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Sphingosine-1-Phosphate Receptor Modulators for the Treatment of Ulcerative Colitis: A Narrative Review Focusing on Safety

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ABSTRACT

Ulcerative colitis is a chronic immune-mediated inflammatory disease of the colon that causes considerable morbidity and increases the risk of colorectal cancer. Several targeted therapies have been developed for moderate-to-severe ulcerative colitis, significantly improving its management. Ozanimod and etrasimod, oral small-molecule drugs, are the latest addition. They belong to the class of sphingosine-1-phosphate receptor (S1PR) modulators and are the first members of this class to be granted approval for ulcerative colitis. They act by blocking lymphocyte trafficking from lymph nodes to inflamed tissues without impairing other immune system functions. This narrative review summarizes current knowledge of sphingosine-1-phosphate receptor modulators, focusing on safety. Safety data from the field of multiple sclerosis (MS) will be discussed because the first S1PR modulator to reach the market, fingolimod, was used extensively for relapsing-remitting MS. Indications for the safe use of ozanimod and etrasimod in ulcerative colitis patients will be provided.

1 | Introduction

Ulcerative colitis (UC), one of the two main forms of inflammatory bowel disease (IBD), is a chronic immune-mediated inflammatory disease of the colon [1]. It is characterized by chronic diarrhea and rectal bleeding, usually with a relapsing and remitting course [2]. UC causes significant morbidity, affects quality of life, and is associated with an increased risk of colorectal cancer [1]. Despite significant advances in UC treatment, colectomy rates remain substantial [3].

UC typically occurs between the second and fourth decades of life [2, 4]. Globally, the incidence of IBD is growing [5] and an increase in the number of incident cases among people aged > 60 years has been reported [4]. Western Europe has elevated incidence rates of UC, ranging from 1.9 to 17.2/100,000 person-years; prevalence rates are estimated between 43.1 and 412/100,000 person-years [5]. In Italy, an estimated age-standardized incidence rate of 15.3/100,000 person-years is reported, with approximately 8300 new cases of UC each year and the burden of IBD reaching 500,000 by 2025 [6].

No curative therapy exists for UC, and treatment goals are the induction and maintenance of disease remission, with treatment based on disease severity and extent [2, 7, 8]. Improved understanding of UC etiology and pathogenesis has supported the development of targeted therapies, including biologics and oral small molecules [1, 4, 9]. Oral modulators of sphingosine-

1-phosphate receptors are a new class of drugs available for UC.

Sphingosine-1-phosphate (S1P), a lysophospholipid signaling molecule produced from the metabolism of sphingomyelin, interacts with cell-surface, G protein-coupled S1P receptors (S1PR) [10]. Five S1PR subtypes (S1PR1-5) are variably expressed in human cells and tissues [11, 12], with S1P/S1PR signaling involved in a range of cellular processes (Figure S1) [11, 13, 14].

Fingolimod, a structural analog of S1P developed to treat relapsing-remitting multiple sclerosis (MS), was the first S1PR modulator to receive regulatory approval [14]. Its primary mechanism of action in MS is the blockade of leukocyte migration into the central nervous system (CNS) [14]. Since leukocyte trafficking plays a role in sustained active intestinal inflammation, S1PR modulators have also been investigated for treating IBD [11, 15]. Two second-generation S1PR modulators are approved for the treatment of adult patients (ozanimod [16]) and patients aged ≥ 16 years (etrasimod [17]) with moderate-to-severe active UC who have had an inadequate response, lost response, or were intolerant to either first-line therapy or a biologic agent [18].

Here, we review current knowledge of S1PR modulators in UC, focusing on safety issues. We also review data from the MS field, which has more extensive experience with S1PR modulators. Finally, we discuss the prevention and mitigation of treatment-related adverse events in UC patients treated with ozanimod or etrasimod.

2 | Sphingosine-1-Phosphate Receptor Modulators

Initial studies showed that binding of fingolimod to S1PR resulted in marked lymphopenia [11]. Subsequent studies demonstrated that S1P signaling via S1PR1 and S1P metabolism by S1P lyase (SPL) were involved in lymphocyte egress from the thymus into the circulation [19]. These studies showed that SPL inhibition (which abolishes the S1P gradient between blood and tissues) or treatment with an S1PR1 modulator (which induces receptor internalization and degradation and reduces signaling via S1PR1) resulted in lymphopenia in mice [19]. Notably, this mechanism was able to block lymphocyte trafficking without impairing other immune functions [19]. Figure 1 depicts the mechanism of action of S1PR modulators acting on S1PR1 in lymphocytes, leading to lymphocyte retention in lymph nodes.

The efficacy and safety of fingolimod were evaluated in three Phase 3 trials in adults with relapsing-remitting MS [23–25] and in pediatric patients with relapsing MS [26]. In these studies, fingolimod was associated with lower relapse rates and improved disease activity on MRI compared with placebo and intramuscular interferon beta-1a and was generally well tolerated in adults but associated with higher rates of severe adverse events compared with interferon beta-1a in children [23–26].

Second-generation S1PR modulators (siponimod [27], ozanimod [16], ponesimod [28], and etrasimod [17]) have increased receptor specificity than fingolimod. Table 1 summarizes the relevant characteristics of currently licensed S1PR modulators.

3 | Sphingosine-1-Phosphate Receptor Modulators for the Treatment of Ulcerative Colitis

3.1 | Clinical Evidence From Studies With Ozanimod and Etrasimod

The main results of the trials evaluating the efficacy and safety of ozanimod [33, 34] and etrasimod [35, 36] are shown in Tables 2 and 3.

The True North Study was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of ozanimod for induction and maintenance therapy in patients with moderate-to-severe UC [34] (Table 2). In the 10-week induction period, patients were divided into two cohorts; patients in cohort 1 (n = 645) were assigned to daily treatment with 1 mg ozanimod or with placebo; in cohort 2 (n = 367), patients received open-label ozanimod at the same daily dose. At week 10, patients with a clinical response to ozanimod in either cohort (n = 457) were again randomized to ozanimod or placebo through week 52 (maintenance period). The primary endpoint for both the induction and the remission period was the percentage of patients with clinical remission (based on the three-component MCS and defined by: a rectal bleeding subscore of 0; a stool frequency subscore ≤ 1, with a decrease ≥ 1 point from baseline; and an endoscopy subscore ≤ 1). Significantly more patients treated with ozanimod than with placebo achieved clinical remission during both induction (18.4% vs. 6%, $p < 0.001$, at week 10) and maintenance (37.0% vs. 18.5%, $p < 0.001$, at week 52). Clinical response rates were also significantly higher with ozanimod than with placebo, during induction (47.8% vs. 25.9%, $p < 0.001$) and maintenance (60.0% vs. 41%, $p < 0.001$). All key secondary clinical, endoscopic, and histologic endpoints were also significantly improved at weeks 10 and 52 with ozanimod versus placebo [34].

The two independent randomized, multicenter, double-blind, placebo-controlled, Phase 3 trials ELEVATE UC 52 and ELEVATE UC 12 evaluated the efficacy of etrasimod for induction and maintenance therapy in patients aged ≥ 16 years with moderate-to-severe active UC [36] (Table 3). ELEVATE UC 52 consisted of a 12-week induction period followed by a 40-week maintenance period ("treat-through" design without re-randomization of responders); ELEVATE UC 12 evaluated induction therapy at 12 weeks. The primary efficacy endpoint was the proportion of patients with clinical remission at weeks 12 and 52 in ELEVATE UC 52, and at week 12 in ELEVATE UC 12 [clinical remission defined as a composite of: stool frequency subscore = 0 (or = 1 with a ≥ 1-point decrease from baseline), rectal bleeding subscore = 0, and endoscopic subscore ≤ 1]. In ELEVATE UC 52, 433 patients were randomly assigned to once-daily 2 mg etrasimod and 354 to placebo; in ELEVATE UC 12, 238 patients were assigned to etrasimod and 116 to placebo. Significantly more patients treated with etrasimod versus placebo achieved clinical remission at 12 weeks (27% vs. 7%, $p < 0.0001$) and at 52 weeks (32% vs. 7%, $p < 0.0001$) in ELEVATE UC 52; greater remission rates with etrasimod were also seen in ELEVATE UC 12 at 12 weeks (25% vs. 15%, $p = 0.026$). In both studies, etrasimod was significantly more efficacious than placebo in all key secondary endpoints and prespecified secondary endpoints.

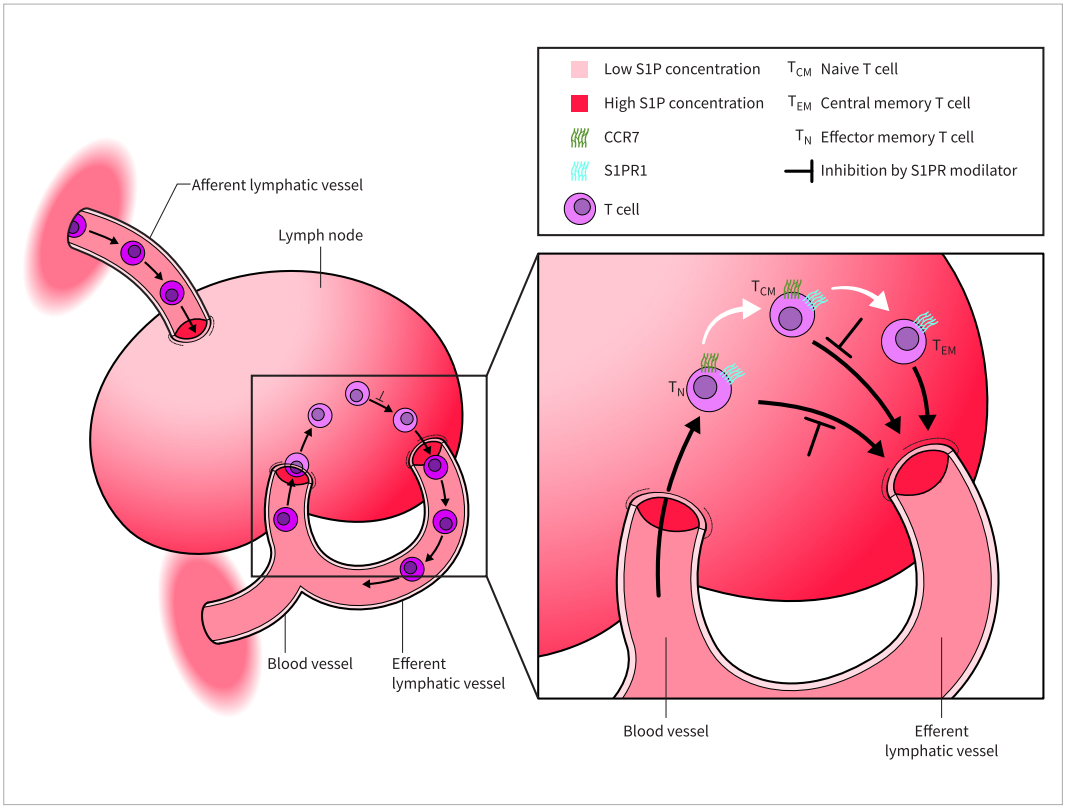

FIGURE 1 | Mechanism of action of S1P receptor modulators. S1PR modulators act primarily by binding to S1PR1 on lymphocytes leading to receptor internalization and degradation [14]. This results in the loss of lymphocyte responsiveness to the S1P gradient (low S1P concentration in lymph nodes and higher concentration in vessels) that drives the egress of lymphocytes from lymph nodes into efferent lymphoid vessels [14]. The sequestration of lymphocytes into lymph nodes results in the reduction of circulating lymphocytes and possibly in the decreased migration of inflammatory cells into inflamed tissues (i.e., CNS in MS and colon in UC) [14]. Shown in the enlarged box of the figure is the egress of specific T lymphocyte subtypes. Naïve T cells (T_N) generally circulate between blood and lymph nodes and egress the lymph node via S1P/S1PR1 [13]. Upon encountering an antigen, T_N are activated, they proliferate and can generate central memory T cells (T_{CM}) and effector memory T cells (T_{EM}) [20]. S1PR modulators block the egress of T_N and T_{CM}, which express on their surface S1PR1 and the lymph node-homing CCR7 receptors [21], but do not block the egress of T_{EM} which lack CCR7 on their surface and exit from lymph nodes via an S1P-S1PR1-independent mechanism [14]. Therefore, the presence of S1PR modulators does not affect T_{EM} recirculation and T_{EM} peripheral levels, thus maintaining immunosurveillance and a prompt response to pathogens [14, 22]. Figure modified from McGinley and Cohen (2021) and Comi et al. (2017) [14, 22]. https://creativecommons.org/licenses/by-nc/4.0/.

The ELEVATE UC studies also included patients with isolated proctitis (i.e., inflammation limited to the rectum), a patient population considered difficult to treat and typically excluded from clinical trials in UC [37]. A post-hoc subgroup analysis of the ELEVATE studies showed that etrasimod was associated with a significant improvement versus placebo in most efficacy endpoints at weeks 12 and 52 in the subgroup of patients with isolated proctitis, consistent with the efficacy data from the overall ELEVATE study population [37].

The open-label extensions of TOUCHSTONE, True North Study, and OASIS have shown that the reported remission and response rates are sustained in the long-term [38–40].

Real-world data documenting the impact of ozanimod and etrasimod in the management of UC in clinical practice are currently limited [41].

4 | Overview of Safety Data of Sphingosine-1-Phosphate Receptor Modulators

4.1 | Mechanisms Underlying Adverse Events Related to Sphingosine-1-Phosphate Receptor Modulation

Initial clinical trials with fingolimod revealed a broad spectrum of adverse events [29]. The mechanisms underlying the effects on heart rate, atrioventricular conduction, blood pressure, and endothelial cell function, are extensively investigated [42–44]. S1PR modulators act initially as potent agonists of S1PR1, but this is transient as continuous stimulation of receptors leads to their internalization and uncoupling from the downstream signaling pathway, resulting in functional antagonism [42, 43]. Initial activation of S1PR1 on cardiomyocytes can explain the transient effects on heart rate and atrioventricular conduction at

TABLE 1 | Overview of currently approved S1P receptor modulators for the treatment of multiple sclerosis and/or ulcerative colitis.[a]

	Fingolimod	Siponimod	Ozanimod	Ponesimod	Etrasimod
Receptor selectivity	S1PR1, S1PR3, S1PR4, S1PR5	S1PR1, S1PR5	S1PR1, S1PR5	S1PR1	S1PR1, S1PR4, S1PR5
Administration route	Oral	Oral	Oral	Oral	Oral
Prodrug (requires activation)	Yes	No	No	No	No
T_{max}	12–16 h	3–8 h	6–8 h	2–4 h	6–8 h
Elimination half-life	6–9 days	~30 h	~20 h[b]	22–33 h	26–32 h
Time to steady-state	1–2 months	6 days	7 days	3–5 days	7 days
Time to lymphocyte count reduction	4–6 h	4–6 h	6–12 h	1–6 h	1–3 h
Lymphocyte decrease from baseline	70%	33%–76%	34%–68%	50%–70%	41%–69%
Time to normal lymphocyte count after drug discontinuation	1–2 months	1–2 weeks	~3 months	10 days	1–2 weeks
Indication (s) (EMA)	Highly active relapsing remitting MS in adults and pediatric patients aged ≥ 10 years	Secondary progressive MS in adults with active disease	• Relapsing remitting MS in adults with active disease • Moderately to severely active UC in patients who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent	Relapsing forms of MS in adults with active disease	Moderately to severely active UC in patients aged ≥ 16 years who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biologic agent
Date of approval	2010 (FDA) 2011 (EMA)	2019 (FDA) 2020 (EMA)	2020 for MS (FDA and EMA) 2021 for UC (FDA and EMA)	2021 (FDA and EMA)	2023 (FDA) 2024 (EMA)

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; MS, multiple sclerosis; S1PR, sphingosine-1-phosphate receptor; UC, ulcerative colitis.

[a]Data reported in the table were extracted from Coyle et al. (2024), Bencardino et al. (2023), Wils and Peyrin-Biroulet (2023), Perez-Jeldres et al. (2021), and the EMA summary of product characteristics of the five drugs [16–18, 27–32].

[b]Ozanimod has two active metabolites with half-lives of 19 and 22 h.

therapy initiation with S1PR modulators [42, 43] (Figure 2). Stimulation of S1PR1 receptors in atrial myocytes activates cell surface G protein-coupled inwardly rectifying potassium (GIRK) channels, which regulate potassium efflux [42, 44]. The modulation of GIRK channels results in a negative chronotropic effect (heart rate decrease) at the sinoatrial node and a negative effect on conduction through the atrioventricular node [42, 44]. The initial activation of S1P1 by fingolimod has been associated also with a short and transient reduction in blood pressure, which is likely due to vasodilation mediated by S1PR1/S1PR3-induced activation of endothelial nitric oxide synthase and release of nitric oxide [42]. Continuous dosing of the S1PR1 modulator (e.g., fingolimod, which does not bind to S1PR2 and has a low affinity for S1PR3) and persistent downregulation of S1PR1 shift the endogenous balance of S1P signaling to S1PR2 and S1PR3, leading to vasoconstriction and disturbances of endothelial cell barrier function (Figure 2) [42]. Vasoconstriction results in a small increase in blood pressure, which reaches a plateau after 6 months of treatment [42]. The impairment of endothelial cell barrier function associated with the downregulation of S1PR1

TABLE 2 | Overview of clinical trials of ozanimod in patients with moderate-to-severe ulcerative colitis.

Trial	Interventions	Primary endpoint	Secondary endpoints	Adverse events
TOUCHSTONE Randomized, double-blind, placebo-controlled, Phase 2 trial $n = 197$ [33]	Ozanimod 0.5 mg, once daily ($n = 65$) Ozanimod 1 mg, once daily ($n = 67$) Placebo ($n = 65$)	Clinical remission at 8 weeks (induction): 14% (0.5 mg; $p = 0.14$), 16% (1 mg; $p = 0.048$), 6% (placebo) At 32 weeks (maintenance): 26% (0.5 mg; $p = 0.01$), 21% (1 mg; $p = 0.002$), 6% (placebo)	Clinical response (8 weeks): 54% (0.5 mg; $p = 0.06$), 57% (1 mg; $p = 0.02$), 37% (placebo) Mucosal healing (8 weeks): 28% (0.5 mg; $p = 0.03$), 34% (1 mg; $p = 0.002$), 12% (placebo) Histologic remission (8 weeks): 14% (0.5 mg; $p = 0.63$), 22% (1 mg; $p = 0.07$), 11% (placebo) Clinical response (32 weeks): 35% (0.5 mg; $p = 0.06$), 51% (1 mg; $p < 0.001$), 20% (placebo) Mucosal healing (32 weeks): 32% (0.5 mg; $p = 0.006$), 33% (1 mg; $p = 0.005$), 12% (placebo) Histologic remission (32 weeks): 23% (0.5 mg; $p = 0.02$), 31% (1 mg; $p < 0.001$), 8% (placebo)	All adverse events[a]: 40% (0.5 mg), 39% (1 mg), 40% (placebo) Serious adverse events[a]: 2% (0.5 mg), 4% (1 mg), 9% (placebo) Adverse events leading to treatment discontinuation[a]: 5% (0.5 mg), 1% (1 mg), 6% (placebo) Adverse cardiac events[a]: 2% (0.5 mg), 0 (1 mg), 3% (placebo)
True North Study Multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial $n = 1012$ [34]	*Induction 10 weeks* Cohort 1 ($n = 645$) treated in a double-blind manner with ozanimod 1 mg, once daily ($n = 429$) or with placebo ($n = 216$) Cohort 2 ($n = 367$) treated in an open-label manner with ozanimod 1 mg, once daily *Maintenance 52 weeks* $n = 457$ (ozanimod-responders during induction) treated with ozanimod 1 mg, once daily ($n = 230$) or with placebo ($n = 227$)	Clinical remission at 10 weeks (induction): 18.4% versus 6% (placebo); $p < 0.001$ Clinical remission at 52 weeks (maintenance): 37% versus 18.5% (placebo); $p < 0.001$	Clinical response (10 weeks): 47.8% versus 25.9% (placebo), $p < 0.001$ Endoscopic improvement (10 weeks): 27.3% versus 11.6% (placebo), $p < 0.001$ Mucosal healing (10 weeks): 12.6% versus 3.7% (placebo), $p < 0.001$ Clinical response (52 weeks): 60% versus 41% (placebo), $p < 0.001$ Endoscopic improvement (52 weeks): 45.7% versus 26.4% (placebo), $p < 0.001$ Mucosal healing (52 weeks): 29.6% versus 14.1% (placebo), $p < 0.001$	*Induction period* All adverse events: 40.1% versus 38% (placebo), cohort 1; 39.8% in cohort 2 Serious adverse events: 4% versus 3.2% (placebo), cohort 1; 6.3% in cohort 2 Serious treatment-related adverse events: 0.2% versus 0.9% (placebo), cohort 1; 0.8% in cohort 2 Adverse events leading to treatment discontinuation: 3.3% versus 3.2% (placebo), cohort 1; 3.8% in cohort 2 *Maintenance period* All adverse events: 49.1% versus 36.6% (placebo)

(Continues)

TABLE 2 | (Continued)

Trial	Interventions	Primary endpoint	Secondary endpoints	Adverse events
			Maintenance of remission (52 weeks): 52% versus 29% (placebo), $p = 0.002$ Glucocorticoid-free remission (52 weeks): 31.7% versus 16.7%, $p < 0.001$ Durable remission (52 weeks): 17.8% versus 9.7% (placebo), $p = 0.003$	Serious adverse events: 5.2% versus 7.9% (placebo) Serious treatment-related adverse events: 0 versus 0.4% (placebo) Adverse events leading to treatment discontinuation: 2.6% versus 1.3% (placebo)

[a]During the entire trial.

results in increased vessel leakage which may explain the cases of macular edema reported in studies of S1PR modulators [42].

4.2 | Safety Data From Studies of Sphingosine-1-Phosphate Receptor Modulators in Multiple Sclerosis

4.2.1 | Cardiac Effects

Cardiac adverse events have raised particular concern and are extensively investigated in terms of clinical implications [29, 42]. A pooled analysis ($n = 3635$) [45] identified a transient, dose-dependent heart rate reduction with a maximum decrease of 8 (fingolimod 0.5 mg) to 11 (fingolimod 1.25 mg) beats per minute (BPM) below baseline 4–5 h after the first dose. Symptomatic bradycardia was rare, occurring in 0.6% and 2.1% of patients treated with fingolimod 0.5 and 1.25 mg, respectively. Most events were mild-to-moderate in severity and resolved spontaneously. Atrioventricular conduction delays observed in a few patients were mostly transient and asymptomatic and disappeared within 24 h of treatment.

The overall clinically benign (i.e., transient, asymptomatic, self-limiting) nature of fingolimod first-dose effects on heart rate and atrioventricular conduction was confirmed in the phase IV EPOC study in 900 fingolimod-treated patients with relapsing MS, which included patients with pre-existing cardiac conditions treated with heart rate-lowering medications [46]. No relevant new safety issues, including cardiovascular (CV) issues, emerged from long-term studies of up to 14-year continuous exposure to fingolimod or in post-marketing studies [29, 42, 47].

Based on MS studies, the toxicity and cardiac effect profile of ozanimod appears favorable [29, 48–50]. In the absence of head-to-head studies, efficacy and safety data from pivotal Phase 3 trials of fingolimod ($n = 1212$) and ozanimod ($n = 1773$) were compared using a matching-adjusted indirect comparison at first-dose cardiac monitoring, 1 year, and 2 years [48]. During first-dose monitoring, ozanimod was associated with a lower risk of heart rate reduction, any conduction abnormalities, atrioventricular block, and the need for extended monitoring, compared with fingolimod. At 1 year, ozanimod was associated with a lower risk of any adverse events, mean lymphocyte count reductions, and liver enzyme abnormalities; at 2 years, ozanimod was associated with a lower risk of any adverse events, adverse events leading to treatment discontinuation, bradycardia, herpetic infections, and liver enzyme abnormalities.

Long-term studies of ozanimod in MS have not reported new safety concerns. An interim analysis of the DAYBREAK study, an extension of the pivotal Phase 3 trials of ozanimod in relapsing MS ($n = 2494$), showed that continuous use of ozanimod for up to 5 years was associated with efficacy and safety outcomes consistent with those established in the registration trials [51].

The favorable cardiac safety profile of ozanimod was further established in a thorough QT/corrected QT (QTc) study in healthy adult subjects showing that ozanimod at therapeutic and supratherapeutic doses had no relevant effects on the QT/QTc interval or heart rate [49]. By contrast, fingolimod (1.25 and 2.5 mg doses) has been reported to prolong the QT/QTc interval by 14 ms [29].

4.2.2 | Hypertension

In studies with fingolimod, hypertension was reported in 8% of patients treated with fingolimod versus 4% of patients receiving placebo [29]. Mean increases were 3 mm Hg for systolic blood pressure and 2 mm for diastolic blood pressure; these increases developed after 1 month of treatment and were persistent with continued treatment [29].

In pivotal studies with ozanimod, 3.9% of patients versus 2.1% of patients in the control arm (interferon beta-1a) reported hypertension. The increase in systolic blood pressure was 1–2 mm Hg, while diastolic blood pressure was not affected [29]. The increase in systolic blood pressure developed after 3 months of treatment and persisted with continued treatment [29].

TABLE 3 | Overview of clinical trials with etrasimod in patients with moderate-to-severe ulcerative colitis.

Trial	Interventions	Primary endpoint	Secondary endpoints	Adverse events
OASIS Proof-of-concept, double-blind, parallel-group, Phase 2 trial $n = 156$ [35]	12-week treatment with: Etrasimod 1 mg, once daily ($n = 50$), or etrasimod 2 mg, once daily ($n = 52$), or placebo ($n = 54$)	Improvement from baseline in the modified MCS at 12 weeks[a]: 1.94 (1 mg; $p = 0.15$) 2.49 (2 mg; $p = 0.009$) 1.50 (placebo)	Endoscopic improvement[b]: 22.5% (1 mg; $p = 0.31$) 41.8% (2 mg; $p = 0.003$) 17.8% (placebo) Improvement in the 2-component MCS[a]: 1.30 (1 mg; $p = 0.09$) 1.75 (2 mg; $p = 0.002$) 0.92 (placebo) Improvement in total MCS[a]: 2.69 (1 mg; $p = 0.13$) 3.35 (2 mg; $p = 0.01$) 2.08 (placebo) Clinical remission[c]: 16% (1 mg; $p = 0.14$) 33% (2 mg; $p < 0.001$) 8.1% (placebo) Clinical response[c]: 43.7% (1 mg; $p = 0.13$) 50.6% (2 mg; $p = 0.03$) 32.5% (placebo) Histologic improvement[c]: 20.4% (1 mg; $p = 0.09$) 31.7% (2 mg; $p = 0.006$) 10.2% (placebo) Histologic remission[c]: 10.2% (1 mg; $p = 0.27$) 19.5% (2 mg; $p = 0.03$) 6.1% (placebo)	Patients with any TEAEs: 59.6% (1 mg); 56% (2 mg); 50% (placebo) Patients discontinuing treatment due to ≥ 1 TEAE: 5.8% (1 mg); 8.0% (2 mg); 0, (placebo) Patients with TEAEs: 5.8% (1 mg); 0 (2 mg); 11.1% (placebo)
ELEVATE UC 52 Randomized, double-blind, Phase 3 trial $n = 433$ [36]	Etrasimod 2 mg, once daily ($n = 289$) Placebo ($n = 144$)	Clinical remission at 12 weeks (induction) and at 52 weeks (maintenance): 27% versus 7% (placebo), $p < 0.0001$ at 12 weeks 32% versus 7% (placebo), $p < 0.0001$ at 52 weeks	Endoscopic improvement at 12 and 52 weeks: 35% versus 14% (placebo), $p < 0.0001$ at 12 weeks Symptomatic remission at 12 and 52 weeks: 46% versus 21% (placebo), $p < 0.0001$ at 12 weeks Endoscopic improvement-histologic remission at 12 and 52 weeks: 21% versus 4% (placebo), $p < 0.0001$ at 12 weeks Clinical response at 12 and 52 weeks (prespecified secondary endpoint): 62% versus 34% (placebo), $p < 0.0001$ at 12 weeks All key secondary endpoints and all prespecified secondary endpoints were met also at 52 weeks	At 52 weeks: Any adverse events, 71% etrasimod, 56% placebo Serious adverse events, 7% etrasimod, 6% placebo Adverse events leading to treatment discontinuation, 4% etrasimod, 5% placebo

(Continues)

TABLE 3 | (Continued)

Trial	Interventions	Primary endpoint	Secondary endpoints	Adverse events
ELEVATE UC 12 Randomized, double-blind, Phase 3 trial $n = 354$ [36]	Etrasimod 2 mg, once daily ($n = 238$) Placebo ($n = 116$)	Clinical remission at 12 weeks: 25% versus 15% (placebo), $p = 0.026$	Endoscopic improvement: 31% versus 19% (placebo), $p = 0.0092$ Symptomatic remission: 47% versus 29% (placebo), $p = 0.0013$ Endoscopic improvement-histologic remission: 16% versus 9% (placebo), $p = 0.036$ Clinical response (prespecified secondary endpoint): 62% versus 41% (placebo), $p = 0.0002$	Any adverse events: 47% etrasimod, 47% placebo Serious adverse events: 3% etrasimod, 2% placebo Adverse events leading to treatment discontinuation: 5% etrasimod, 1% placebo

Abbreviations: MCS, Mayo Clinic Score; TEAE, treatment-emergent adverse event.
[a]Least squares mean.
[b]Percentage of patients achieving endoscopic improvement.
[c]Exploratory efficacy outcomes.

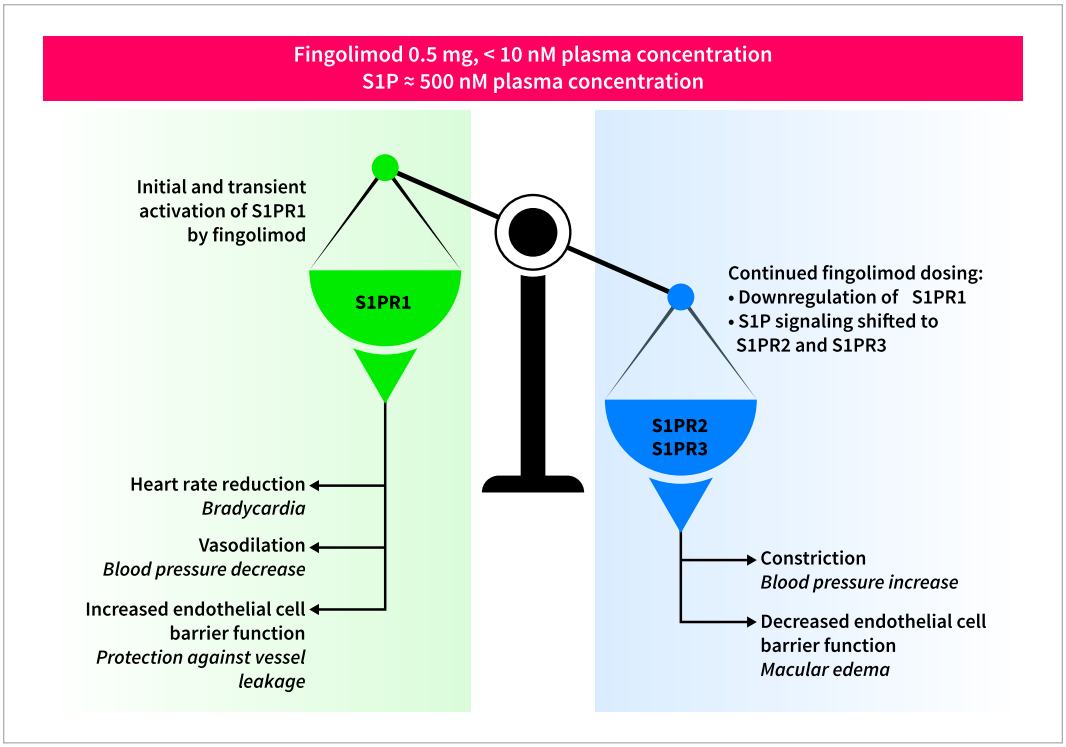

FIGURE 2 | Mechanisms of non-therapeutic effects of S1P receptor modulators. Figure modified from Camm et al. (2014) and Constantinescu et al. (2022) [42, 44].

4.2.3 | Macular Edema

Macular edema has been reported in 0.5% of patients treated with fingolimod versus 0.4% of patients treated with placebo, across studies with MS patients [29]. The risk of macular edema increased in a dose-dependent manner; macular edema occurred during the first 3–4 months of treatment and generally resolved after fingolimod discontinuation [29].

In studies with ozanimod, the reported proportion of patients with macular edema was 0.3% and was identical to that reported in the control arm (interferon beta-1a) [29].

4.2.4 | Pulmonary Effects

Reductions in forced expiratory volume (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) have been reported in studies with fingolimod. Decreases from baseline in the predicted values for FEV1 and DLCO were 2.8% and 3.3% respectively (1.0% and 0.5% respectively, in the placebo arm) [29]. FEV1 reductions appeared to be reversed by fingolimod discontinuation [29].

Dose-dependent FEV1 reductions have been reported also with ozanimod, after 3 months of treatment [29]. Compared to the control arm (interferon beta-1a), patients treated with ozanimod had a decline in FEV1 from baseline to 12 months of 60 mL (mean difference 1.9%) [29]. It is unclear whether FEV1 changes associated with ozanimod are reversible [29].

4.2.5 | Hepatic Effects

In studies with fingolimod, increases in the serum levels of transaminase have been reported: alanine transaminase (ALT) levels ≥ 3 times the upper level of normal (ULN) were seen in 14% of patients treated with fingolimod versus 3% of patients receiving placebo; ALT levels ≥ 5 x ULN were seen in 4.5% versus 1% of patients respectively, within 6–9 months from treatment start [29]. Transaminase levels returned to normal 1–2 months after fingolimod discontinuation [29]. In the post-marketing setting of fingolimod, cases of clinically relevant liver injury have occurred [29].

Ozanimod has also been associated with ALT elevations, though less markedly than fingolimod: ALT ≥ 3 × ULN in 5.5% treated patients versus 3.1% control (interferon beta-1a) patients; ALT ≥ 5 × ULN in 1.6% versus 1.3%, respectively [29]. Transaminase elevations typically resolved within 2–4 weeks of continued treatment [29].

4.2.6 | Infections

In clinical studies, common infections (bronchitis, herpes zoster, influenza, sinusitis and pneumonia) were more frequent in patients treated with fingolimod or ozanimod than in patients from the control arms [29]. Overall, serious infections have occurred in 2.3% of patients treated with fingolimod versus 1.6% of patients treated with placebo, and in 1% of patients treated with ozanimod versus 0.8% of patients treated with interferon beta-1a [29].

Cases of progressive multifocal leukoencephalopathy (PML) have also been described, especially in clinical studies with fingolimod. As of August 2022, 61 cases have been reported, corresponding to an incidence rate of 5.88 per 100,000 person-years [29]. In studies with ozanimod, so far one case of PML has been reported (per ≈40,000 person-years) [29].

4.2.7 | Teratogenic Effects

Evidence from animal studies has shown that S1P receptor modulators can cause fetal harm [29]. Based on these findings, the summaries of product characteristics for all S1P receptor modulators mention the potential fetal risk and recommend the use of effective contraception. The analysis of pooled data from the clinical trials with fingolimod has reported 66 pregnancies; of these, 28 ended with live births, 9 were spontaneous abortions, 24 elective abortions, and 5 were ongoing or lost to follow-up [29]. According to the data from the post-marketing fingolimod pregnancy exposure registry [52], major congenital malformations in live births have a prevalence of 6.6% (95% CI 3.3–11.5), which is higher than the prevalence in the general population (2.09% [95% CI 2.08–2.10]) and in the untreated MS population (5.0 [95% CI 2.3–9.3]).

The analysis of the pooled data of the clinical trials of ozanimod has reported 78 pregnancies; of these 42 ended with live births (with 1 report of duplex kidney), 12 were spontaneous abortions, and 15 elective abortions [29].

4.2.8 | Drug-Drug Interactions

In general, the coadministration of S1P receptor modulators with drugs acting on the cardiovascular system or drug with immune-modulating or immunosuppressive action should be considered with caution due to possible additive effects [29].

Ozanimod should not be administered with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) because some of its major metabolites are inhibitors of monoamine oxidase B (MAO-B), which is involved in serotonin breakdown [53]. The concomitant administration of ozanimod and SSRIs/SNRIs might therefore result in serious adverse events, including serotonin accumulation and hypertensive crisis [53].

4.3 | Safety Data From Studies of Ozanimod in Ulcerative Colitis

In the Phase 3 True North study, the incidence of adverse events in patients with moderate-to-severe UC treated with ozanimod was similar to placebo during induction but numerically higher during maintenance treatment [34] (Table 2). At 52 weeks, the rates of patients discontinuing treatment due to adverse events were low, both in the group treated with ozanimod (2.6%) and in the placebo group (1.3%) [34]. The most frequent adverse events reported by patients treated with ozanimod at 52 weeks were ALT increases (4.8%), headache (3.5%), nasopharyngitis (3%), arthralgia (3%), γ-glutamyltransferase increases (3%), and anemia (1.3%). Serious adverse events were reported at 52 weeks in 5.2% and 7.9% of patients treated with ozanimod and placebo, respectively (none were related to ozanimod).

With regard to adverse events of special interest for the treatment with S1P receptor modulators, bradycardia was more frequent in patients treated with ozanimod during the induction period but not during maintenance; bradycardia had an overall low incidence (< 1%) with no clinically relevant consequences [34]. During induction, hypertension was reported in 1.4% and 1.9% of patients in cohorts 1 and 2, respectively, and in no

patients receiving placebo; during maintenance, hypertension was reported in 1.7% of patients treated with ozanimod and 1.3% of those receiving placebo [34]. One patient (0.2%) treated with ozanimod in cohort 1 had hypertensive crisis during induction; during maintenance, one patient in each treatment arm (0.4%) developed this adverse event [34]. Macular edema was reported in 0.2%–0.3% of patients during induction with ozanimod and in 0.4% during maintenance; there were no reports of macular edema in patients receiving placebo during induction or maintenance [34]. During the maintenance period, infections (nasopharyngitis, upper respiratory tract infection, herpes zoster) occurred in 23% of ozanimod-treated patients versus 11.9% on placebo; serious infections occurred in 0.9% versus 1.8%, respectively [34].

Overall, the tolerability and adverse event profile of ozanimod in UC patients overlapped those reported in MS patients treated with ozanimod [29]. The 7-day dose-escalation strategy used in True North may have prevented clinically relevant cardiac effects [34]. According to the interim analysis of the True North OLE (≈3 years of continued ozanimod treatment), 109 patients of the 131 (83.2%) enrolled in the OLE had treatment-emergent adverse events (TEAEs), 18.3% had serious TEAEs, and 6.1% discontinued treatment due to TEAEs [39]. The exposure-adjusted incidence rate per 100 patient-years for adverse events of special interest was highest for serious infections (1.9/100) and herpes zoster (1.7/100) and lowest for cancer (0.7/100), complete atrioventricular block, bradycardia, and macular edema (0.2/100 each).

In a recent analysis of True North and its OLE ($n = 823$, up to 146 weeks ozanimod corresponding to 2219 patient-years) [54], 3.8% of patients had cardiac events and 8.5% vascular events; most were rare (< 1%) except for hypertension, which was reported by 6% of patients. First-dose ozanimod decreased mean heart rate by 0.2 BPM from pretreatment to 6 h, and two patients reported bradycardia, which resolved without treatment modification. An increase in blood pressure at week 52 was reported by 12.2% of patients, with mean increases in systolic and diastolic blood pressure of 5.1 and 2.2 mmHg, respectively.

In conclusion, ozanimod, when used as indicated, is well tolerated by patients with UC with an acceptable profile of CV and other relevant adverse events.

4.4 | Safety Data From Studies of Etrasimod in Ulcerative Colitis

Etrasimod is generally considered safe based on evidence from preclinical and clinical studies [18]. No first-dose up-titration is required to improve the tolerability of etrasimod. Studies in healthy adults and the pivotal Phase 3 studies in adult patients with moderate-to-severe UC showed that 2 mg fixed-dose etrasimod had a CV safety profile similar to S1PR modulators administered via dose titration [17, 55]. Most adverse events reported by patients participating in the ELEVATE studies were of mild-to-moderate severity [36]. In both ELEVATE UC 12 and ELEVATE UC 52, the rates of severe adverse events (< 10%) and of permanent discontinuation due to adverse events were low and similar between treatment groups (at 52 weeks, 4% in etrasimod-treated patients and 5% in placebo-treated patients) (Table 3) [36]. There were no deaths or malignancies, and the most frequently reported adverse events included anemia, headache, and worsening of UC or UC flare. The incidence rates of overall infections, serious infections, and opportunistic infections were low (≤ 3%), and similar between treatment groups. The incidence rate of other adverse events of special interest (hypertension, bradycardia, atrioventricular block, macular edema) was low (≤ 3%), similar in ELEVATE UC 12 and ELEVATE UC 52, but overall higher in patients treated with etrasimod than in those receiving placebo [36].

The long-term safety of etrasimod in UC is being evaluated in an ongoing OLE study of the OASIS and ELEVATE trials [56]. Patients who received either placebo or etrasimod (1 or 2 mg) were divided into two cohorts for analysis: the "placebo-controlled cohort" (i.e., patients who received either placebo or etrasimod in the OASIS Phase 2 study or the two ELEVATE Phase 3 studies) and the "all UC cohort" (i.e., patients who received ≥ 1 dose of etrasimod in OASIS, OLE of ELEVATE UC 12, and NCT04176588; $n = 956$, 769.3 patient-years of exposure to etrasimod). Preliminary data show similar rates of adverse events, serious adverse events, and infections between treatment arms (i.e., etrasimod and placebo) and between study cohorts (i.e., "placebo-controlled cohort" and "all UC cohort"). Bradycardia occurred in 1.8% of patients treated with etrasimod and in 1.5% of patients in the "all UC cohort". Most bradycardia events were asymptomatic. The incidence of other adverse events of special interest was low and similar between treatment arms and study cohorts (hypertension < 2.5%; macular edema < 0.5%).

A thorough QT/QTc study in healthy subjects receiving multiple ascending doses of etrasimod (2–4 mg, once daily) showed that etrasimod was not associated with clinically relevant effects on the QT/QTc interval; the impact on heart rate was mild, transient, and asymptomatic [57].

5 | Recommendations for the Safe Use of Ozanimod and Etrasimod for the Treatment of Patients With Ulcerative Colitis

Despite the improved receptor specificity of ozanimod (selective for S1PR1 and S1PR5) and etrasimod (selective for S1PR1, S1PR4, and S1PR5) and encouraging safety data emerging from clinical studies, precautions in clinical practice are warranted. The prescribing information provides detailed recommendations for the prevention and management of adverse events related to S1PR modulators, including CV events (cardiac events and hypertension), macular edema, liver injury, and infections [16, 17]. Cardiac events are transient and typically occur with the first dose of S1PR modulator during induction, while hypertension occurs during maintenance and is usually persistent; macular edema can present between 2 weeks and 1 year from the first dose, while other typical adverse events can present any time during treatment [15]. As part of the additional risk minimization measures, the European Medication Agency has created a Healthcare Professional Information Pack, which should be provided to all healthcare professionals who intend to

TABLE 4 | Recommendations for the safe and effective use of ozanimod and etrasimod in patients with moderate-to-severe ulcerative colitis.

Contraindications	• Immunodeficient state • Myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or NYHA class III/IV heart failure • History or presence of second-degree atrioventricular block type II or third-degree atrioventricular block or sick sinus syndrome unless a functioning pacemaker is being used • Severe active infections, active chronic infections • Active malignancies • Severe hepatic impairment (Child-Pugh class C) • Pregnancy and in women of childbearing age not using effective contraception	
Posology	Ozanimod:	Etrasimod:
	0.92 mg once daily, orally	2 mg once daily, orally
First-dose titration	Ozanimod:	Etrasimod:
	7-day regimen: Days 1–4: 0.23 mg; days 5–7: 0.46 mg; day 8 and thereafter: 0.92 mg	Not required
Reinitiation after drug interruption	Ozanimod:	Etrasimod:
	First-dose titration required if: ≥ 1 day interruption during first 14 days of treatment > 7 consecutive days of interruption during 15–28 days of treatment > 14 consecutive days of interruption after 28 days of treatment	If treatment is interrupted for ≥ 7 consecutive days, it is recommended to resume treatment with food for the first three doses
First-dose monitoring	Ozanimod:	Etrasimod:
	6-h monitoring in patients with certain pre-existing cardiac conditions	4-h monitoring in patients with certain pre-existing cardiac conditions
Principal warning and precautions of use		
Cardiac function	Ozanimod: • Pre-treatment ECG required to exclude a pre-existing cardiac condition • Caution required in initiating treatment in patients using a beta-blocker or a calcium channel blocker • 6-h first-dose monitoring recommended in patients with: Resting heart rate < 55 bpm, second-degree (Mobitz type I) atrioventricular block, or history of myocardial infarction or heart failure • First-dose monitoring includes hourly pulse and blood pressure measurements; ECG prior and at the end of the 6-h period is also recommended • Cardiologist advice required before initiating treatment in patients: — With history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnea, history of recurrent syncope or symptomatic bradycardia	Etrasimod: • Pre-treatment ECG required to exclude a pre-existing cardiac condition • Caution required in initiating treatment in patients using a beta-blocker or a calcium channel blocker, QT prolonging drugs, class IA and class III antiarrhythmic drugs • 4-h first-dose monitoring for signs of bradycardia recommended in patients with: Resting heart rate < 50 bpm, second-degree (Mobitz type I) atrioventricular block, or history of myocardial infarction or heart failure • Cardiologist advice required before initiating treatment in patients: — With history of symptomatic bradycardia, recurrent cardiogenic syncope, or severe untreated sleep apnea — With unstable ischemic heart disease, history of cardiac arrest, cerebrovascular disease (occurring > 6 months prior to treatment initiation), or uncontrolled hypertension

(Continues)

TABLE 4 | (Continued)

	— With pre-existing significant QT interval prolongation or other risks for QT prolongation, and patients on drugs other than beta-blockers and calcium channel blockers that may potentiate bradycardia — On class Ia or class III antiarrhythmic drugs, which have been associated with cases of torsades de pointes in patients with bradycardia	— With significant QT interval prolongation — With arrhythmias requiring treatment with class Ia or class III anti-arrhythmic drugs
Liver function	• Pre-treatment transaminase and bilirubin levels before treatment initiation required • Monitor transaminase and bilirubin levels at 1-, 3-, 6-, 9-, and 12-month during treatment and periodically after • Discontinue treatment in patients with confirmed liver injury • Pre-existing liver disease may increase the risk of treatment-related liver enzyme elevations	
Infections	• Recent (within 6 months) complete blood cell count before treatment initiation • Delay treatment initiation if any active infection is present • Assess complete blood cell count periodically during treatment • Interrupt treatment if lymphocyte count $< 0.2 \times 10^9$/L; reinitiate treatment when count $> 0.5 \times 10^9$/L • Interrupt treatment in case of a severe infection	
Macular edema	• Ophthalmologic evaluation prior to treatment initiation and periodically during treatment in patients with: Diabetes mellitus, uveitis, or history of retinal disease • Discontinue treatment in case of confirmed macular edema	
Blood pressure	Monitor blood pressure regularly during treatment	
Respiratory function	Use with caution in patients with severe respiratory disease, pulmonary fibrosis, asthma, and chronic obstructive disease	
Drug interactions	Ozanimod: • The coadministration with inhibitors of monoamine oxidase, or CYP2C8 inducers is not recommended • Concomitant anti-neoplastic, immunomodulatory or non-corticosteroid immunosuppressive therapies are not recommended either • Caution required when treatment is initiated in patients taking a beta-blocker or a calcium channel blocker	Etrasimod: • Avoid coadministration with drugs that are moderate to strong inhibitors of two or more of CYP2C8, CYP2C9, and CYP3A4 • Avoid coadministration with drugs that are moderate to strong inducers of two or more of CYP2C8, CYP2C9, and CYP3A4 • Not recommended in patients who are CYP2C9 poor metabolizers and who take drugs that are moderate or strong inhibitors of CYP2C8 and/or CYP3A4

Note: For further information readers are referred to the drug labels of ozanimod and etrasimod [16, 17].
Abbreviations: ECG, electrocardiogram; NYHA, New York Heart Association.

prescribe ozanimod or etrasimod [16, 17]. The educational pack (included in the summary of product characteristics) contains information on where to find the latest summary of product characteristics, a checklist for healthcare professionals, a patient/caregiver guide, and a pregnancy-specific patient reminder card. Table 4 summarizes the principal recommendations for the safe and effective use of ozanimod and etrasimod.

6 | Conclusions

Evidence from clinical studies with ozanimod and etrasimod has further confirmed that targeting lymphocyte egress from lymph nodes to the bloodstream is a valuable strategy for reducing inflammation in UC. Notably, these S1PR modulators have been shown to improve UC symptoms and achieve objective outcomes like endoscopic and histologic remission. The available evidence suggests that both ozanimod and etrasimod, when used as recommended and with cardiologic support if needed, have a manageable profile of adverse events. Cardiac events related to first-dose ozanimod and etrasimod are rare, transient, asymptomatic, and self-limiting. Long-term and post-marketing data, which have just begun to emerge, will help define the real-life and long-term safety profile of S1PR modulators in UC. Head-to-head comparisons between S1PR modulators and between S1PR modulators and other targeted UC

therapies will determine the position of S1PR modulators in current treatment algorithms.

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Conflicts of Interest

Massimo C. Fantini was a paid consultant to Pfizer in connection with the development of this manuscript, and has acted as a consultant for: AbbVie, Celgene, Celltrion, Gilead, Pfizer, MSD, Bristol-Meyer, Eli-Lilly, Takeda, Janssen-Cilag, Roche, Galapagos, Biogen, Alfasigma, Sandoz. He has also received financial support for research from Janssen-Cilag, Pfizer. Diego Centonze was a paid consultant to Pfizer in connection with the development of this manuscript, and has acted as an Advisory Board member and received honoraria for speaking or consultation fees from Alexion, Almirall, Amicus, Bayer, Biogen, BMS, Celgene, Chiesi, GW Pharmaceuticals, Horizon, Janssen, Lundbeck, Merck Serono, Novartis, Roche, Sandoz, Sanofi-Genzyme, Viatris, and Teva. He is also the Principal Investigator in clinical trials of Biogen, BMS, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Actelion. His preclinical and clinical research has been supported by grants from Bayer Schering, BMS, Biogen, Celgene, Lundbeck, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva. Giovanni Giacobazzi and Silvia Benemei are full employees of Pfizer. Emanuele Romeo was a paid consultant to Pfizer in connection with the development of this manuscript.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.