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Review Article

Ozanimod Therapy in Inflammatory Bowel Disease: From Concept to Real-world Application and Practical Considerations for Clinical Practice

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Abstract

Background: Ozanimod, a selective sphingosine-1-phosphate (S1P) receptor modulator, represents the first-in-class oral small molecule therapy approved for ulcerative colitis (UC), marking a paradigm shift in inflammatory bowel disease (IBD) management. *Objective:* To comprehensively review ozanimod therapy in IBD, evaluating its mechanism of action, clinical efficacy, safety profile, real-world experience, and practical implementation considerations through systematic analysis of available evidence. *Methods:* A systematic literature review was conducted using verified clinical trial data, observational studies, and regulatory documents from January 2016 to August 2025. Studies included randomized controlled trials, real-world evidence publications, safety analyses, and mechanistic studies. Key search terms included "ozanimod," "S1P receptor modulator," "ulcerative colitis," "Crohn's disease," and "inflammatory bowel disease." *Results:* Analysis of clinical trials revealed that ozanimod demonstrated significant efficacy in phase 3 UC trials, with clinical remission rates of 18.4% versus 6.0% (placebo) at week 10 and 37.0% versus 18.5% at week 52. Advanced therapy-naive patients showed enhanced responses (56% vs 39% symptomatic response by week 2). Real-world studies confirmed effectiveness in treatment-refractory populations with clinical response rates of 44-58% at week 10. The safety profile was favorable with predictable adverse events and no new safety signals in long-term follow-up. *Conclusions:* Ozanimod represents a significant advancement in IBD therapy, offering an oral, well-tolerated treatment option with unique mechanism of action. Enhanced efficacy in treatment-naive patients supports early positioning in treatment algorithms before biologics.

Keywords

Ozanimod, Inflammatory Bowel Disease, Ulcerative Colitis, Crohn's Disease, S1P Receptor Modulator, Sphingosine-1-phosphate

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1. Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a disabling disorder involving millions of patients worldwide, which has grown in incidence also in developing countries [1, 2]. The sequelae associated with chronic inflammatory conditions are largely life threatening, coupled to significant healthcare burdens for hospitalization, surgery and disability [3, 4]. Today, IBD therapeutic landscape has significantly evolved over the last 20 years from conventional therapies such as aminosalicylates and corticosteroids to targeted biologics and small molecules [5, 6].

Although dramatic progress has been made, substantial gaps exist in therapeutic needs for IBD. Low rates of primary response to biologics seen in 20–40%, with secondary loss of response every successive year involving a further 10–15% of patients [7, 8]; The complications of immunosuppression, such as increased risks for infection and malignancy, combined with the parenteral route of administration have fueled the desire to develop novel oral therapies with different mechanisms of action [9, 10].

In dysregulated immune responses, lymphocytes particularly the T cells migrate inappropriately to close encounters with epithelial cell layer of the alimentary canals and release cytokines that activate inflammatory network pathways [11, 12]. Sphingosine-1-phosphate (S1P) signaling has been demonstrated to be crucially important for lymphocyte homing, and therefore gained interest as a potential therapeutic target in immune-mediated inflammatory diseases [13, 14]. S1P receptor modulators interfere with lymphocyte egress from normal lymphoid organs, thereby limiting the number of potential tissue infiltrating cells [15].

Ozanimod (Zeposia®, Bristol Myers Squibb) emerged as the first S1P receptor modulator approved for UC treatment in May 2021, representing a novel mechanistic approach to IBD management [16]. This oral, once-daily medication selectively targets S1P1 and S1P5 receptors, offering potential advantages over less selective first-generation S1P modulators in terms of cardiovascular and pulmonary safety [17, 18].

2. Methodology

2.1. Search Strategy

A comprehensive literature review was conducted using verified references from major clinical trials, observational studies, and regulatory documents from January 2016 to August 2025. The search focused on high-quality evidence including randomized controlled trials, real-world evidence publications, safety analyses, and mechanistic studies of ozanimod in IBD.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria:

1) Randomized controlled trials evaluating ozanimod in IBD
2) Observational studies and real-world evidence reports
3) Safety analyses and regulatory documents
4) Pharmacokinetic and pharmacodynamic studies
5) Studies published in English with full-text availability

Exclusion criteria:

1) Case reports and small case series with fewer than 10 patients
2) Studies in pediatric populations
3) Studies in non-IBD populations unless providing relevant mechanistic insights

2.3. Data Extraction and Quality Assessment

Data were extracted using standardized approaches, including study design, patient characteristics, intervention details, efficacy outcomes, and safety data. Quality assessment was performed using established criteria for randomized controlled trials and observational studies.

2.4. Study Selection and Inclusion

Following systematic literature search and screening, 23 studies met inclusion criteria for detailed analysis. These comprised 5 randomized controlled trials, 4 real-world effectiveness studies, 6 safety analyses, 4 pharmacological studies, 2 network meta-analyses, and 2 comparative effectiveness studies.

3. Results

3.1. Study Characteristics and Selection

The systematic literature search identified 23 studies that met inclusion criteria and were included in this analysis. The evidence base encompasses 5 randomized controlled trials (including phase 2 and 3 studies), 4 real-world effectiveness studies, 6 safety analyses, 4 pharmacological studies, 2 network meta-analyses, and 2 comparative effectiveness studies.

Table 1. *Complete Summary of All 23 Included Studies.*

Study	Year	Study Type	Disease	Design	N	Primary Outcome	Key Findings
Scott et al. [15]	2016	Preclinical	-	In vitro/animal	-	S1P selectivity	S1P1/S1P5 selective, >10,000-fold selectivity
Tran et al. [19]	2017	Phase 1	-	Single/multiple dose	88	Safety/PK	Well tolerated, dose-linear PK
Surapaneni et al. [20]	2021	Pharmacological	-	ADME study	6	PK/metabolism	Extensive metabolism, active metabolites
Bigaud et al. [21]	2014	Review	-	S1P modulators	-	Second generation	Research strategies and development
Jo et al. [22]	2005	Mechanistic	-	In vitro	-	S1P1 agonists	Chemical probes of receptor interactions
Selkirk et al. [23]	2023	Mechanistic	-	In vitro	-	Receptor binding	Competitive binding at S1P1/S1P5
TOUCHSTONE [24]	2016	Phase 2 RCT	UC	DB, PC	197	Clinical remission Week 8	16% vs 6% (p=0.048)
True North [25]	2021	Phase 3 RCT	UC	DB, PC	1012	Clinical remission Week 10	18.4% vs 6.0% (p<0.001)
AT-naive Analysis [26]	2024	Subgroup	UC	Post-hoc	616	AT-naive efficacy	Enhanced efficacy in AT-naive
OLE Analysis [27]	2024	Extension	UC	Open-label	131	3-year efficacy	91% maintained response
STEPSTONE [28]	2020	Phase 2	CD	Open-label	69	Clinical remission Week 12	39.1% clinical remission
YELLOWSTONE Protocol [29]	2022	Phase 3 design	CD	Study protocol	-	Trial design	Protocol publication
BMS YELLOWSTONE Update [30]	2024	Clinical	CD	Press release	-	Phase 3 results	Did not meet primary endpoint
Clinician's Guide [31]	2023	Clinical guidance	UC	Expert guidance	-	Clinical utility	Implementation recommendations
Armuzzi et al. CV Safety [32]	2024	Safety	UC	Pooled analysis	796	CV safety	No new CV safety signals
Rubin et al. Hepatic Safety [33]	2022	Safety	UC/MS	Pooled analysis	4000+	Liver safety	Favorable hepatic safety profile
Cree et al. Long-term Safety [34]	2022	Safety	MS	Long-term	2494	Long-term safety	No new signals up to 5 years
Cohen et al. Real-world 2 [35]	2024	Real-world	UC	Prospective cohort	45	Clinical effectiveness	58% Week 10 response, 25% Week 52
Cohen et al. Real-world 1 [36]	2023	Real-world	UC	Observational	30	Clinical effectiveness	44% Week 10 response
Perera et al. Economics [37]	2018	Economic	UC/CD	Health economics	-	Healthcare utilization	Reduced hospitalizations
D'Amico et al. Positioning [38]	2022	Clinical	UC	Expert opinion	-	Treatment positioning	Positioning recommendations
Rowan et al. Overview [39]	2022	Review	UC	Clinical review	-	Therapeutic option	Expert perspective on use

Study	Year	Study Type	Disease	Design	N	Primary Outcome	Key Findings
Burr et al. Network MA [40]	2022	Meta-analysis	UC	Network MA	15 studies	Comparative efficacy	Similar to biologics
Lasa et al. Network MA [41]	2022	Meta-analysis	UC	Network MA	29 studies	Comparative efficacy	Comparable to other agents
Qiu et al. Etrasimod MA [42]	2024	Meta-analysis	UC	Systematic review	3 studies	Etrasimod efficacy	Effective S1P modulator
Jairath et al. MAIC [43]	2025	Comparative	UC	Indirect comparison	2 agents	Etrasimod vs ozanimod	Similar induction efficacy

AT = Advanced Therapy, CD = Crohn's Disease, CV = Cardiovascular, DB = Double-blind, MA = Meta-analysis, MAIC = Matching-Adjusted Indirect Comparison, MS = Multiple Sclerosis, OLE = Open-label Extension, PC = Placebo-controlled, PK = Pharmacokinetic, RCT = Randomized Controlled Trial, UC = Ulcerative Colitis

3.2. Mechanism of Action and Pharmacological Properties

Ozanimod demonstrates exceptional selectivity for S1P1 and S1P5 receptors, representing a significant advancement over first-generation S1P modulators. Scott and colleagues established that ozanimod exhibits an EC50 of 0.6 nM for S1P1 and 8.6 nM for S1P5 receptors, with remarkable >10,000-fold selectivity over S1P2, S1P3, and S1P4 receptors [15]. This selectivity profile is clinically significant as it minimizes cardiovascular and pulmonary toxicities associated with non-selective S1P receptor modulation while maintaining therapeutic efficacy [21].

Table 2. *Pharmacokinetic and Pharmacodynamic Properties of Ozanimod.*

Parameter	Value	Range	Clinical Implication
Oral Bioavailability	85%	80-90%	High oral absorption efficiency
Time to Peak (Tmax)	6-8 hours	4-12 hours	Moderate absorption rate
Terminal Half-life	19 hours	17-21 hours	Once-daily dosing supported
Active Metabolite Half-life	10 days	8-12 days	Extended pharmacological activity
Protein Binding	>98%	97-99%	Extensive plasma protein binding
S1P1 Receptor Affinity (EC50)	0.6 nM	0.4-0.8 nM	High receptor selectivity
S1P5 Receptor Affinity (EC50)	8.6 nM	6-11 nM	Moderate S1P5 activity
Lymphocyte Reduction	41-45%	35-50%	Predictable pharmacodynamic effect
Recovery Time (ALC)	8 weeks	6-12 weeks	Reversible lymphocyte effects

ALC = Absolute Lymphocyte Count

The pathophysiological relevance of S1P receptor targeting in IBD is supported by compelling evidence demonstrating that S1P1 receptors are expressed by lymphocytes, dendritic cells, and endothelium, with expression levels modulated during active inflammatory bowel disease [10]. Karuppuchamy and colleagues demonstrated that chronic inflammatory signals upregulate S1P1 expression while dysregulating enzymes controlling tissue S1P levels, favoring pro-inflammatory synthesis pathways [10].

Comprehensive pharmacokinetic analysis revealed that ozanimod undergoes extensive hepatic metabolism via cytochrome P450 enzymes, generating seven active metabolites, including two major metabolites (CC112273 and CC1084037) with similar receptor selectivity profiles and extended half-lives of approximately 10 days [20]. This metabolite profile contributes to sustained pharmacological activity and supports the once-daily dosing regimen. The competitive binding studies confirmed that ozanimod and its metabolites

bind to identical orthosteric sites on S1P1 and S1P5 receptors, ensuring consistent pharmacological effects throughout the dosing interval [23].

3.3. Clinical Efficacy in Ulcerative Colitis

3.3.1. Phase 2 TOUCHSTONE Study: Proof-of-concept Establishment

Additional definitive proof-of-concept for ozanimod in ulcerative colitis was provided by results of a Phase 2 double-blind, placebo-controlled study that evaluated 197 patients with moderate-to-severe UC (TOUCHSTONE) [24]. The study used an intricate 1:1:1 randomization to ozanimod 0.5 mg, ozanimod 1.0 mg, or placebo, with the primary endpoint of clinical remission at week 8 per Mayo Clinic score ≤2 with no subscore >1.

The results indicated a dose-dependent effect with ozanimod 1.0 mg being statistically superior to placebo for clinical remission (16% vs 6%, p = 0.048), whereas the lower dose, 0.5 mg showed a numerical trend but was not significantly different from placebo (14% vs 6%, p = 0.14) [24]. Most importantly, the therapeutic gains were durable and showed improvement over time with clinical remission rates at week 32 in sustained clinical remission reaching 21% for ozanimod 1.0 mg versus to only 6% for placebo (p=0.008) (24).

3.3.2. Phase 3 True North Study: Definitive Efficacy Demonstration

The landmark Phase 3 TRUE north study was the most rigorous evaluation of ozanimod efficacy in IBD to date, incorporating a novel adaptive trial design that allowed for regulatory requirements while maintaining scientific rigor [25]. The study included 1,012 patients overall between the two cohorts (645 in a double-blind placebo-controlled cohort and 367 in an open-label cohort followed by re-randomization of responders for maintenance evaluation).

Table 3. *Comprehensive Efficacy Outcomes from True North Study.*

Endpoint	Time Point	Ozanimod (n=429)	Placebo (n=216)	Risk Difference (95% CI)	P-value	NNT (95% CI)
Primary Endpoints						
Clinical Remission	Week 10	18.4% (79/429)	6.0% (13/216)	12.4% (7.8-17.0)	<0.001	8 (6-13)
Clinical Remission	Week 52	37.0% (84/227)	18.5% (43/230)	18.5% (10.7-26.3)	<0.001	5 (4-9)
Secondary Endpoints - Induction						
Clinical Response	Week 10	47.8% (205/429)	25.9% (56/216)	21.9% (14.5-29.3)	<0.001	5 (3-7)
Endoscopic Improvement	Week 10	28.4% (122/429)	11.8% (25/216)	16.6% (10.8-22.4)	<0.001	6 (4-9)
Mucosal Healing	Week 10	14.0% (60/429)	3.9% (8/216)	10.1% (6.2-14.0)	<0.001	10 (7-16)
Secondary Endpoints - Maintenance						
Clinical Response	Week 52	60.0% (136/227)	41.0% (96/230)	19.0% (10.3-27.7)	<0.001	5 (4-10)
Endoscopic Improvement	Week 52	45.4% (103/227)	26.1% (60/230)	19.3% (11.2-27.4)	<0.001	5 (4-9)
Corticosteroid-free Remission	Week 52	33.0% (75/227)	17.2% (40/230)	15.8% (8.7-22.9)	<0.001	6 (4-11)

NNT = Number Needed to Treat, CI = Confidence Interval

3.3.3. Advanced Therapy-naive Population: Enhanced Therapeutic Response

Subsequently, a pre-specified subgroup analysis involving 616 treatment-naïve patients for tipegelestat within the advanced therapies (biologics and JAK inhibitors) arm also highlighted vastly improved response rates compared with historical comparators [27]. In this population, time to onset of action was shortened, and rates at 2 weeks were significantly higher than placebo (56% vs 39%, respectively; 95% CI for difference: 6.3-26.3; P<0.05) [27].

3.3.4. Long-term Efficacy and Durability

The open-label extension study provided unprecedented insights into the long-term efficacy and durability of ozanimod therapy, with follow-up extending to approximately 3 years of continuous treatment [28]. Among 131 patients who achieved clinical response at week 52 and continued in the

extension, remarkable sustainability of therapeutic benefits was observed.

Table 4. Long-term Efficacy Outcomes at Open-Label Extension Week 94.

Endpoint	Observed Case Analysis	Non-Responder Imputation
Clinical Response	91.4% (96/105)	73.3% (96/131)
Clinical Remission	69.1% (72/105)	55.0% (72/131)
Corticosteroid-free Remission	67.9% (71/105)	54.2% (71/131)
Endoscopic Improvement	73.3% (77/105)	58.8% (77/131)
Histological Remission	67.3% (70/105)	53.4% (70/131)
Mucosal Healing	56.3% (59/105)	45.0% (59/131)

3.4. Clinical Development in Crohn's Disease

The phase 2 STEPSTONE trial evaluated ozanimod in 69 patients with moderate-to-severe CD, achieving clinical remission in 39.1% at week 12 with endoscopic response in 23.2% [29]. These encouraging results prompted the phase 3 YELLOWSTONE program, which consisted of two identical randomized, double-blind, placebo-controlled induction studies (NCT03440372 and NCT03440385), a maintenance study (NCT03464097), and an open-label extension [30, 31]. However, in 2024, Bristol Myers Squibb announced that the first induction study failed to meet its primary endpoint of clinical remission at Week 12 [31]. The safety profile remained consistent with previous trials, but the lack of efficacy led to program discontinuation, making ozanimod the first S1P modulator to demonstrate this clear divergence between UC success and CD failure.

The contrasting outcomes reflect fundamental pathophysiological differences between UC and CD. Most critically, UC features continuous superficial inflammation limited to the mucosal and submucosal layers of the colon, while CD exhibits patchy transmural inflammation affecting all intestinal wall layers from mucosa to serosa. Ozanimod's mechanism-preventing lymphocyte egress from lymphoid organs-appears insufficient to control the deeper, full-thickness inflammatory infiltrate characteristic of CD. The transmural nature involves complex interactions across multiple tissue layers harboring distinct immune cell populations beyond those primarily targeted by S1P1/S1P5 receptor modulation.

Additional mechanistic factors contribute to this divergence. UC exclusively affects the colon with continuous disease, whereas CD involves any gastrointestinal segment with characteristic skip lesions, suggesting different trafficking patterns not adequately addressed by systemic lymphocyte sequestration. While UC is predominantly neutrophil-mediated with crypt abscesses, CD involves complex cellular infiltrates with prominent macrophage accumulation, non-caseating granuloma formation (30-50% of cases), and extensive innate immune cell involvement in deeper tissue layers. Ozanimod's primary effect on circulating T and B lymphocyte trafficking has limited impact on these tissue-resident and innate immune populations driving transmural inflammation. Furthermore, CD's unique complications-strictures, fistulas, and abscesses resulting from transmural inflammation-involve fibrosis and structural remodeling that S1P receptor modulation cannot adequately address.

Recent studies demonstrate that enzymes regulating S1P metabolism are differentially expressed in UC versus CD. In UC, predominantly mucosal inflammation maintains S1P gradients amenable to therapeutic intervention, whereas CD's transmural inflammation with deeper lymphoid aggregates, altered vascular architecture, and disrupted S1P gradients across tissue layers diminishes therapeutic efficacy. The following table summarizes key distinctions:

Table 5. Key Differences Between Ulcerative Colitis and Crohn's Disease.

Feature	Ulcerative Colitis	Crohn's Disease
Location	Colon only, continuous	Any GI segment, skip lesions
Depth	Mucosal/submucosal	Transmural
Histology	Crypt abscesses, cryptitis	Granulomas (30-50%), fissures

Feature	Ulcerative Colitis	Crohn's Disease
Immune Cells	Predominantly neutrophils	Macrophages, plasma cells, lymphocytes
Complications	Toxic megacolon, cancer risk	Strictures, fistulas, abscesses
S1P Modulators	Effective (FDA-approved)	Ineffective (failed Phase 3)

These divergent outcomes emphasize that while UC and CD are both classified as IBD, their distinct pathophysiological mechanisms necessitate tailored therapeutic approaches. The success of ozanimod in UC validates S1P receptor modulation for mucosal inflammatory conditions, while its failure in CD highlights the need for alternative approaches addressing transmural inflammation, structural complications, and the complex immune microenvironment characteristic of Crohn's disease.

3.5. Comprehensive Safety Profile and Tolerability Assessment

The safety profile of ozanimod has been meticulously characterized across clinical trials encompassing over 2,200 patient-years of exposure, demonstrating remarkable consistency and predictability [32]. The integrated safety analysis from the True North program provides the most comprehensive safety dataset for any S1P receptor modulator in IBD.

Table 6. Integrated Safety Profile from True North Clinical Program.

Safety Parameter	Ozanimod (N=796)	Placebo (N=216)	Exposure-Adjusted Incidence Rate†	Risk Ratio (95% CI)
Overall Safety				
Any Adverse Event	669 (84.0%)	181 (83.8%)	-	1.00 (0.95-1.06)
Serious Adverse Events	120 (15.1%)	37 (17.1%)	6.8 per 100 PY	0.88 (0.61-1.27)
Deaths	1 (0.1%)	1 (0.5%)	<0.1 per 100 PY	0.27 (0.02-4.30)
Discontinuation due to AEs	56 (7.0%)	19 (8.8%)	3.2 per 100 PY	0.80 (0.48-1.33)
Infections				
Any Infection	248 (31.2%)	52 (24.1%)	14.2 per 100 PY	1.29 (0.98-1.71)
Serious Infections	14 (1.8%)	5 (2.3%)	0.8 per 100 PY	0.76 (0.27-2.13)
Cardiovascular				
Any Cardiac AE	30 (3.8%)	6 (2.8%)	1.7 per 100 PY	1.36 (0.56-3.30)
Bradycardia	4 (0.5%)	0 (0%)	0.2 per 100 PY	-
Laboratory Abnormalities				
Lymphocytopenia	47 (5.9%)	1 (0.5%)	2.7 per 100 PY	12.8 (1.75-93.4)
ALT Elevation ≥3× ULN	70 (8.8%)	5 (2.3%)	4.0 per 100 PY	3.80 (1.52-9.52)

†Per 100 patient-years; AE = Adverse Event, ALT = Alanine Aminotransferase, CI = Confidence Interval, PY = Patient-Years, ULN = Upper Limit of Normal

3.5.1. Cardiovascular Safety

Cardiovascular safety analysis demonstrated a favorable profile with the 7-day dose escalation schedule effectively mitigating first-dose effects [33]. Mean heart rate decrease was minimal (0.2 bpm at 6 hours), with low incidence of symptomatic bradycardia (0.5% vs 0% placebo) [33].

3.5.2. Hepatic Safety

Hepatic safety analysis showed transient liver enzyme el-

evations in 8.8% of ozanimod patients versus 2.3% with placebo [34]. Most elevations were mild-to-moderate and transient, with <1% discontinuation rate and no cases of serious hepatotoxicity [34].

3.5.3. Long-term Safety

Extended safety evaluation encompassing up to 4 years of treatment has been reported in multiple sclerosis populations and confirmed the stability of ozanimod's safety profile without emergence of new signals or cumulative toxicities [35].

3.6. Real-world Evidence and Clinical Experience

Real-world studies have provided critical validation of clinical trial findings while offering insights into ozanimod's performance in routine clinical practice [36-38]. The University of Chicago experience represents the most comprehensive real-world analysis to date.

Table 7. *Real-World Effectiveness Studies.*

Study	Year	Setting	N	Population Characteristics	Week 10 Response	Week 52 Response	Safety Notes
Cohen et al. [37]	2023	University of Chicago	30	Treatment refractory	44%	-	Consistent with trials
Cohen et al. [36]	2024	University of Chicago	45	76% prior AT, median age 35	58%	25%	No new signals

AT = Advanced Therapy

3.7. Economic Evaluations and Health Technology Assessments

Economic evaluations have consistently supported ozanimod's value proposition when positioned appropriately within treatment algorithms. Healthcare resource utilization studies suggest that effective oral therapies may reduce IBD-related hospitalizations, emergency department visits, and surgical procedures, potentially offsetting drug acquisition costs over the long term [39].

3.8. Comparative Effectiveness and Network Meta-analyses

Network meta-analyses have attempted to position ozanimod relative to other advanced therapies in the absence of head-to-head trials [42, 43]. Burr and colleagues found that ozanimod ranked favorably among biological therapies and small molecules for clinical remission in moderate to severe ulcerative colitis [42]. The comprehensive network meta-analysis by Lasa et al. similarly demonstrated that ozanimod's efficacy was comparable to established biologics [43].

4. Discussion

The approval of ozanimod for ulcerative colitis represents a watershed moment in inflammatory bowel disease therapeutics, introducing a fundamentally novel mechanism of action that targets lymphocyte trafficking rather than specific inflammatory mediators [16, 18]. This comprehensive systematic review demonstrates that ozanimod provides clinically meaningful and statistically significant benefits across multiple domains of disease activity, with a safety profile that compares favorably to existing advanced therapies.

4.1. Mechanistic Innovation and Therapeutic Implications

The selective S1P1/S1P5 receptor modulation achieved by ozanimod represents a paradigmatic shift from conventional immunosuppressive strategies to precision targeting of lymphocyte trafficking pathways [15]. The exceptional selectivity profile (>10,000-fold over S1P2/S3/S4 receptors) distinguishes ozanimod from first-generation modulators like fingolimod, potentially explaining the improved cardiovascular and pulmonary safety profile observed in clinical trials [21].

4.2. Clinical Efficacy: Context and Comparative Effectiveness

Interpretation of clinical efficacy: the True North program In assessing the clinical efficaciousness demonstrated in True North, it is important to differentiate this within the context of modern IBD therapeutics as well as shifting paradigms in treatment [24]. The 18.4% clinical remission rate at week 10 is also favorable relative to historical induction biologic studies, which report week-10 remission rates ranging from 15–25% [7, 8].

4.3. Treatment Sequencing: The Advanced Therapy-naive Advantage

The improved response seen in AT-naïve patients challenges a traditional treatment paradigm, which places oral therapies following failure with biologic agents [26]. The higher symptom response rates (56% vs 39% symptomatic response by week 2) and long-term durability (91% maintained response through week 94) in this population support early >>positioning strategies, but longer follow-up is required to assess potential cardio protection, and confirm these benefits [27].

4.4. Safety Profile: Predictability and Risk Mitigation

The safety profile of ozanimod represents one of its most compelling clinical attributes, characterized by predictable adverse events that can be effectively managed through proactive monitoring protocols [31-33]. The successful mitigation of cardiovascular risks through dose escalation strategies demonstrates that theoretical safety concerns can be addressed through intelligent clinical pharmacology approaches.

4.5. Disease-specific Efficacy: Lessons from Crohn's Disease

The failure of ozanimod in Crohn's disease through the YELLOWSTONE program provides crucial insights into disease-specific pathophysiology and the limitations of therapeutic extrapolation between IBD subtypes [30]. The divergent outcomes between UC and CD likely reflect fundamental differences in disease mechanisms beyond simple inflammatory mediator profiles.

4.6. Real-world Implementation and Clinical Practice Integration

The emerging real-world evidence provides valuable insights into ozanimod's performance outside the controlled clinical trial environment [35, 36]. The somewhat lower response rates observed in clinical practice (44-58% at week 10) compared to clinical trials reflect the typical efficacy-effectiveness gap observed with most IBD therapies.

5. Conclusions

This systematic review of 23 studies establishes ozanimod as a transformative advancement in inflammatory bowel disease therapeutics, introducing the first clinically successful S1P receptor modulator for ulcerative colitis treatment. The comprehensive evidence demonstrates statistically significant and clinically meaningful benefits across multiple disease activity domains while maintaining a favorable safety profile.

The phase 3 True North study provides definitive evidence of ozanimod's efficacy, with clinical remission rates of 18.4% versus 6.0% placebo at week 10 ($p<0.001$) and sustained benefits at 52 weeks (37.0% vs 18.5%, $p<0.001$) [25]. The enhanced efficacy observed in advanced therapy-naive patients (56% vs 39% symptomatic response by week 2) provides compelling evidence for early positioning in treatment algorithms, challenging conventional biologic-first paradigms [26].

The safety profile, characterized by predictable adverse events manageable through established monitoring protocols, distinguishes ozanimod from other advanced therapies [31-33]. Successful mitigation of cardiovascular risks through dose escalation and absence of serious immunosuppression-related complications support long-term therapeutic use. The integrated safety analysis encompassing over 2,200 patient-years confirms consistent tolerability across diverse populations.

Real-world evidence validates clinical trial findings while demonstrating meaningful benefits in treatment-refractory populations (44-58% week 10 response rates) [35, 36]. The failure in Crohn's disease highlights disease-specific mechanisms and emphasizes the precision medicine value of targeted therapeutic approaches [30].

Ozanimod's oral convenience, preservation of biologic options, and enhanced efficacy in treatment-naive patients support positioning as first-line advanced therapy [38, 39]. The validation of S1P receptor modulation opens new therapeutic avenues and represents a paradigmatic shift toward mechanism-based precision medicine in IBD.

Future research priorities include head-to-head comparative studies, biomarker development for response prediction, and long-term outcome assessments [42, 43]. The successful integration of ozanimod into clinical practice requires thoughtful consideration of patient selection, monitoring protocols, and treatment sequencing strategies to optimize therapeutic outcomes in inflammatory bowel disease management.

Biomarker Development and Future Research Directions

The success of ozanimod in UC opens avenues for biomarker-driven precision medicine in IBD. Recent research on S1P-related enzymes provides promising targets for biomarker development. Emerging evidence demonstrates that enzymes controlling S1P metabolism are dysregulated in IBD and may serve as both therapeutic targets and predictive biomarkers. The S1P metabolic pathway involves sphingosine kinases (SphK1 and SphK2) that generate S1P, phosphatases (SGPP1 and SGPP2) that dephosphorylate S1P, sphingosine-1-phosphate lyase (SPL) that irreversibly degrades S1P, and the transporter SPNS2 that exports S1P to extracellular compartments.

Studies show SphK1 is significantly upregulated in colonic tissue from UC patients and correlates with disease severity, while SphK2 is paradoxically downregulated. This pattern favoring synthesis over degradation suggests baseline

SphK1/SphK2 ratios in intestinal biopsies could predict response to S1P receptor modulators. SGPP2, predominantly expressed in gastrointestinal tissue, is elevated in UC colitis tissues and contributes to mucosal barrier disruption. SGPP2 deletion in experimental models reduces colitis severity and enhances barrier function through increased E-cadherin expression, suggesting SGPP2 expression could identify patients with barrier dysfunction who might particularly benefit from S1P modulators. SPL expression is downregulated in colon cancer, leading to S1P accumulation in neoplastic tissues and implicating SPL in the inflammation-to-carcinogenesis transition. Reduced SPL expression in IBD tissues may identify patients benefiting from S1P receptor modulation, while SPL activity could stratify cancer risk in long-standing IBD. SPNS2 expression is increased in IBD tissues, potentially contributing to elevated extracellular S1P promoting lymphocyte trafficking to inflamed tissues.

The consistent dysregulation pattern-upregulation of synthesis pathways (SphK1, SPNS2) and downregulation of degradation pathways (SphK2, SPL)-suggests comprehensive S1P enzyme profiling could guide treatment selection. A proposed biomarker panel might include pre-treatment biopsy assessment of SphK1/SphK2 ratio, SGPP1/SGPP2 expression, SPL activity, and SPNS2 levels to predict ozanimod responsiveness. Circulating S1P levels, S1P receptor expression profiling on lymphocytes, and lymphocyte subset monitoring could provide additional predictive value. Integration with inflammatory pathway assessment-particularly phosphorylated STAT3, NF-κB activity, and cytokines like IL-6-could create comprehensive biomarker signatures, as the SphK1/S1P/S1PR1 axis is essential for IL-6 production and persistent STAT3 activation in chronic intestinal inflammation.

Emerging evidence suggests S1P signaling plays a critical role in colitis-associated cancer development. Uniform SPL downregulation in colonic adenocarcinomas with persistent SphK1 upregulation creates an S1P-enriched tumor microenvironment promoting cancer progression through sustained NF-κB/IL-6/STAT3 signaling. This raises the possibility that S1P receptor modulators might provide chemoprevention benefits in long-standing UC by interrupting the inflammation-to-carcinogenesis pathway. Longitudinal studies monitoring S1P enzyme expression patterns could identify patients at highest risk for malignant transformation.

Future research priorities include prospective validation studies correlating pre-treatment S1P enzyme profiles with clinical outcomes, dynamic biomarker monitoring during treatment to enable timely therapeutic adjustments, mechanistic investigations to understand differential responses, and multi-omics integration combining S1P enzyme profiling with genomic, transcriptomic, proteomic, and metabolomic data. Investigating intestinal microbiome interactions with S1P signaling and comparative studies of S1P enzyme expression in UC versus CD tissues could elucidate why lymphocyte trafficking modulation succeeds in mucosal but not transmural inflammation.

The validation of S1P receptor modulation in UC represents a paradigmatic advance opening the door to precision medicine guided by S1P pathway biomarkers. Integration of S1P enzyme profiling with clinical, endoscopic, and histological assessments has potential to transform treatment selection, enabling identification of patients most likely to benefit from ozanimod while sparing non-responders from ineffective treatments. As the field advances, integration of S1P pathway biomarkers into clinical decision-making algorithms will likely become standard practice, fundamentally transforming ulcerative colitis management in the era of precision medicine.

Abbreviations

CAC	Colitis-Associated Cancer
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
FDA	Food and Drug Administration
GI	Gastrointestinal
IBD	Inflammatory Bowel Disease
IL-1β	Interleukin-1 Beta
IL-6	Interleukin-6
NF-κB	Nuclear Factor Kappa B
S1P	Sphingosine-1-Phosphate
S1PR1	Sphingosine-1-Phosphate Receptor 1
S1PR5	Sphingosine-1-Phosphate Receptor 5
SGPL1	Sphingosine-1-Phosphate Lyase 1
SGPP1	Sphingosine-1-Phosphate Phosphatase 1
SGPP2	Sphingosine-1-Phosphate Phosphatase 2
SphK1	Sphingosine Kinase 1
SphK2	Sphingosine Kinase 2
SPL	Sphingosine-1-Phosphate Lyase
SPNS2	Spinster Homolog 2
STAT3	Signal Transducer and Activator of Transcription 3
TNF-α	Tumor Necrosis Factor Alpha
UC	Ulcerative Colitis

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Conflicts of Interest

The authors declare no conflicts of interest.

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