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Therapeutic Potential of Etrasimod in the Management of Moderately-to-Severely Active Ulcerative Colitis: Evidence to Date

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Abstract: Etrasimod is a sphingosine 1 phosphate (S1P) receptor modulator approved for the treatment of moderate to severely active ulcerative colitis (UC). Etrasimod selectively activates $S1P_{1,4,5}$ receptors with no detectable activity on $S1P_{2,3}$. The ELEVATE clinical trials evaluated the efficacy and safety of etrasimod for UC. Etrasimod showed clinically significant improvement in clinical remission at weeks 12 and 52 compared to placebo. Etrasimod showed greater efficacy in patients who were biologic naive. Etrasimod was also effective in a subgroup of patients with isolated proctitis. The medication should be avoided in pregnancy and lactation, certain cardiac conditions including brady-arrythmias, and those with a history of skin cancer. Etrasimod has a shorter half-life and fewer drug–drug and food interactions as compared to the S1P receptor modulator ozanimod. In addition, no dosing titration is required. Etrasimod is a promising treatment option for UC patients with moderate to severe inflammation, particularly those who have no prior biologic exposure, are not considering pregnancy, and prefer oral therapy.

Keywords: etrasimod, inflammation, ulcerative colitis, small molecule, sphingosine 1 phosphate modulator

Introduction

Ulcerative colitis (UC) is a chronic immune mediated disease that results in inflammation in the colon. This is thought to be caused by a combination of genetic predisposition and environmental factors that lead to changes in the gut microbiome and interaction with the immune system.[1] Most often, UC starts in the rectum and extends more proximally throughout the colon to varying degree; this is termed proctitis with rectal involvement, left sided with involvement up to the splenic flexure or pancolitis with involvement proximal to the splenic flexure. UC has periods of active inflammation interchanged with periods of disease control or remission. In 2023, the prevalence of UC was estimated to be 5 million cases around the world.[1]

Patients with ulcerative colitis often have symptoms of diarrhea, rectal bleeding, urgency, and abdominal pain. Patients with mild to moderate disease activity can be treated with mesalamine therapy. However, those that have moderate to severe disease need advanced therapies.[2] Although biologic medications have been approved for treatment of moderate to severe UC, many patients prefer to take oral therapy over intravenous or subcutaneous medications. There is an unmet need for new medications to treat UC in regard to different modes of administration, as well as a therapeutic ceiling of current treatments. With the approval of etrasimod for moderate to severely active UC, one needs to understand the therapeutic potential, overall efficacy and safety data, and positioning of this medication amongst the growing armamentarium of treatment options. To date, there are no head-to-head trials of etrasimod with other approved agents, however this review provides an overview of the evidence to date in the above areas.

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Indications

Etrasimod is an FDA (Food & Drug Administration) approved oral sphingosine 1-phosphate receptor modulator for the treatment of moderately to severely active ulcerative colitis in adults.[3]

Mechanism of Action

Figure 1, Mechanism of sphingosine phosphate modulation.

Sphingosine 1-phosphate (S1P) is a membrane-derived lysophospholipid signaling molecule that interacts with S1P receptors. S1P regulates angiogenesis, vascular stability and permeability and is recognized as a regulator of T-cell and B-cell trafficking.[4] Modulating the $S1P_1$ receptor can reversibly sequester specific lymphocyte subsets in lymph nodes, leading to less peripheral immune cell availability and activation with decreased trafficking to sites of inflammation, such as the colon in ulcerative colitis.[5–8] Fingolimod was the first S1P modulator to be approved for multiple sclerosis, and the modulation of $S1P_2$ and $S1P_3$ was thought to contribute to adverse events including pulmonary and cardiac complications, malignancies and macular edema. Ozanimod, a selective $S1P_{1,5}$ receptor modulator, is approved for the treatment of multiple sclerosis and ulcerative colitis and avoids $S1P_{2,3}$ therefore avoiding these complications, but due to its effect on $S1P_1$ requires a dosing titration. Etrasimod, a once-daily, oral, S1P receptor modulator, selectively activates $S1P_{1,4,5}$ leading to its efficacy in treating UC and does not require dose titration.

Pharmacokinetics

Etrasimod reaches steady state within 7 days with an accumulation of approximately 2 to 3 fold compared to the first dose. After oral administration, maximum plasma concentration is reached in approximately 4 hours. There are no significant differences in absorption with or without meals. The mean plasma elimination half life of etrasimod is 30 hours and the drug is metabolized by oxidation and dehydrogenation mediated mainly by CYP2C8, 2C9 and 3A4 with a minor contribution from CYP 2C19 and 2J2. Etrasimod undergoes conjugation via UGT's with a minor contribution by sulfotransferases and is eliminated predominantly in the feces (82%) with a lesser extent in the urine (5%). No significant differences were found in patients over the age of 65, or based on sex, body weight, race, ethnicity, presence of UC (vs healthy control) or with severe renal impairment (eGFR < 30). In patients with mild hepatic impairment (Child-Pugh A), Etrasimod AUC increased by 13%, 29% in moderate (Child-Pugh B) and 59% in severe (Child-Pugh C), compared with patients with normal liver function. Therefore, use in patients with Child-Pugh Class C hepatic impairment should be avoided.[4]

Key Clinical Trials

The key registration studies for etrasimod were the ELEVATE UC 52 and ELEVATE UC 12 studies for adults with active moderate-to-severe UC.[9] ELEVATE UC 52 enrolled patients from 315 centers in 40 countries while ELEVATE UC 12 enrolled patients from 407 centers in 37 countries. Patients aged 16–80 with ≥10 cm of rectal involvement, modified

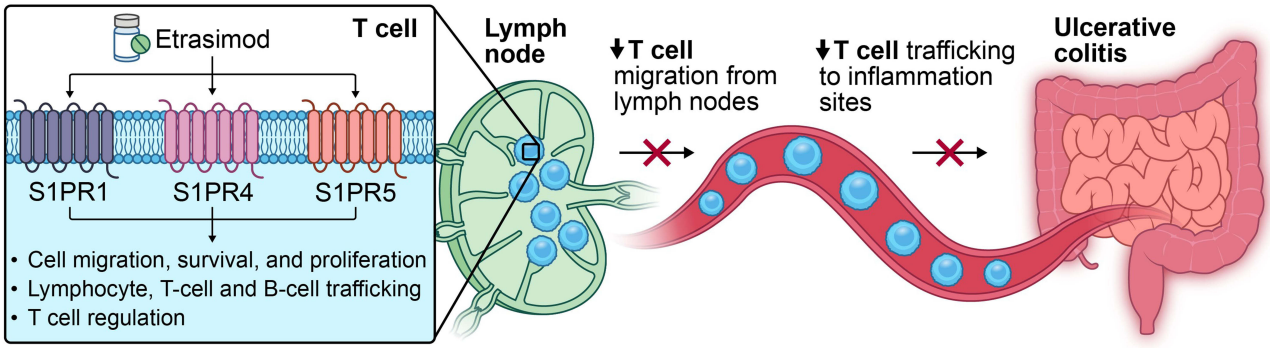

Figure 1 Mechanism of action of etrasimod: Etrasimod works on the sphingosine-1 phosphate receptors that prevent the migration of T cells from lymph nodes to reduce their trafficking to inflammation sites in the colon in ulcerative colitis.

Mayo score (MMS) of 4–9, endoscopic subscore (ES) ≥ 2 and rectal bleeding subscore (RBS) ≥ 1 with inadequate response, loss of response, or intolerance to one approved therapy for UC treatment were eligible for the study. Of note, patients with isolated proctitis, a group typically excluded from clinical trials, were included. However, they were limited to 15% of the total study population.

Exclusion criteria included previous treatment with 3 biologic agents or 2 biologic agents and a Janus kinase (JAK) inhibitor for ulcerative colitis, high risk for colectomy in the next 3 months, clinically relevant cardiac comorbidity including myocardial infarction, stroke or second- or third-degree atrioventricular block, recently decompensated heart failure, opportunistic infections, macular edema or pregnancy/lactation.

ELEVATE UC 52 had a treat-through design starting with a 12-week induction period, followed by a 40-week maintenance period and 4-week follow-up period. ELEVATE UC 12 had a 12-week induction period and a 4-week follow-up period with the possibility of enrolling in an open-label extension study. This is in direct contrast to the TrueNorth clinical trials of ozanimod in UC, which had only induction responders that were re-randomized during the maintenance component of the study, making direct comparisons of these two S1P modulators difficult.[10]

Patient Selection

The key induction and maintenance trials comprised a diverse group of patients across Europe, North and South America, Australia, Africa, and the Asia-Pacific region. However, most patients were white (89% of etrasimod group vs 90% of placebo in ELEVATE UC 52, 74% of etrasimod group vs 76% of the placebo group in ELEVATE UC12). The mean age of patients included in the studies was 38.9–41.2. In both studies, there was a greater percentage of males than females enrolled, 53–63% of the groups. Patients had a mean disease duration of 5–7 years. The mean fecal calprotectin baseline ranged from 4251 to 5325 mg/kg. In terms of prior medication exposure, 37–38% had prior exposure to a JAK inhibitor or biologic, most tumor necrosis factor antagonists or anti-integrins with fewer exposed to interleukin 12/23 inhibitors. About a third of patients were on corticosteroids at baseline.[9]

Efficacy

The co-primary endpoints in Elevate UC 52 were the proportion of patients who achieved clinical remission at week 12 (induction period) and week 52 (maintenance period). Clinical remission was defined as stool frequency (SF) subscore = 0 (or = 1 with a ≥1-point decrease from baseline), RBS = 0, ES ≤ 1. The primary endpoint for Elevate UC 12 was the proportion of patients in clinical remission at the end of the week 12 induction period, see (Tables 1 and 2).[9]

Table 1 Primary and Secondary Endpoints from Induction Studies

	Elevate UC 12			Elevate UC 52		
	Etrasimod n=222	**Placebo n=112**	**P Value**	**Etrasimod n=274**	**Placebo n=135**	**P Value**
Primary Endpoint						
Clinical Remission at week 12	55(25%)	17(15%)	0.026	74(27%)	10(7%)	<0.0001
Secondary Endpoints						
Endoscopic Improvement at week 12	68(31%)	21(19%)	0.0092	96(35%)	19(14%)	<0.0001
Endoscopic Improvement with Histologic Remission week 12	36(16%)	10(9%)	0.036	58(21%)	6(4%)	<0.0001
Endoscopic Normalization at week 12	38(17%)	9(8%)	0.0093	40(15%)	6(4%)	0.0027
Symptomatic Remission at week 12	104(47%)	33(29%)	0.0013	126(46%)	29(21%)	<0.0001
Clinical Response (MMS) at week 12	138(62%)	46(41%)	0.0002	171(62%)	46(34%)	<0.0001

Table 2 Primary and Secondary Endpoints in Maintenance Study

Elevate UC 52			
	Etrasimod n=274	**Placebo n=135**	**P Value**
Primary Endpoint			
Clinical Remission (Adapted Mayo) week 52	88 (32%)	9 (7%)	<0.0001
Secondary Endpoints			
Sustained clinical remission (Adapted Mayo)	49 (18%)	3(2%)	<0.0001
Corticosteroid-free clinical remission	88(32%)	9(7%)	<0.0001
Endoscopic Normalization	72(26%)	8(6%)	<0.0001

The secondary endpoints for the Elevate UC 52 study included endoscopic improvement (ES ≤ 1*), symptomatic remission (SF subscore = 0 [or = 1 with a ≥1-point decrease from baseline], RBS = 0), and endoscopic improvement-histological remission (ES ≤ 1, with histologic remission measured by a Geboes Index score of <2·0 [on a scale from 0 to 5·4, with higher scores indicating more severe inflammation]) at week 12 and 52. Corticosteroid-free clinical remission (clinical remission at week 52 and had not been receiving corticosteroids for ≥12 weeks before week 52) and sustained clinical remission (clinical remission at both weeks 12 and 52) were additional key secondary endpoints assessed at week 52. Other endpoints included clinical response (a ≥2-point and ≥30% decrease from baseline in MMS and a ≥1-point decrease from baseline in RBS or an absolute RBS ≤ 1) at weeks 12 and 52, 4 week and 12-week corticosteroid-free remission among patients with baseline steroid use, endoscopic normalization (ES = 0) at week 12 and 52 and change from baseline per visit in symptomatic remission, rectal bleeding subscores (RBS, 0 = none, 1 = visible blood with stool less than half the time, 2 = visible blood with stool half the time or more, 3 = passage of blood alone), SF subscores, RBS plus SF subscores, lymphocyte counts, fecal calprotectin and high sensitivity C-reactive protein.

Key secondary endpoints for ELEVATE UC 12 included endoscopic improvement, symptomatic remission, and endoscopic improvement-histologic remission at week 12. Other endpoints included clinical response, endoscopic normalization, and change from baseline per visit in symptomatic remission, rectal bleeding subscores, stool frequency composite subscores, lymphocyte counts, fecal calprotectin, and high sensitivity C-reactive protein at 12 weeks.

All primary and secondary endpoints were met at week 12 in both ELEVATE UC 12 and 52.

All primary and key secondary endpoints in ELEVATE UC 52 were also achieved. In addition, a greater number of patients treated with etrasimod had symptomatic remission by week 2 in ELEVATE UC 52 and week 4 in ELEVATE UC 12 as well as decreases in RBS and SF subscores as early as week 2 in both trials. Decreases in fecal calprotectin and high-sensitivity CRP were also observed in those treated with etrasimod compared to placebo in both trials.

Patients with isolated proctitis were included in the ELEVATE 12 and 52 studies. A post hoc analysis of patients with isolated proctitis in the ELEVATE 12 and 52 studies demonstrated that etrasimod was more effective than placebo with 18/42 (42.9%) vs 3/22 (13.6%) achieving clinical remission at week 12, p < 000.1 and 12/27 (44.4%) vs 1/9 (11.1%) at week 52, p < 0.001, respectively.[11] Of note, data at week 12 was pooled from both trials. Although this was a first-in-kind advanced therapy registration trial that included proctitis patients, and the findings were positive, it is important to note that the number of patients studies was small (42 total in the etrasimod arm). When analysis was performed excluding patients with isolated proctitis but included the remainder of patients with left-sided to pan-colitis, and the findings were still unchanged.

Patients who were bionaive and those who had previous biologic/JAK inhibitor exposure both achieved significant improvements in clinical remission at week 12. However, clinical remission rates were lower in those with biologic/JAK inhibitor exposure 14/80 (18%) vs placebo 1/42 (2%), p = 0.004 compared to biologic naive patients 60/194 (31%) vs 9/93 (10%), p < 0.001. All other endpoints were achieved in both biologic exposed and naive patients, except for symptomatic remission at week 12 and 52 and sustained clinical remission at week 52, which were not achieved in the biologic/JAK inhibitor-exposed group.

Safety of Etrasimod

In both Phase 2 and Phase 3 clinical trials, etrasimod has demonstrated generally favorable tolerability in patients with moderate to severe ulcerative colitis.[9,11,12] In both ELEVATE UC 12 and 52, the most commonly reported adverse events included headache, anemia, and worsening of UC or UC flare (Table 3). These adverse events were thought to be mild to

Table 3 Adverse Reactions in Subjects with Ulcerative Colitis in a Placebo-Controlled 12 and 52-Week Study

		Elevate UC 52		Elevate UC 12	
		Etrasimod Group (n=289)	**Placebo Group (n=144)**	**Etrasimod Group (n=238)**	**Placebo Group (n=116)**
Any adverse events		206 (71%)	81 (56%)	112 (47%)	54 (47%)
Any serious adverse events		20 (7%)	9 (6%)	6 (3%)	2 (2%)
Any adverse event leading to study treatment discontinuation		12 (4%)	7 (5%)	13 (5%)	1 (1%)
Adverse events leading to death		0	0	0	0
Most common adverse events					
	Worsening of ulcerative colitis or ulcerative colitis flare	22 (8%)	13 (9%)	9 (4%)	1 (1%)
	Anemia	24 (8%)	14 (10%)	14 (6%)	8 (7%)
	Headache	24 (8%)	7 (5%)	11 (5%)	2 (2%)
	Nausea	9 (3%)	2 (1%)	10 (4%)	2 (2%)
	COVID-19	20 (7%)	9 (6%)	3 (1%)	3 (3%)
	Dizziness	15 (5%)	1 (1%)	3 (1%)	0
	Pyrexia	14 (5%)	6 (4%)	8 (3%)	3 (3%)
	Arthralgia	13 (4%)	3 (2%)	4 (2%)	3 (3%)
	Abdominal pain	11 (4%)	5 (3%)	3 (1%)	3 (3%)
Adverse events of special interest					
	Serious infections	3 (1%)	5 (3%)	0	0
	Herpes zoster	2 (1%)	0	0	2 (2%)
	Opportunistic infections	0	1 (1%)	1 (<1%)	0
	Hypertension	8 (3%)	1 (1%)	3 (1%)	1 (1%)
	Sinus bradycardia	0	0	4 (2%)	0
	Bradycardia	4 (1%)	0	1 (<1%)	0
	Atrioventricular block, first degree	1 (<1%)	0	1 (<1%)	0
	Atrioventricular block, second degree (Mobitz I)	1 (<1%)	0	0	0
Macular oedema		1 (<1%)	0	1 (<1%)	1 (1%)

moderate in nature. Rates of serious and opportunistic and serious infections were similar between the treatment and the placebo groups.[9] Herpes zoster infections were reported in 2 patients (1%) in the treatment groups in UC 52 and 2 (1%) patients in the placebo arm in UC 12. Similar rates of infection were seen in the open label extension studies.[13] In both the ELEVATE UC 52 and UC 12 studies, serious adverse events were uncommon among patients. In ELEVATE UC 52, 7% of those in the etrasimod group and 6% in the placebo group experienced serious adverse events. In ELEVATE UC 12, these rates were 3% for etrasimod and 2% for placebo. Overall, these findings suggest that serious adverse events were infrequent and showed similar occurrence rates between etrasimod and placebo across both studies. Rates of study discontinuation due to adverse events were low, with 12 (4%) patients in ELEVATE UC 52 and 13 (5%) patients in UC 12 compared to 5% and 1% of the placebo groups, respectively.[9]

Cardiac events have been previously reported in the S1P inhibitor class due to the expression of S1P receptors on cardiac tissue.[14,15] In both induction and maintenance trials, there were a total of nine events of bradycardia in patients receiving etrasimod with no events in the placebo arms.[9] Two of these events were symptomatic and led to study discontinuation, but both resolved without pharmacological intervention and all study patients who discontinued the medication due to AV block or bradycardia had resolution of these events without additional intervention. There were no reports of Mobitz type II or higher events reported in either trial and no patients had a heart rate less than 40 beats per minute. Overall, no serious events of bradycardia or AV block were reported. Together, the overall cardiac risk is low with etrasimod in appropriately selected patients who have been screened for major cardiovascular abnormalities. Consultation with a cardiologist prior to initiation of etrasimod should be considered in patients who are taking medications that can delay cardiac conduction such as calcium channel blockers, beta blockers, and anti-arrhythmics.

During both ELEVATE UC 52 and ELEVATE UC 12, macular edema occurred in a total of two patients receiving etrasimod and one patient receiving placebo. This led to discontinuation of the study drug in one patient in the etrasimod group, while the other continued without interruption of the study drug.[9] Importantly, all cases of macular edema were successfully resolved. Although relatively low risk, it is prudent to obtain an evaluation of the fundus near the initiation of etrasimod.[3]

Although not considered an adverse reaction, but more consistent with the proposed mechanism of action, the reduction in mean lymphocyte count decreased to around 50% of the baseline value by week 2 and was maintained throughout the study period in both UC52 and UC12.[9] Once etrasimod was stopped, the absolute lymphocyte count returned to baseline within 2 weeks in the majority (77% and 83%) of patients, respectively. It is important to remember that despite the reduction in lymphocyte count, there was no difference in risk of serious infections compared to placebo. Etrasimod works by sequestering specific lymphocytes in the lymph nodes, so it is not surprising that circulating lymphocyte counts in the peripheral blood were decreased. Despite the potential for lower lymphocyte counts, there is no FDA label requirement for lab monitoring on etrasimod, but it is recommended to withhold the medication if lymphocyte counts are below 200. Therefore, we recommend the use of clinical judgement in determining the frequency and necessity of blood count checks in individual patients taking etrasimod and as the drug is metabolized by the liver to monitor liver enzymes at the discretion of the provider. The concomitant use of immunosuppressive, immunomodulator, or anti-neoplastic agents, except steroids, would not be preferred in patients on etrasimod. No data exists on the efficacy of vaccinations on patients on etrasimod or similar S1P agents. However, vaccination against shingles is recommended in those patients starting the medication.

Currently, there is a paucity of data regarding the safety of etrasimod in pregnancy. Animal studies have established that S1P signaling genes are prominent in uterine and placental tissue and may be crucial to fetal and placental development.[16] Taking these safety data into account, the use of etrasimod would not be preferred in patients who are pregnant or planning to get pregnant soon. Due to the short half-life of etrasimod, women planning pregnancy should stop the drug one week prior to conceiving. In addition, it would not be preferred in those patients with significant cardiac conduction abnormalities or macular edema. It is contraindicated in patients who have had a myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, or decompensated heart failure requiring hospitalization in the past 6 months.[3] It is also contraindicated in patients with Class III or IV heart failure. It is contraindicated in patients with Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-

atrial block, unless the patient has a functioning pacemaker.[3] For this reason, we recommend obtaining an EKG, portable EKG, or reviewing the rhythm strip during endoscopy to rule out major brady-arrhythmias.

Positioning of Etrasimod Based on Its Therapeutic Potential

There have not been head-to-head trials of etrasimod versus other agents for UC or any updated systematic review/meta-analyses that include etrasimod to help determine placement of etrasimod for UC. When considering where to place etrasimod among our current first line options for UC, there are several factors that should be considered including prior biologic/JAK exposure, preferred route of administration, disease location, concomitant immune mediated conditions, extra-intestinal manifestations, desire for pregnancy and history of cardiovascular comorbidities.

For patients who have previously failed mesalamine, etrasimod is an excellent option. Etrasimod is more effective in bionaive patients so should be considered as a first-line therapy. Many patients prefer the oral route of administration over other injection or infusion options. With thiopurines as an alternative oral treatment option, etrasimod provides certain benefits. There is no need to assess metabolic activity (TPMT) prior to prescribing the drug. There is one single dose and does not require weight-based dosing. There is no requirement for every 3-month lab monitoring of blood counts or liver enzymes, and it can be done at the discretion of the provider. There is no black box risk of lymphoma. Finally, the onset of action is over weeks rather than months.

Patients with isolated proctitis were included as a subgroup in the ELEVATE UC 52 and 12 trials. This group of patients are often undertreated due to having only a small area of mucosal involvement. However, rectal involvement can lead to severe distressing symptoms affecting patients' quality of life significantly. After failure of mesalamine, etrasimod should be considered for this group of patients.

Although not approved for use in multiple sclerosis, based on the mechanism of action it may be reasonable to try to treat patients who have both UC and MS with one agent. This should be done in consultation with the patient's treating neurologist. Further studies are also needed to assess the efficacy of etrasimod in the improvement of extraintestinal manifestations in patients with ulcerative colitis. In patients with concomitant rheumatologic conditions, such as psoriasis, psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis, alternative medications should be considered.

For women of childbearing age who are planning pregnancy, this medication should be avoided. There is currently no data to support safety in pregnancy or lactation. Etrasimod may be considered over ozanimod in women of childbearing age due to the shorter half-life compared to ozanimod, making it easier to stop if pregnancy occurs or if the patient desires pregnancy. In addition, there are fewer drug–drug and food interactions, and the lack of dosing titration may allow for quicker onset of efficacy. Patients previously treated with ozanimod were excluded in the etrasimod clinical trials and due to the similar mechanism of action, use after ozanimod failure should be avoided. Etrasimod should also be avoided in patients with macular edema, bradycardia or other cardiac conduction delays, myocardial infarction, stroke, opportunistic infection and history of skin cancer. These preferences are summarized in Table 4.

Table 4 Etrasimod Use in Moderate to Severe Ulcerative Colitis

Etrasimod Use in Moderate to Severe UC	
Etrasimod Preferred	**Etrasimod Not Preferred/Contraindicated**
Bionaive	Prior ozanimod failure
Male	Lack of efficacy with >2 biologics
Women not considering pregnancy/on contraception	Pregnancy/lactation
Oral option preferred by patient	History of skin cancer Conduction delay abnormalities/ bradyarrythmias, MI, CVA/TIA, decompensated heart failure Opportunistic infection

Assessment Prior to Initiating Etrasimod

Before initiation of treatment, it is important to screen for active infections, obtain a baseline complete blood count with lymphocyte levels and liver function tests (within 6 months), and obtain an electrocardiogram to determine whether preexisting conduction abnormalities are present. If found, consultation with a cardiologist is recommended. The patient should also have a baseline ophthalmic assessment to evaluate the fundus and macula and ensure they have had a skin exam to evaluate for any skin cancers. Medications should be reviewed and those that may cause bradyarrthmias, interact with etrasimod via CYP pathways, or possess additive immunosuppressive effects should be identified. Age-associated vaccinations should be completed, especially against varicella zoster virus. If any live vaccines are required or have been given recently, delay etrasimod initiation by at least 4 weeks.

Conclusions

Etrasimod, an oral sphingosine 1 phosphate inhibitor, holds significant therapeutic potential in the management of moderate to severe UC, especially in bionaive patients, and potentially as a niche in those with proctitis. The efficacy and safety of this medication are promising, especially with appropriate vaccinations and screening tests completed. More studies will be needed to understand the safety of use in pregnancy and breastfeeding.

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