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S1PR MODULATORS IN THE MANAGEMENT OF ULCERATIVE COLITIS: CONSIDERATIONS FOR PRACTICE

KEY TAKEAWAYS

- Data support S1PR modulators as effective therapies for the management of patients with moderate-to-severe UC
- They are safe, non-immunogenic, once daily oral therapies
- More head-to-head trials are needed to optimally place S1PR modulators in the treatment algorithm for UC

Introduction

Sphingosine-1-phosphate receptor (S1PR) modulators are novel oral small-molecule therapies that offer a unique profile compared to other advanced therapies in the treatment of ulcerative colitis (UC), including oral administration, linear pharmacokinetic profiles, reduced immunogenicity, and lower costs associated with manufacturing.[1]

The activation of S1P G-protein coupled receptors plays an inflammatory role in UC by promoting lymphocyte egress from lymphoid organs into circulation and colonic mucosa. S1PR modulators lead to internalization and degradation of these receptors, thereby reducing inflammation. Ozanimod was the first S1PR modulator approved for treating moderately-to-severely active UC and is also approved for multiple sclerosis. More recently, a second agent, etrasimod, was approved for UC. Etrasimod acts on different S1PR subtypes to avoid off target vascular and cardiac effects, has no up-titration regimen during initiation, a shorter half-life and less propensity for drug interactions. This review summarizes clinical trial and real-world data and provides guidance on the clinical uses of S1PR modulators.

Mechanism of Action of Sphingosine-1-Phosphate Receptor Modulators

S1PRs are G protein-coupled receptors that regulate immune cell trafficking. Among the five S1PR subtypes, S1PR1 is the most relevant for UC management. Sphingosine-1-phosphate (S1P) is a lipid signalling molecule that binds to S1PR1 on lymphocytes, facilitating their exit from lymphoid organs into the circulation. This leads to excessive lymphocyte migration into the intestinal mucosa as demonstrated in **Figure 1**.

Ozanimod is a selective agonist for S1P1 and S1P5 receptors which promotes S1P1 receptor internalization and degradation, decreasing T-cell migration from lymphoid organs. This results in a reduction of circulating B cells and CCR7+ T lymphocytes, thereby diminishing inflammation, mononuclear cell infiltration, and mucosal thickness. Certain traditional and advanced immune suppressive therapies affect multiple immune cell types and functions. S1PR modulators target lymphocyte egress as opposed to their function and their selective targeting of lymphocyte cells reduces the potential to develop certain toxicities and malignancies associated with other treatments. The current generation of S1PR modulators also has significantly less systemic side effects relative to previous generations. **Table 1** outlines various S1PR receptor subtypes, locations and their functions.[1,2]

Etrasimod is an S1PR modulator that selectively activates S1PR1, S1PR4, and S1PR5 with no activity on S1PR2 or S1PR3. By avoiding S1PR2, it prevents off target vascular side effects such as vasoconstriction. In addition, avoiding S1PR3 reduces the risks of bradycardia and hypertension, ensuring cardiovascular safety.[3]

Selective S1PR modulators, such as ozanimod and etrasimod, specifically target S1PR1 to prevent lymphocytes from exiting lymphoid tissues and infiltrating into the gut mucosa. This action decreases intestinal inflammation.[2] Unlike broad immunosuppressive therapies, S1PR modulators offer a targeted mechanism, minimizing systemic immune suppression while effectively controlling localized inflammation in the gastrointestinal tract. This makes them an attractive therapeutic option for patients with moderate-to-severe UC, who require long-term management of inflammation while limiting systemic side effects.

Efficacy of Ozanimod

In the phase 2 TOUCHSTONE trial, 197 adults with UC were randomly assigned to receive either a placebo, ozanimod 0.5 mg, or ozanimod 1 mg. The study's primary endpoint was clinical remission, defined as a Mayo score ≤2 without any individual subscore > 1 at 8 weeks.

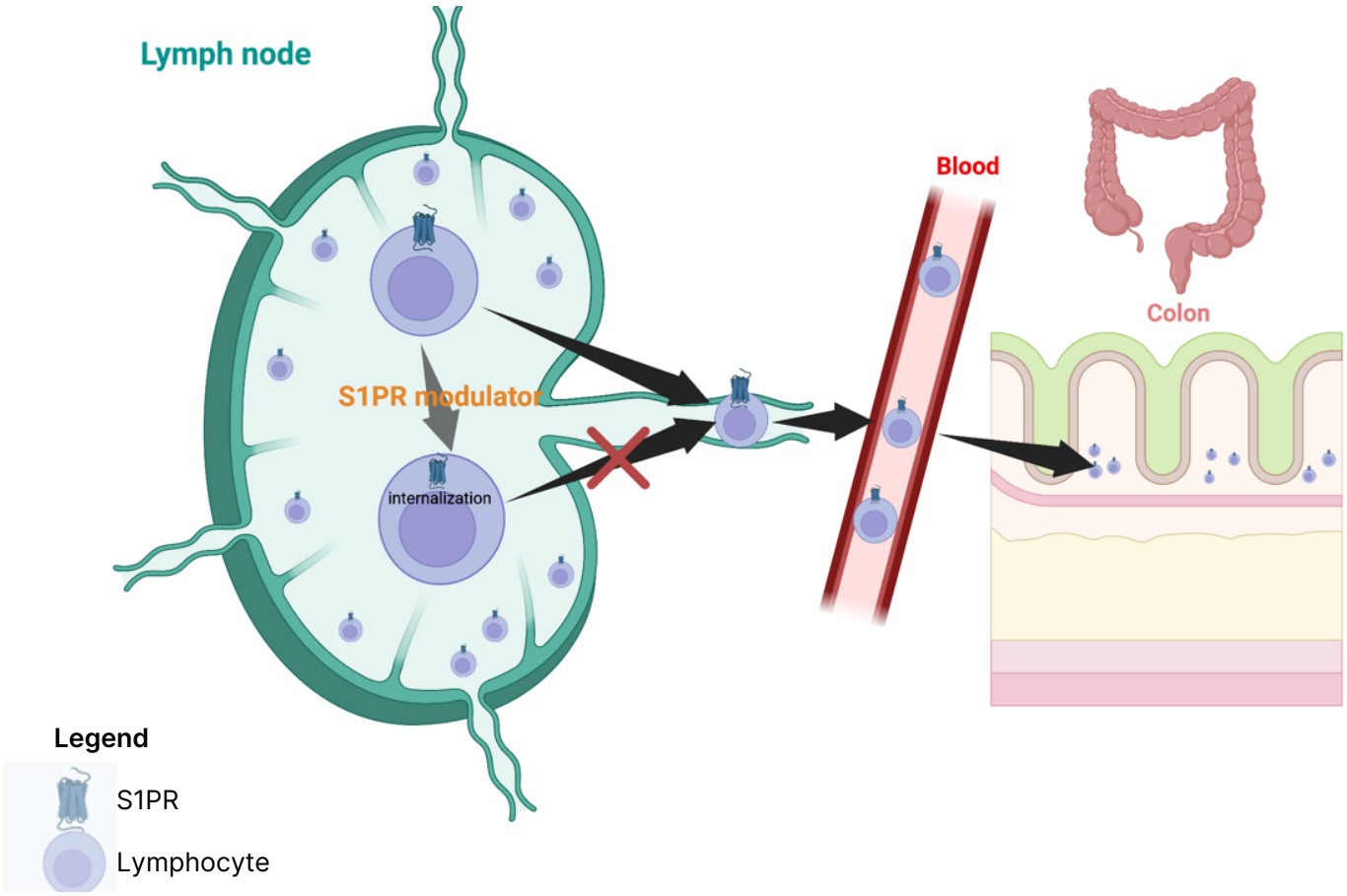

Figure 1: Mechanism of action of S1PR modulators; *courtsey of BioRender. Hass, A. (2024) BioRender.com/b88y627*

At week 8, 16% of patients on ozanimod 1 mg achieved clinical remission compared to 6% on placebo (P=.048). Additionally, 57% of the 1 mg group showed a clinical response vs. 37% in the placebo group. Mucosal healing was observed in 34% of patients on ozanimod 1 mg compared to 12% on placebo (P=.002).[4,5]

In the phase 3 True North trial, the primary endpoint of clinical remission was assessed at week 10 for the induction period and week 52 for the maintenance period. Clinical remission was defined using the three-component Mayo score (rectal bleeding subscore of 0, stool frequency subscore of ≤1 with a decrease of at least 1 point from baseline, and an endoscopy subscore of ≤1). At 10 weeks, remission was achieved in 18.4% of patients on ozanimod compared to 6% on placebo (P<0.0001). Secondary endpoints included clinical response (based on three-component Mayo subscore), endoscopic improvement (endoscopic subscore ≤1 without friability), and mucosal healing (endoscopic improvement plus histologic remission with mucosal endoscopy score of ≤1 and a Geboes score of <2). All secondary endpoints were significantly improved in the ozanimod group. The True North trial also showed sustained efficacy over time, with 37% of patients on ozanimod in clinical remission at week 52, compared to 18.5% in the placebo group (*P*<0.0001). This remission was accompanied by significant improvements in key secondary endpoints such as endoscopic improvement in the ozanimod group compared to placebo (45.7% vs. 26.4%; *P*<0.001) and corticosteroid-free clinical remission (31.7% vs. 16.7%; *P*<0.001).[4,6]

Efficacy of Etrasimod

The phase 2 12-week OASIS trial evaluated the efficacy of 2 mg of etrasimod in 156 patients with moderate-to-severe UC. The primary endpoint, which included improvements in Mayo Clinic scores (stool frequency, rectal bleeding and endoscopic appearance) was reached, along with endoscopic improvement.[7] In a 52-week open-label extension of this trial, 2 mg of etrasimod showed a 64% clinical response, 33% clinical remission, and 43% endoscopic improvement. This included patients who were on placebo during the original 12-week trial. Numerous patients who achieved a clinical response at 12 weeks maintained these benefits, while 22% of all patients achieved steroid-free remission.[8]

This was followed by two double-blind phase 3 trials, ELEVATE UC 52 and ELEVATE UC 12. The primary endpoints of ELEVATE 52 were clinical remission at weeks 12 and 52. This trial used a treat-through trial design, comprising a 12-week induction

S1P Receptor Subtype	Primary Locations	Functions
S1PR1	Immune cells, endothelial cells, nervous system	Regulates lymphocyte egress from lymph nodes, vascular stability, and endothelial cell barrier integrity. Involved in immune cell migration.
S1PR2	Brain, endothelial cells, smooth muscle cells	Modulates vascular tone and endothelial permeability; influences brain and cardiovascular function. Plays a role in inflammatory responses.
S1PR3	Immune cells, heart, lungs, kidneys, vascular smooth muscle cells	Involved in inflammatory and immune responses, heart rate regulation, and vascular tone. Higher expression in organs involved in hemodynamic control.
S1PR4	Immune cells, especially in lymphoid tissues	Predominantly found in immune cells like T and B lymphocytes. Plays a role in immune regulation and modulation of inflammatory responses.
S1PR5	Central nervous system (CNS), especially oligodendrocytes; some expression in spleen and natural killer (NK) cells	Important in neural development, especially in myelination; involved in oligodendrocyte survival and function. Also plays a role in immune responses.

Table 1: Cell locations of various S1PR subtypes and reception functions; *courtsey of* Aaron Hass, MD, Laetitia Amar, MD, Robert Battat, MD, FRCPC

period followed by a 40-week maintenance phase without re-randomizing the induction responders. In the induction period of ELEVATE 52, the clinical remission rate was 27.0 % with etrasimod vs. 7 % with placebo ($p<0.0001$). At week 52, the remission rate was 32% with etrasimod vs. 7% with placebo ($p<0.0001$). Secondary endpoints were also achieved at both weeks 12 and 52. At 52 weeks, treatment with etrasimod led to symptomatic remission (24.9% higher than placebo; $p<0.0001$), endoscopic improvement, with an endoscopic subscore ≤1 (26.7% higher than placebo; $p<0.0001$), and mucosal healing with histologic remission incorporated (18.4% higher than placebo; $p<0.0001$). Some patients on etrasimod experienced steroid-free remission at 12 weeks (32% with etrasimod vs. 7% with placebo; $p<0.0001$), and sustained remission (18% with etrasimod vs. 2% with placebo; $p<0.0001$). The ELEVATE UC 12 trial was shorter in duration, ending at 12 weeks, and also demonstrated positive outcomes, including a clinical remission rate of 25% with etrasimod vs. 15% with placebo.[9]

What About Predictors of Efficacy?

S1PR modulators can inhibit lymphocyte egress while biologics can block specific pro-inflammatory cytokines. However, there has been no clear correlation to date between therapeutic effectiveness and lymphocyte counts. There are currently no predictors of responsiveness to therapy, though conducting analyses involving immunophenotyping of cell subtypes could be a worthwhile avenue to further explore.[10] In a study on Crohn's disease, ozanimod reduced circulating levels of all B-cell and most T-cell subsets but not monocytes or natural killer cells. This study also suggested that levels of non-switched memory B cells could serve as a biomarker for response, given their positive association with clinical, endoscopic, and histologic endpoints in Crohn's disease.[11]

Safety Profiles and Considerations

Although no direct comparisons exist, the safety profiles of ozanimod and etrasimod appear similar. In the phase 3 True North trial, treatment-emergent adverse events (TEAEs) with ozanimod were similar to placebo during the induction phase but were more frequent in the maintenance phase compared with placebo (49.1% vs 36.6%). Few serious adverse events led to discontinuation (1.3-3.8%). In the 3-year open-label extension (OLE) of True North, the most common cause of TEAEs causing discontinuation was herpes zoster (1.5%).[6,12] In the open-label extension of the

Baseline testing

- Complete blood count, including lymphocyte count
- Liver enzymes and liver function testing (hepatitis serologies prudent)
- VZV serology if no history of chickenpox or vaccination with varicella vaccine
- Latent tuberculosis screening in high-risk populations
- Ophthalmic exam (of fundus, including macula) if history of diabetes, uveitis or macular edema
- Electrocardiogram
- Pregnancy testing in women of child-bearing potential recommended
- Skin examination (baseline or shortly after initiation)

Monitoring during treatment

- Blood pressure should be monitored regularly while on treatment
- Complete blood count and lymphocyte counts periodically (often done every 3 months with liver testing) and after stopping therapy (at 3 months for ozanimod and 5 weeks for etrasimod)
- Liver transaminases and bilirubin levels at 1,3,6,9 and 12 months of therapy and then periodically
- Ophthalmic: Monitor for symptoms of macular edema and vision changes. Regular ophthalmic exams if history of diabetes, uveitis, or macular oedema
- Infections should be assessed for regularly during treatment and after treatment discontinuation (up to 3 months for ozanimod, up to 5 weeks for etrasimod)
- Pulmonary function (spirometry) testing if clinically indicated (eg., dyspnea)

Contraindications (Canada and US)

- Myocardial infarction, unstable angina, stroke, transient ischaemic attack, decompensated heart failure requiring hospitalisation, or class III or IV heart failure in the past 6 months
- Mobitz type II second-degree or third-degree AV block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker
- Concomitant use of an MAO inhibitor (eg., selegiline) with ozanimod
- There are some significant drug interactions which can be found in the product monograph or a drug interactions database

Additional Contraindications According to Canadian Product Labeling

- Hypersensitivity to ozanimod or any component to the formulation
- Patients at increased risk of opportunistic infection including those who are immunocompromised due to other treatments (eg. immunomodulating therapies and bone marrow transplant) or disease (eg., immunodeficiency syndrome)
- Severe active infections, including chronic bacterial, fungal or viral infections (eg., hepatitis or tuberculosis), until resolution of the infection
- Known active malignancy (excluding basal cell carcinoma)
- Pregnancy and women of childbearing years not using effective contraception

Some Practical Considerations

- There is an up-titration regimen with ozanimod, but not with etrasimod.
- Is the patient pregnant or do they plan to be pregnant?
- Does the patient have an active infection or malignancy?
- Is the patient on other immunosuppressive therapies?
- Is the baseline ECG normal? If the baseline ECG is normal, without known or new cardiac disease/ symptoms, no further ECGs are needed.
- Is the patient on drugs that could reduce AV node conduction? If they are in sinus rhythm and on a stable dose of beta blocker, etrasimod use is considered safe. In other cases, consider a cardiology referral.
- Is the patient on drugs that could interact with S1PR modulators? There are some important drug interactions other than with MAO-B inhibitors (ozanimod), related to effects on certain CYP enzymes; refer to a drug interaction database or product monograph for more information.

Table 2: Baseline testing, monitoring, contraindications and practical considerations for S1PR modulator use;[15] *courtsey of* Aaron Hass, MD, Laetitia Amar, MD, Robert Battat, MD, FRCPC

Abbreviations: AV: atrioventricular; **ECG:** electrocardiogram; **MAO:** monoamine oxidase; **VZV:** varicella zoster virus.

phase 2 TOUCHSTONE trial, TEAEs were similar in the ozanimod and placebo groups. The most commonly reported serious TEAEs were UC exacerbation (3.5%), anemia (1.2%), and ischemic stroke (1.2%).[13]

Etrasimod's safety profile was evaluated in the OLE of the phase II OASIS trial with 2 mg of etrasimod. The most common TEAEs were UC worsening (19%) and anemia (11%). Out of 112 patients, 14 experienced serious adverse events, and ten patients stopped the therapy (eight due to worsening UC).[8] In the ELEVATE UC 52 trial, 71% of patients experienced TEAEs with etrasimod compared to 56% with placebo, while in the shorter ELEVATE UC 12 trial, the event rates were similar (47% etrasimod vs. 47% placebo). The rate of adverse events leading to discontinuation was similar in the 52-week trial (4% with etrasimod vs. 5% with placebo), and in the 12-week trial (5% with etrasimod vs. 1% with placebo). Serious events were low and comparable to placebo.[9] Unlike ozanimod, no dose titration is needed for etrasimod.

Non-serious infections with ozanimod were more frequent in the maintenance phase of True North at 22.2% as compared to 10.1% with placebo, while a rate of 45.8% was observed in the OLE with ozanimod. The overall serious infection rate with ozanimod in the original True North trial was ≤1.6%. In the ELEVATE UC trials both non-serious and serious infection rates for etrasimod were each ≤1%. Patients on ozanimod experienced a 54% decrease in mean absolute lymphocyte counts from baseline at 10 weeks, while those on etrasimod had approximately a 50% decrease by week 12. No patients on ozanimod who developed serious or opportunistic infections had lymphocyte counts less than 200 cells/mm^3. During induction with ozanimod, 0.6% of patients experienced asymptomatic bradycardia and no patients had high-degree atrioventricular blocks, likely mitigated by the 7-day gradual dose escalation regimen used in the trial. In both ELEVATE trials, patients taking etrasimod had a ≤1% rate of bradycardia with two symptomatic, self-limited events leading to discontinuation. There was no up-titration regimen for the initiation of etrasimod. Less than 0.4% of patients on ozanimod developed macular edema which improved with the discontinuation of therapy. For etrasimod, rates were <1%, with one discontinuation. Asymptomatic liver enzyme elevations were more common with both ozanimod and etrasimod than placebo. These elevations infrequently led to discontinuation (<1%), and no patients met Hy's law criteria for drug-induced liver injury.[6,9]

There is a potential risk of drug-drug interactions with S1PR modulator use. Ozanimod has been shown to inhibit the monoamine oxidase B (MAO-B) enzyme in vitro, thus, concomitant use with MAO-B inhibitors is not recommended given the risk of precipitating serotonin syndrome and hypertensive crisis. Considering effects of S1PR modulators on certain cytochrome P450 (CYP450) enzymes, current recommendations are to avoid co-administration of these agents with medications such as gemfibrozil and rifampin. That said, in vitro studies suggest that etrasimod at 2 mg likely has a lesser impact on CYP450 enzymes compared to ozanimod. There is limited safety data on the use of S1PRs with arrhythmic and beta blocking agents. A cardiology opinion is prudent in such cases due to the additive effects on heart rate. However, etrasimod use in patients on stable beta blocker doses is considered a safe practice.[14] While unchanged etrasimod has a half-life of approximately 30 hours and is the primary circulating component in plasma, ozanimod has two major active metabolites in circulation each possessing a longer mean half-life of around 10 days. Therefore, ozanimod has a washout period of up to 3 months. Details on pre-initiation testing for S1PR modulators, monitoring during treatment, and some additional considerations for practice can be found in **Table 2**.

Future Perspectives of S1PR Modulators

S1PR modulators provide new treatment options for UC patients. They are now one of two classes of oral advanced therapies and may result in lower loss of response rates amongst responders due to their lack of immunogenicity. S1PR modulators may provide a lower infection risk, and do not have black box warnings for infection, malignancy or venous thromboembolism, unlike Janus kinase inhibitors.[16] Additionally, studies on etrasimod included patients with isolated ulcerative proctitis and demonstrated effectiveness, whereas these patients were generally excluded from other UC trials.[17]

Head-to-head randomized trials and analyses of cost-effectiveness between different S1PR modulators, biological agents, and small molecules are needed to help alter our current standards of care. A systematic review and meta-analysis by Lasa et al. showed that ozanimod had comparable efficacy to other small molecules and biologics in UC.[18] Another systematic review by Solitano et al. assessed oral small molecules, with S1PR modulators proven to be effective for clinical, endoscopic, and histologic end points (though etrasimod did not achieve the latter).[19]

While more head-to-head trials would be beneficial to optimally place S1PRs into our treatment algorithms for UC, these therapies remain as important modulators of the immune system that have shown promising data and are already used in clinical practice for this purpose. Cardiac concerns are rare and tend to occur within hours of treatment. Therefore, for patients without cardiac conduction disease, a history of heart failure, or myocardial infarction, a normal pre-treatment ECG should suffice. No further cardiac monitoring is necessary unless clinical changes or a cardiac event develop subsequent to therapy. Also, while lymphopenia is a pharmacodynamic effect reflecting S1PR modulation, it is not associated with an increased risk of infections, nor has it been proven to be related to drug efficacy. Lastly, there are many possibilities to explore for S1PR modulator use. Based on available

data and clinical experience, we believe that S1PR modulators should be evaluated in the future as an add-on therapy for UC patients with moderate disease activity who have failed to improve with mesalamine. The combination of S1PR modulators with biologics may be a promising future area of investigation as a therapy for UC.[20]

Conclusion

Sphingosine-1-phosphate receptor modulators are safe, effective, and well tolerated oral therapies for moderate-to-severe UC. With a novel mechanism of action, they could complement existing therapies. Their advantages include daily oral dosing, rapid action, lack of immunogenicity, and a low infection risk. These agents are generally easy to initiate, requiring some pre-initiation testing. Recent evidence of their safety, effectiveness, and ease of use is compelling, making them a consideration for early-line therapy in moderate-to-severe disease for those who have failed conventional treatments.

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