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ETRASIMOD IN THE TREATMENT OF ULCERATIVE COLITIS: EFFICACY, SAFETY, AND ITS ROLE IN THERAPY - REVIEW

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ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory disease of the large intestine, often associated with significant impacts on patients' quality of life and public health systems. Traditional treatments, such as aminosalicylates, are not always effective, especially in moderate to severe cases. Etrasimod, a novel oral selective modulator of sphingosine-1-phosphate (S1P) receptors, offers an innovative therapeutic approach by regulating immune cell migration and reducing intestinal inflammation. This review explores the efficacy, safety, and potential role of Etrasimod in the treatment of UC. Recent clinical trials have demonstrated its significant effectiveness in both the induction and maintenance of remission in patients with moderately to severely active UC. The drug also shows a favorable safety and tolerability profile. These findings position Etrasimod as a promising alternative for patients who do not respond to standard therapies. As research progresses, Etrasimod may represent a step forward in the development of more targeted, disease-modifying treatments for ulcerative colitis.

Aim of the study: This review investigates Etrasimod's role in ulcerative colitis treatment, in particular focusing on its mechanism of action, clinical efficacy, and safety. It seeks to determine whether it could serve as an alternative for patients resistant to conventional treatments.

Methodology: A literature review was conducted using PubMed, Google Scholar, and clinical trial registries.

Summary: Ulcerative colitis treatment remains challenging, with many patients experiencing limited benefits from existing therapies. Etrasimod, a selective modulator targeting S1P receptors, has demonstrated efficacy in induction and maintenance therapy in patients with moderately to severely active ulcerative colitis. Findings from clinical trials, particularly ELEVATE UC 12, 40 JAPAN and 52, suggest its potential in ulcerative colitis treatment. Further long-term studies are needed to confirm its benefits.

KEYWORDS

Etrasimod, Sphingosinephospate Receptor Modulation, Ulcerative Colitis Treatment, ELEVATE UC

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1. Introduction

Ulcerative colitis (UC) is a chronic, idiopathic form of inflammatory bowel disease (IBD) that selectively affects the colonic mucosa, inducing continuous, superficial inflammation that typically begins in the rectum and may extend proximally to varying extents within the colon. UC is clinically characterized by a relapsing-remitting disease course. The cardinal clinical manifestations include hematochezia, often accompanied by rectal urgency and tenesmus (Gajendran et al., 2019). Although the precise etiopathogenesis remains incompletely understood, accumulating evidence implicates a dysregulated immune response, suggesting a potential autoimmune basis. A substantial proportion of patients with UC also develop extraintestinal manifestations (EIMs), which may involve multiple organ systems and exhibit clinical overlap with other autoimmune conditions (Boal Carvalho & Cotter, 2017).

1.1. Epidemiology

Ulcerative colitis exhibits a bimodal distribution of incidence, with the primary peak occurring between the ages of 15 and 30 years, and a secondary, less pronounced peak observed between 50 and 70 years of age. Epidemiological studies generally report no significant sex predilection, although some data suggest a slight male predominance. The incidence of ulcerative colitis has risen in countries undergoing industrialization, implicating environmental factors as potentially critical contributors to disease pathogenesis and onset. In Europe it is estimated that incidence is from nine to 20 cases per 100 000 person-years, and prevalence rates from 156 to 291 cases per 100 000 people (Ordás et al., 2012).

1.2. Risk factors

Susceptibility to ulcerative colitis has been linked to genetic alterations, particularly in the human leukocyte antigen region, where specific single nucleotide polymorphisms (SNPSs) appear to play a contributory role. Furthermore, perinuclear anti-neutrophil cytoplasmic antibodies (ANCA) have been proposed as promising indicators of disease activity, offering potential utility in clinical assessment (Liang et al., 2024). Approximately 8 to 14 percent of individuals diagnosed with ulcerative colitis report a family history of inflammatory bowel disease. First-degree relatives of affected patients exhibit a fourfold increased risk of developing the condition compared to the general population. The global increase in the incidence of ulcerative colitis underscores the potential role of environmental determinants in disease pathogenesis. Among these, a history of former cigarette smoking has been identified as one of the most significant risk factors (odds ratio [OR] 1.79, 95% confidence interval [CI] 1.37–2.34). In contrast, current smokers demonstrate a reduced likelihood of developing ulcerative colitis compared to former and never-smokers (OR 0.58, 95% CI 0.45–0.75), and tend to experience a milder disease course. Appendectomy, particularly when performed for acute appendicitis at a young age, appears to exert a protective effect against the development of the disease. Certain pharmacological agents, including oral contraceptives, hormone replacement therapy, and non-steroidal anti-inflammatory drugs, have been associated with an elevated risk of ulcerative colitis, whereas exposure to antibiotics does not appear to confer a similar risk. Additionally, breastfeeding has been associated with a reduced risk of developing ulcerative colitis, while residing in urban environments has been linked to increased susceptibility (Ungaro et al., 2017). Engaging in fewer than two sporting activities per week during childhood was identified as a potential risk factor for the development of ulcerative colitis in the current study. This finding aligns with prior research, including a study by Persson et al., which demonstrated an inverse association between physical activity and the risk of Crohn's disease. Specifically, individuals who engaged in weekly or daily exercise had a reduced relative risk (RR) of developing the disease, with RRs of 0.6 (95% CI: 0.4–0.9) and 0.5 (95% CI: 0.3–0.9), respectively. Similar trends were observed in an Israeli population-based study conducted by Klein et al. Regular physical activity exerts broad and multifaceted health benefits. It promotes muscle development and strength, supports bone health, enhances cardiovascular and pulmonary function, modulates immune responses, and mitigates the physiological impact of stress. Despite these well-documented effects, the precise mechanisms by which physical activity may confer protection against the onset of inflammatory bowel disease remain unclear (Hlavaty et al., 2013). In UC, smoking has been identified as a protective factor, both in reducing the risk of disease onset and in lowering relapse rates. Additionally, it has been linked to decreased rates of hospitalization, alleviation of clinical symptoms, and improved remission outcomes. The underlying protective mechanisms are thought to involve modulation of immune responses, alterations in proinflammatory cytokine profiles, changes in mucus composition, as well as effects on vascular tone, coagulation pathways, and intestinal permeability (de Campos Silva et al., 2020).

1.3. Microbiota:

In UC, a decrease in protective gut bacteria, particularly those producing short-chain fatty acids (SCFA) such as Ruminococcaceae and Lachnospiraceae, has been observed alongside an increased abundance of pro-inflammatory microorganisms, including members of Enterobacteriaceae like Escherichia coli, as well as Fusobacteriaceae. It remains unclear whether this microbial imbalance, known as dysbiosis, is a contributing factor to gut inflammation in ulcerative colitis or merely a consequence of it. Nonetheless, faecal microbiota transplantation using stool from healthy donors has shown therapeutic benefit in ulcerative colitis, as supported by several controlled clinical trials. One proposed explanation for its effectiveness is the restoration of microbial diversity, including the reintroduction of SCFA-producing species present in the donor material. Dysbiosis in ulcerative colitis may therefore contribute to impaired epithelial function, which can increase the susceptibility of the intestinal lining to inflammation. This concept is further supported by the observation that fecal diversion from the rectum can exacerbate inflammation, resulting in a condition referred to as diversion colitis (Porter et al., 2020).

1.4. Pathophysiology:

A genome-wide association study (GWAS) of inflammatory bowel disease (IBD) has identified numerous genetic susceptibility loci linked to ulcerative colitis (UC), including genes involved in immune-mediated Th17 signaling pathways such as IL23R and IL12B, as well as genes related to intestinal epithelial barrier integrity. Additionally, early-onset colitis, which presents clinically similarly to adult-onset UC, has

been associated with mutations in the IL-10 receptor, emphasizing the importance of immune regulation in disease pathogenesis. Although single-nucleotide polymorphisms (SNPs) in genes affecting epithelial barrier function may contribute to the development of non-early-onset UC, the presence of a GWAS-identified SNP does not necessarily lead to disease onset. For example, whole-exome sequencing has revealed a distinct pattern of somatic mutations in the inflamed epithelium of UC patients, suggesting that chronic inflammation may drive long-term epithelial alterations (Nakase et al., 2022).

1.5. Moderate to severe UC:

In the American Gastroenterological Association Institute Clinical Guideline for the Management of Moderate to Severe Ulcerative Colitis, disease severity is defined using the Truelove and Witts criteria as well as the Mayo Clinic score. Following the exclusion of concomitant infections, such as *Clostridium difficile*, patients are classified as having moderate to severe ulcerative colitis if they are corticosteroid-refractory or -dependent, exhibit severe endoscopic activity (e.g., visible ulcerations), or are considered at high risk for colectomy. When reported, Mayo Clinic scores ranging from 6 to 12, with an endoscopic subscore of 2 or 3, are consistent with moderate to severe disease. Acute severe ulcerative colitis (ASUC) is defined in this guideline as hospitalization with ≥6 bloody stools per day, accompanied by at least one sign of systemic toxicity, including tachycardia (heart rate >90 bpm), fever (temperature >37.8°C), anemia (hemoglobin <10.5 g/dL), or elevated erythrocyte sedimentation rate (>30 mm/h) (Feuerstein et al., 2020).

1.6. Extraintestinal manifestations:

UC is a systemic condition that can extend beyond the gastrointestinal tract. A proportion of patients experience extraintestinal manifestations, most frequently involving the musculoskeletal, dermatologic, hepatobiliary, ocular, and hematologic systems. These manifestations are often correlated with more extensive colonic inflammation and have been linked to a less favorable disease course. A notable subgroup within the UC population includes individuals who also develop primary sclerosing cholangitis (PSC). This comorbidity is associated with a distinct clinical trajectory, characterized by a higher prevalence of pancolitis and a significantly increased risk of colorectal cancer (CRC). Meta-analytic data by Soetikno and colleagues indicate that the coexistence of PSC elevates the odds of developing dysplasia and CRC nearly fivefold. Longitudinal analysis by Kornfeld et al. further illustrates the progressive nature of this risk, with CRC incidence rising to 25% after 10 years, 33% after 20 years, and 40% after 30 years from the initial UC diagnosis (da Silva et al., 2014). Over the past decade, the association between inflammatory bowel disease (IBD) and venous thromboembolism (VTE) has been evaluated in three meta-analyses encompassing data from 18 studies. The most recent analysis reported a relative risk (RR) of 2.03 (95% confidence interval: 1.72–2.39), indicating a more than twofold increased risk of VTE in individuals with IBD. These findings have been corroborated by recent population-based studies, despite the significant evolution in therapeutic strategies for IBD over the last three decades. Supporting this trend, data from a nationwide administrative database in the United States suggest that VTE incidence continues to rise among hospitalized patients with IBD (Gordon et al., 2024). Cutaneous manifestations occur in approximately 15–20% of individuals with inflammatory bowel disease (IBD). These dermatologic extraintestinal manifestations (EIMs) can be categorized into four groups based on their underlying pathophysiological mechanisms. The first group includes reactive lesions that share similar immunopathogenic pathways with IBD, such as pyoderma gangrenosum, erythema nodosum, Sweet's syndrome, and aphthous ulcers. The second group comprises lesions with histopathological features identical to those seen in the intestinal mucosa, exemplified by metastatic Crohn's disease. A third category consists of skin conditions associated with IBD, including psoriasis, hidradenitis suppurativa, and atopic dermatitis. The final group includes drug-induced skin reactions resulting from IBD therapies (Faggiani et al., 2024).

1.7. Methods of treatment:

5-aminosalicylic acid (5-ASA) agents are the first-line treatment for inducing and maintaining remission in patients with mild to moderate ulcerative colitis (UC). In cases of mild to moderate proctitis, rectal 5-ASA suppositories are recommended as the initial therapeutic approach. If the clinical response is inadequate, oral 5-ASA should be added to the regimen. For patients who continue to experience symptoms, escalation of therapy with a corticosteroid suppository and/or dose optimization of oral 5-ASA is advised. Individuals with left-sided colitis or extensive disease should be managed with a combination of oral and rectal 5-ASA formulations to enhance therapeutic efficacy (Segal et al., 2021). Systemic glucocorticoids are indicated when

remission cannot be achieved with first-line therapies and are also considered the primary treatment for patients presenting with acute severe ulcerative colitis. In such cases, intravenous administration is preferred over oral delivery due to superior efficacy. Given their well-documented and potentially serious adverse effects, glucocorticoids should be used only for short-term induction of remission and are not appropriate for maintenance therapy. A steroid-dependent disease course is defined by the inability to taper glucocorticoids below 10 mg/day within three months without clinical relapse, or by the occurrence of early recurrence shortly after discontinuation. Thiopurines, such as azathioprine and 6-mercaptopurine, are commonly used in the management of steroid-dependent ulcerative colitis. As their therapeutic effect typically becomes apparent only after approximately three months of treatment, concomitant glucocorticoid therapy may be required as a bridging strategy. Alternative options include biologic agents such as the TNF inhibitors infliximab, adalimumab, and golimumab (along with their respective biosimilars), the anti-integrin antibody vedolizumab, and more recently introduced therapies like tofacitinib and ustekinumab. Biosimilars of infliximab and adalimumab are increasingly used as first-line biologics (Kucharzik et al., 2020). Approximately 15% of patients with UC will eventually require colectomy. Surgical intervention is indicated in cases of refractory disease unresponsive to medical therapy, as well as in the presence of complications such as toxic megacolon, bowel perforation, severe hemorrhage, or confirmed dysplasia or malignancy (Adams et al., 2022).

2. Etrasimod - mechanism of action:

Sphingosine 1-phosphate (S1P) is a bioactive lysophospholipid derived from cell membranes, known to influence numerous physiological and pathological pathways. Its effects are mediated through five distinct G protein–coupled receptor subtypes, designated $S1P_1$ to $S1P_5$. The biological role of each receptor varies depending on the cellular context and tissue distribution. While $S1P_1$, $S1P_2$, and $S1P_3$ are broadly expressed across many organ systems, $S1P_4$ and $S1P_5$ are more selectively localized, with predominant expression in specific immune cell populations and the central nervous system. Evidence suggests that $S1P_2$ and $S1P_3$ contribute to the modulation of endothelial barrier function, fibrotic signaling, and vascular tone. In contrast, $S1P_4$ has been associated with the regulation of dendritic cell dynamics, and $S1P_5$ is thought to control the trafficking of natural killer (NK) cells. The $S1P_1$ receptor expressed on lymphocytes plays a crucial role in regulating their egress from lymphoid organs, thereby controlling lymphocyte trafficking. Synthetic $S1P_1$ modulators bind to the receptor and promote its internalization and sustained removal from the cell surface. This loss of surface-expressed $S1P_1$ disrupts the ability of lymphocytes to sense and migrate along S1P gradients, leading to their sequestration within lymphoid tissues and a consequent reduction in lymphocyte presence in peripheral compartments. Etrasimod is a selective modulator targeting $S1P_1$, $S1P_4$, and $S1P_5$ receptors and used for the treatment of moderately to severely active ulcerative colitis (Sandborn et al., 2020). Although the roles of S1P4 and S1P5 remain incompletely characterized, available data indicate their involvement in dendritic cell migration and the positioning of natural killer cells, respectively. Unlike some other therapies, etrasimod does not require a dose-escalation strategy. Early-phase clinical data suggest that its metabolism involves three cytochrome P450 isoenzymes in roughly equal proportions, which could minimize the likelihood of interactions with other drugs or food (Sandborn et al., 2023).

3. Clinical Trials – safety, efficiency, role in therapy:

3.1. Efficacy:

The ELEVATE UC 12 and ELEVATE UC 40 Japan trials evaluated clinical remission as the primary efficacy endpoint. Remission was defined as a stool frequency subscore (SFS) of 0, or 1 with a reduction of at least 1 point from baseline, a rectal bleeding subscore (RBS) of 0, and an endoscopic subscore (ES) of 1 or less, excluding friability. Assessments were conducted at weeks 12 and 52. Key secondary endpoints included the proportion of patients achieving: (1) endoscopic improvement (ES $\leq$1); (2) symptomatic remission, defined as an SFS of 0 or 1 (with a $\geq$1-point reduction from baseline) and RBS of 0; and (3) endoscopic improvement with histological remission (EIHR), defined as ES $\leq$1 accompanied by a Geboes Index score below 2.0. Additional outcomes included corticosteroid-free clinical remission, defined as clinical remission at week 52 without corticosteroid use during the final 12 weeks of the study, as well as sustained clinical remission, defined as meeting remission criteria at both weeks 12 and 52. All efficacy outcomes were analyzed in patients with a baseline modified Mayo score (MMS) ranging from 5 to 9, in alignment with the global populations of the ELEVATE UC 52 and ELEVATE UC 12 studies. In the Japan cohort, 14.3% (4/28) of patients treated with etrasimod achieved clinical remission at week 12, compared to 7.1% (1/14) in the placebo group. By

week 52, these rates increased to 25.0% (7/28) for etrasimod and remained at 7.1% (1/14) for placebo. At both time points, a higher proportion of patients receiving etrasimod demonstrated endoscopic improvement (week 12: 17.9% vs. 7.1%; week 52: 28.6% vs. 7.1%), symptomatic remission (week 12: 39.3% vs. 14.3%; week 52: 39.3% vs. 7.1%), and EIHR (week 12: 10.7% vs. 0%; week 52: 25.0% vs. 7.1%) when compared to placebo. Corticosteroid-free clinical remission at week 52 was achieved in 25.0% (7/28) of patients in the etrasimod group, versus 7.1% (1/14) in the placebo group. Sustained clinical remission through week 52 was observed in 7.1% (2/28) of patients receiving etrasimod, whereas no patients in the placebo group met this outcome (Takeuchi et al., 2025). In the ELEVATE UC 52 trial, etrasimod was significantly more effective than placebo in achieving clinical remission, clinical response, endoscopic improvement, and corticosteroid-free remission at Weeks 12 and 52, in both bio/JAKi-naïve and -experienced patients. Among bio/JAKi-naïve individuals, etrasimod also led to higher rates of symptomatic remission, EIHR, and sustained remission. These endpoints were not significantly improved in bio/JAKi-experienced patients. In ELEVATE UC 12, etrasimod showed significant benefits at Week 12 in bio/JAKi-naïve patients across multiple endpoints, while in bio/JAKi-experienced patients, only clinical response reached significance. Subgroup analysis from ELEVATE UC 52 revealed that patients with prior exposure to one biologic or JAKi benefited significantly from etrasimod across several efficacy outcomes, whereas those with exposure to two or more therapies showed only numerical, non-significant improvements. Similar trends were observed in ELEVATE UC 12, where significant benefits were limited to patients with a single prior biologic or JAKi. In JAKi-exposed subgroups, etrasimod led to numerically higher rates of clinical remission and endoscopic improvement, though outcomes at Week 52 were inconsistent and lacked statistical significance (Vermeire et al., 2024).

3.2. Safety:

Safety outcomes in the Japan cohort were evaluated through week 52, with treatment-emergent adverse events (TEAEs) documented accordingly. Adverse events that began during the ELEVATE UC 12 study and persisted into ELEVATE UC 40 JAPAN were counted as a single continuous event. Safety data were listed and summarized by treatment group for all participants who received at least one dose of the study drug. TEAEs were reported in 84.4% (27/32) of patients receiving etrasimod and in 62.5% (10/16) of those receiving placebo. Serious adverse events (SAEs) occurred in 3.1% (1/32) of patients in the etrasimod group and 6.3% (1/16) in the placebo group. One patient in each treatment arm discontinued therapy due to worsening ulcerative colitis. Among patients treated with etrasimod, the most frequently reported TEAEs were pyrexia (21.9%), headache (12.5%), and malaise (12.5%). Single cases of sinus arrhythmia, sinus bradycardia, and macular edema (3.1% each; 1/32) were also observed in the etrasimod group. No cases of bradycardia, atrioventricular block, or abnormalities in pulmonary function tests were reported. There were no deaths in either group (Takeuchi et al., 2025). Safety data from the pooled analysis of ELEVATE UC 52 and ELEVATE UC 12 showed that treatment-emergent adverse events (TEAEs) occurred in 59.9% of bio/JAKi-naïve and 61.3% of bio/JAKi-experienced patients receiving etrasimod, compared to 48.9% and 58.3% in the respective placebo groups. The most frequently reported TEAEs among etrasimod-treated patients, regardless of prior biologic or JAKi exposure, were headache and ulcerative colitis (including disease flares). Serious adverse events (SAEs) were reported in 4.4% of bio/JAKi-naïve and 6.1% of bio/JAKi-experienced patients receiving etrasimod, versus 5.1% and 2.4%, respectively, in the placebo groups. Adverse events leading to treatment discontinuation were numerically more common in bio/JAKi-experienced patients receiving placebo. No deaths were reported in any subgroup. The incidence of infections, including herpes zoster, was comparable across treatment arms and prior therapy status (Vermeire et al., 2024).

3.3. Role in therapy:

Etrasimod demonstrates a general therapeutic benefit over placebo in patients with ulcerative colitis; however, the proportion of individuals achieving a durable response remains relatively low. Treatment outcomes were generally less favorable among patients with prior exposure to biologic agents or Janus kinase (JAK) inhibitors. Etrasimod does not require dose titration to mitigate first-dose bradycardia. In addition, etrasimod has a relatively short elimination half-life of approximately 30 hours, allowing for faster recovery of lymphocyte counts following treatment discontinuation. This feature may be clinically relevant in circumstances requiring rapid drug clearance, such as planned pregnancy, whereas ozanimod's active metabolite has a prolonged half-life of up to 11 days ('Etrasimod for Moderate to Severe Ulcerative Colitis', n.d.).

4. Conclusions:

Recent clinical trials have demonstrated that etrasimod is an effective treatment option for ulcerative colitis, particularly in patients who have not responded adequately to standard therapies. In comparison with placebo, etrasimod has shown meaningful improvements in clinical remission, endoscopic improvement, symptomatic remission, EIHR, CS-free remission, and sustained clinical remission. The ELEVATE UC 12, ELEVATE UC 40 Japan, and ELEVATE UC 52 trials further support the superiority of etrasimod over placebo as both induction and maintenance therapy, while also demonstrating a favorable safety profile during longer treatment durations.These studies reported ongoing symptom relief with a low incidence of serious adverse events, highlighting etrasimod's potential as a viable long-term therapeutic strategy. Acting as a selective modulator of the $S1P_1$, $S1P_4$, and $S1P_5$ receptors, etrasimod represents a novel mechanism of action that may help expand the current treatment landscape for ulcerative colitis. Future investigations should explore its long-term effectiveness and assess its role in combination regimens to further enhance disease management.

Disclosure

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