing for etrasimod in CD. Although ozanimod has been proposed as first-line therapy in IBD, its appropriate positioning in the therapeutic algorithm for the treatment of UC treatment has not yet been defined, while its potential therapeutic activity in CD remains to be clarified[105]. KRP-203 has been shown to be safe and well tolerated in UC

patients without reaching the relevant threshold for efficacy, indicating the need for improved study design and recruitment of a larger population[96]. Determining the appropriate treatment duration of S1P modulators may pose another problem in their therapeutic use in IBD, considering that an increased risk of progressive multifocal leukoencephalopathy was observed during treatment with ozanimod and fingolimod, which was associated with a longer treatment duration in patients with multiple sclerosis[104,106,107]. The satisfactory efficacy and safety profile of S1P modulators in clinical trials, combined with their structure and advantageous production characteristics underscores their novel perspective for the treatment of IBD. Ongoing studies need to further elucidate their positioning within current treatment algorithms, their potential as combination therapies, and potential complications associated with their treatment regimens.

FOOTNOTES

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