

Sphingosine-1 Phosphate Receptor Modulators: The Next Wave of Oral Therapies in Inflammatory Bowel Disease

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Abstract: The armamentarium of medical therapy for inflammatory bowel disease (IBD) has expanded significantly during the past decade. A major change has been the introduction of novel, orally targeted, small molecule therapies, which are promising alternatives to traditional biomolecular drugs. Sphingosine-1 phosphate (S1P) receptor-modulating therapies are the newest class of oral small molecules to be approved by the US Food and Drug Administration (FDA) for the treatment of ulcerative colitis (UC) and are currently being studied in Crohn's disease. They work by targeting the interaction between S1P and S1P1 receptors, which regulate lymphocyte egress from the spleen and lymph nodes into the systemic circulation, thereby reducing intestinal inflammation in IBD. In May 2021, ozanimod was the first S1P receptor modulator approved by the FDA for the treatment of moderately to severely active UC. This article summarizes the mechanism of action, efficacy, and safety of S1P receptor modulators based on currently available clinical studies as well as examines practical considerations and positioning in treating patients with UC.

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic, inflammatory diseases that affect the gastrointestinal tract and usually require lifelong therapy. Historically, these diagnoses have carried a poor prognosis, but there have been significant improvements in both understanding of the disease processes as well as therapeutic approaches. Although there remains no curative therapy, the mainstay of medical therapy involves using immunosuppression and immunomodulation to induce remission and improve quality of life. The introduction of anti-tumor necrosis factor (TNF) therapies in the late 1990s revolutionized the realm of medical therapy. Following the initial approval of infliximab, multiple intravenous and subcutaneous biologic agents have joined the medical armamentarium.¹⁻³

In May 2021, ozanimod (Zeposia, Bristol Myers Squibb) was the first sphingosine-1 phosphate (S1P) receptor modulator approved by the US Food and Drug Administration (FDA) for the treatment of moderately to severely active UC.⁴ This article discusses the mechanism of action, efficacy, and safety of S1P receptor-modulating therapies as well as considers their appropriate positioning in treating patients with UC.

Keywords

Sphingosine-1 phosphate receptor modulators, ozanimod, ulcerative colitis, inflammatory bowel disease, Crohn's disease, small molecule therapies

Table 1. Expression, Function, and Clinical Relevance of S1P Receptor Subtypes

	Expression ⁸	Biologic Outcomes ⁸	Clinical Relevance ⁸	Targeted Therapies
S1P1	Broad, including B, T, and dendritic cells, endothelium, cardiac tissue, and neurons	Lymphocyte migration, dendritic cell migration, vascular barrier function, bradycardia, nociception, proliferation	Autoimmune modulation, bradycardia, tumor maintenance	Fingolimod, ozanimod, etrasimod
S1P2	Broad, including vascular smooth muscle, endothelium, cardiac tissue, lung fibroblasts, and tumor cells	Vasoconstriction, inflammation, fibrosis, inhibition of B-cell survival, proliferation	Renal injury, fibroblast contraction, tumor maintenance	Fingolimod
S1P3	Broad, including vascular smooth muscle, endothelium, cardiac tissue, and lung fibroblasts	Vasoconstriction, fibrosis, proliferation	Hypertension, tumor maintenance	Fingolimod
S1P4	Restricted; T cells, dendritic cells, breast cancer cells	Inhibition of effector cytokines, secretion of IL-10	Autoimmune modulation	Fingolimod, etrasimod
S1P5	Restricted; natural killer cells, endothelial cells, oligodendrocytes	Natural killer cell migration, blood-brain barrier integrity, oligodendrocyte function	Autoimmune modulation, myelination	Fingolimod, ozanimod, etrasimod

Modified from Peyrin-Biroulet et al.⁸

IL, interleukin; S1P, sphingosine-1 phosphate.

Leukocyte Trafficking

Altered leukocyte recruitment is recognized as a key contributor to chronic inflammation in the pathogenesis of inflammatory bowel disease (IBD). There are multiple molecules that regulate the trafficking of leukocytes out of lymph nodes and into sites of inflammation in the gastrointestinal tract. One target is the $\alpha_4\beta_7$ integrin, a glycoprotein residing on the surface of T- and B-cell lymphocytes that interacts with mucosal addressin-cell adhesion molecule 1 on intestinal vasculature, allowing for efflux of lymphocytes into the intestine.⁵ Vedolizumab (Entyvio, Takeda), a humanized monoclonal antibody specific for the $\alpha_4\beta_7$ integrin, allows for selective gut blockade of lymphocyte trafficking and is currently a widely used therapeutic modality for both induction and maintenance of remission in both CD and UC.^{6,7}

Sphingosine-1 Phosphate Receptor Modulators

S1P is a membrane-derived lysophospholipid signaling molecule that primarily functions through the activation of 5 cell-surface G protein-coupled receptors

(S1P1-S1P5; Table 1).^{8,9} S1P1, S1P2, and S1P3 are widely expressed throughout the body, and S1P4 and S1P5 are expressed in more limited tissues, mainly the lymphoid, hematopoietic, and central nervous system tissues.^{10,11} S1P1 is the most ubiquitous S1P receptor, as it is expressed on endothelial cells and lymphocytes.¹² The interaction between S1P and S1P1 regulates lymphocyte egress from the spleen and lymph nodes into the systemic circulation.¹³ Targeting this interaction, S1P receptor modulators bind to the S1P receptors and therefore keep them intracellular. This process of receptor internalization prevents the cell surface agonist from signaling, and in turn causes degradation of S1P inside the cells. The overall effect of reduced lymphocyte egress results in fewer circulating lymphocytes in the blood, leading to decreased inflammation and tissue damage.¹⁴

The first S1P receptor modulator developed for the treatment of inflammatory conditions was the nonselective S1P receptor modulator fingolimod for the treatment of relapsing-remitting multiple sclerosis (MS). Fingolimod was approved by the FDA in 2010 for MS after multiple clinical trials showed reduction in both clinical symptoms and brain-volume loss on magnetic resonance imaging.^{15,16} With oral administration of fingolimod,

there is a rapid reduction of peripheral blood lymphocytes without any activity on effector memory C-C chemokine receptor 7–negative T cells, allowing for a selective immunomodulatory effect. Adverse events (AEs) such as bradyarrhythmias, atrioventricular blocks, basal cell carcinoma, and respiratory and liver injuries have been attributed to the effects of fingolimod's pan-S1P receptor antagonism.¹⁷ There are ongoing multiple trials for the evaluation of more selective S1P receptor modulators with the expectation of fewer AEs.

Within the realm of IBD, 2 S1P receptor modulators, ozanimod and etrasimod, have been developed. Ozanimod is an S1P receptor modulator that is selective for the S1P1 and S1P5 receptors, which are located on endothelial cells and oligodendrocytes, respectively, whereas etrasimod is selective for the S1P4 receptor in addition to the S1P1 and S1P5 receptors.¹⁸ At a dose of 1 mg ozanimod daily, overall lymphocyte suppression was demonstrated in approximately 65% of healthy adults and approximately 50% of patients with MS and IBD. Similarly, at a dosage of 2 mg etrasimod daily, lymphocyte suppression was noted in 60% of healthy adults and 40% of patients with MS and IBD. This reduction normalized upon cessation of the drug within 3 days to 3 months in ozanimod-treated patients and within 7 days in patients who received etrasimod. The quicker lymphocyte recovery time can be attributed to the shorter half-life of etrasimod (approximately 33 hours) compared with ozanimod (approximately 20 hours, but with a half-life of active metabolites of 11 days).

Ozanimod

The efficacy of ozanimod for induction and maintenance for moderately to severely active UC was examined in the phase 2 TOUCHSTONE trial.¹⁹ This was a double-blind, placebo-controlled trial of 197 adults with moderately to severely active UC, defined as a Mayo score of 6 to 12 and endoscopic subscore of 2 or 3, conducted at 57 centers in 13 countries. Patients were randomly assigned in an equivalent ratio to receive placebo, ozanimod 0.5 mg, or ozanimod 1 mg for 32 weeks. Enrolled patients could be on stable doses of oral 5-aminosalicylates or prednisone (≤ 30 mg per day) but had discontinued biologic agents or azathioprine, mercaptopurine, or methotrexate at least 5 half-lives prior to starting the trial regimen.

The primary outcome was clinical remission at 8 weeks, defined as a Mayo score of 2 or less with no individual subscore greater than 1.¹⁹ The higher ozanimod dose at 1 mg daily met the primary outcome with 16% of patients achieving clinical remission, as compared with placebo at 6% ($P=.048$). This difference was not statistically significant in the lower dosing arm of 0.5 mg ($P=.14$), although 14% of those patients did achieve clinical remission.

Clinical response, defined as a reduction from baseline in the Mayo score of 30% or greater and at least 3 points as well as a decrease in rectal bleeding subscore of at least 1 point or a stool frequency subscore of 1 or less, was reached in 57% of patients taking ozanimod 1 mg and 54% of patients taking ozanimod 0.5 mg, as compared with 37% of patients on placebo ($P=.02$ and $P=.06$, respectively).¹⁹ Mucosal healing at week 8, defined as an endoscopy subscore of 1 point or less, was noted in 34% of patients on ozanimod 1 mg daily and 28% of patients on ozanimod 0.5 mg daily, as compared with 12% of patients on placebo ($P=.002$ and $P=.03$, respectively). Histologic remission at week 8, defined as a Geboes Score (GS) less than 2, was achieved in 22% of patients on ozanimod 1 mg daily and 14% of patients on ozanimod 0.5 mg daily, as compared with 11% of patients on placebo ($P=.07$ and $P=.63$, respectively).

At week 32, clinical remission was demonstrated in 21% of patients on ozanimod 1 mg, 26% of patients on ozanimod 0.5 mg, and 6% of patients on placebo ($P=.1$ and $P=.002$, respectively).¹⁹ Of the 11 patients in the ozanimod 1 mg group who achieved clinical remission at week 8, 5 patients maintained remission at week 32. The maintenance outcomes at 32 weeks were exploratory and therefore had nominal and not significant P values.

True North was the subsequent, placebo-controlled, phase 3 clinical trial that evaluated the efficacy of ozanimod as induction and maintenance therapy in adult patients with moderately to severely active UC.²⁰ The study population consisted of 645 patients randomized in a 2:1 fashion to ozanimod 1 mg daily or placebo. These were adult patients who had moderately to severely active UC (defined as a Mayo score 6–12, endoscopic subscore ≥ 2 , rectal bleeding subscore ≥ 1 , and stool frequency subscore ≥ 1) and were not receiving any biologic or immunomodulator therapy other than stable oral 5-aminosalicylates, prednisone 20 mg or less daily, or budesonide multimatrix, which would be continued throughout the induction period.

The primary outcome was clinical remission, defined as a rectal bleeding score of 0, a stool frequency score of 1 or less and at least a 1-point reduction from baseline, and a mucosal endoscopy subscore of 1 or less without friability.²⁰ At week 10, significantly more patients achieved clinical remission with ozanimod compared with placebo (18.4% vs 6.0%; $P<.0001$). Additionally, patients in the ozanimod treatment group had significantly higher improvement in all key secondary endpoints, which included clinical response (47.8% vs 25.9%; $P<.0001$), endoscopic improvement (27.3% vs 11.6%; $P<.0001$), and mucosal healing (12.6% vs 3.7%; $P<.001$). In the group of patients who had prior exposure to TNF inhibitors, 36.9% of patients on ozanimod vs 18.5% of patients

on placebo achieved clinical response ($P=.0008$) but not clinical remission (10% ozanimod vs 4.6% placebo; $P=.195$).

Through a post hoc analysis of the randomized induction phase, the onset of action of ozanimod was evaluated by assessing time to improvement of clinical symptom scores (rectal bleeding scores and stool frequency scores) as well as the inflammatory biomarkers fecal calprotectin and C-reactive protein.²¹ Clinical symptom scores were obtained at baseline and at each weekly study visit for weeks 2 through 10. Improvement in symptoms was observed as early as 2 weeks in the ozanimod group, and this trend was maintained through week 10. Biochemical markers showed a similar reduction at weeks 5 and 10 in the ozanimod group.

After the 10-week induction period, patients with clinical response were rerandomized 1:1 to ozanimod 1 mg daily or placebo with the aim of studying efficacy in maintenance therapy at week 52.²² The primary endpoint of clinical remission at week 52 was reached in 37% of patients in the ozanimod treatment group compared with 18.5% in the placebo group ($P<.0001$). The secondary endpoints of clinical response (60% vs 41%; $P=.0001$), endoscopic improvement (45.7% vs 26.4%; $P<.001$), corticosteroid-free clinical remission (31.7% vs 16.7%; $P<.001$), and mucosal healing (29.6% vs 14.1%; $P<.001$) were all achieved in the ozanimod treatment group when compared with placebo. In the group of patients who had prior TNF inhibitor exposure (31% of the study population), both clinical remission and clinical response were statistically significant in the ozanimod treatment group compared with placebo at week 52.²³

The phase 2, uncontrolled, multicenter STEPSTONE trial investigated the efficacy and safety of ozanimod induction therapy in patients with moderately to severely active CD.²⁴ Sixty-nine patients, including more than one-half with previous biologic exposure, were included. At week 12, clinical remission, defined by a Crohn's Disease Activity Index of less than 150 points, was observed in 39.1% (95% CI, 27.6%-51.5%) of patients. Sixteen patients (23.2%; 95% CI, 13.9%-34.9%) also experienced endoscopic response as assessed by the Simple Endoscopic Score for Crohn's Disease. There were also notable reductions in histologic activity as assessed by the GS and the Robarts Histopathology Index. Multiple phase 3 studies currently underway are investigating the safety and efficacy of ozanimod in patients with CD (NCT03440372, NCT03464097, NCT03440385, and NCT03467958).²⁵⁻²⁸

Adverse Events In the phase 2 TOUCHSTONE trial, absolute lymphocyte counts in blood decreased from baseline by a mean of 49% in patients who received

ozanimod 1 mg and 32% in patients who received ozanimod 0.5 mg by week 8 of treatment.²⁹ Of patients receiving ozanimod 1 mg, 53% had absolute lymphocyte counts lower than normal range, with most patients having grade 1 or 2 reduction and 13% of patients with grade 3 reduction (200-499/mm³ lymphocytes). There were no patients with grade 4 lymphopenia.

No differences in significant AEs were noted between the 2 treatment groups and placebo in the initial induction study.²⁹ Key AEs noted in the ozanimod groups included 1 patient in the ozanimod 0.5 mg group developing first-degree atrioventricular block and sinus bradycardia on day 8 that was asymptomatic and self-resolved without intervention. Of note, this patient had evidence of preexisting bradycardia prior to ozanimod treatment. Additionally, 4 patients in the treatment group (3 patients on ozanimod 1 mg and 1 patient on ozanimod 0.5 mg) had an increase in alanine aminotransferase (ALT) level of more than 3 times the upper limit of normal (ULN).

In the open-label extension of the TOUCHSTONE study, which had a mean exposure of 2.8 person-years, no long-term safety signals were associated with ozanimod.³⁰ The most reported serious AEs were worsening UC (6 patients), anemia (2 patients), and ischemic stroke (2 patients), none of which were considered to be related to the study treatment. Despite reduction in lymphocyte counts in 9 patients, there were no instances of serious or opportunistic infections associated with these events. Only 10% of patients discontinued the study because of a treatment-related AE.

During the True North phase 3 induction period, the most common treatment-emergent AEs (TEAEs) with ozanimod compared with placebo were anemia (4.2% vs 5.6%), nasopharyngitis (3.5% vs 1.4%), and headache (3.3% vs 1.9%).^{20,31} The overall rates of serious TEAEs were similar between the ozanimod and placebo groups (4% vs 3.2%). During the maintenance period, the most common TEAEs were increased ALT, headaches, nasopharyngitis, arthralgia, and increased γ -glutamyl transferase levels. Despite elevations in these liver enzymes, there were no events of serious or severe hepatic injury within the maintenance period of 52 weeks. There was 1 occurrence of macular edema in a patient who had risk factors at baseline, which resolved after discontinuation of the drug. The rates of TEAEs leading to treatment discontinuation were similar in the ozanimod and placebo groups (2.6% vs 1.3%, respectively).

In the STEPSTONE CD study, similar AEs were noted, with CD flare being the most common and occurring in 18 (26%) patients.²⁴ TEAEs of special interest included 2 patients who developed herpes zoster infection classified as mild, and severe sepsis in a patient

Table 2. Practical Clinical Considerations With Ozanimod

<p>Contraindications</p> <ul style="list-style-type: none"> • History of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or class III or IV heart failure within the past 6 months • Presence of Mobitz type II second-degree or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker • Severe, untreated sleep apnea • Concurrent use of a monoamine oxidase inhibitor
<p>Baseline Clinical Assessment Prior to Drug Initiation</p> <ul style="list-style-type: none"> • Complete blood count (including lymphocyte count) • Liver function tests • Electrocardiogram to screen for any preexisting conduction abnormalities • Varicella zoster virus antibodies (if negative, vaccination prior to initiation) • Ophthalmic evaluation if prior history of macular edema or uveitis, or any risk factors
<p>Dosing</p> <ul style="list-style-type: none"> • Initiated as a 7-day titration pack, starting with 0.23 mg once daily for days 1-4, then subsequent 0.46 mg once daily for days 5-7, until maintenance dose of 0.92 mg daily is reached at day 8 and continued thereafter • If a dose is missed during the first 2 weeks of treatment, reinitiation with the titration pack is recommended. If a dose is missed after the first 2 weeks of treatment, continue maintenance treatment as planned
<p>Follow-Up Monitoring</p> <ul style="list-style-type: none"> • Monitor liver function tests and complete blood count (including lymphocyte counts)

with small intestinal fistula who eventually died. There were liver enzyme abnormalities 3 or more times above the ULN in 5 patients, none of whom required treatment discontinuation. There were no clinically relevant changes in heart rate.

Safety Considerations Based on these data, as well as prior data from studies in MS, there are several safety considerations with the use of ozanimod, as outlined by the FDA.³² Prior to initiation of ozanimod, the following assessments are advised in all patients: complete blood count (including lymphocyte count), electrocardiogram to screen for any preexisting conduction abnormalities, and liver function tests. In patients with a history of uveitis or macular edema, an ophthalmic assessment, including evaluation of the fundus and macula, should be performed. Antibodies for varicella zoster virus should be assessed and, if negative, vaccination is recommended prior to starting ozanimod (Table 2).

Ozanimod is contraindicated in patients who, in the past 6 months, have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or class III or IV heart failure. Additional cardiac contraindications

include patients with the presence of Mobitz type II second-degree or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker. Severe untreated sleep apnea and concurrent use of a monoamine oxidase inhibitor are also contraindications.

Etrasimod

Etrasimod is another S1P receptor modulator that is currently being evaluated in the ELEVATE UC 52 phase 3 clinical trial for efficacy in induction and maintenance in moderate-to-severe UC.³³ Previously, the phase 2 proof-of-concept OASIS trial in adults with moderate-to-severe UC yielded promising results.³⁴ Patients were randomized in a 1:1:1 ratio to etrasimod 1 mg daily, etrasimod 2 mg daily, or placebo for 12 weeks. The primary endpoint was an increase in the mean improvement of modified Mayo score from baseline to week 12. Secondary endpoints included endoscopic improvement (subscores of 1 or less) from baseline to week 12. At week 12, only the etrasimod 2 mg group achieved the primary endpoint, leading to a significantly greater increase in mean improvement in modified Mayo score from baseline compared with placebo (difference from placebo, 0.99 points; 90%

CI, 0.30-1.68; $P=0.009$). Endoscopic improvement was achieved in 41.8% of patients who received etrasimod 2 mg compared with 17.8% of patients receiving placebo ($P=0.003$). Three patients had a transient, asymptomatic, low-grade atrioventricular block on day 1 that resolved spontaneously, and all 3 patients had prior evidence of atrioventricular block.

In the open-label extension study, among patients who had clinical response, clinical remission, or endoscopic improvement in the initial induction double-blind study, these treatment effects were maintained at the end of the extension period for most patients.³⁵ In terms of safety, the most common TEAE was worsening UC. One patient experienced a TEAE of bradycardia that did not lead to medication discontinuation. There were no treatment-related serious infections, and no new safety signals were observed.

There is currently an ongoing phase 2/3 study evaluating the efficacy, safety, and tolerability of etrasimod in adults with moderately to severely active CD who have been refractory to at least 1 prior therapy (NCT04173273).³⁶

Conclusion

The phase 2 and 3 trials of ozanimod and the phase 2 trial of etrasimod demonstrate efficacy in induction and maintenance of response and remission for moderately to severely active UC, with corresponding endoscopic and histologic improvements. These medications are oral, rapid-acting, once-daily tablets that provide an alternative disruptive mechanism of action to the currently available therapies. As with other therapies, TNF inhibitor-naïve patients have improved response compared with TNF inhibitor-exposed patients. Therefore, these S1P receptor modulators could be positioned as a first-line drug option for moderately to severely active UC when 5-aminosalicylates are inadequate. Although there are multiple safety considerations, pretreatment screening and continued follow-up can minimize any risks, and the overall safety profile remains favorable based on comparable AEs in placebo groups in the clinical trials.

Disclosures

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