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INFLAMMATORY BOWEL DISEASE (S HANANAUER, SECTION EDITOR)

# Novel Non-biologic Targets for Inflammatory Bowel Disease

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## Abstract

**Purpose of Review** The biologic era revolutionized the medical management of inflammatory bowel disease (IBD) and allowed for a paradigm shift away from a therapeutic strategy that traditionally relied on corticosteroids and immunomodulators. IBD treatment has now further evolved to encompass novel non-biologic agents.

**Recent Findings** An electronic database search, spanning up to September 2018, was conducted using PubMed, Web of Science, Google Scholar, and Scopus. Abstracts were also reviewed from Digestive Diseases Week, European Crohn's and Colitis Organization congress, Canadian Digestive Diseases Week, and United European Gastroenterology Week.

**Summary** The JAK1/3 inhibitor, tofacitinib, was shown to both induce and maintain clinical remission and mucosal healing in ulcerative colitis (UC). Also, the sphingosine-1-phosphate (SIP) S1P1/S1P5 receptor agonist ozanimod showed benefit with clinical remission and mucosal healing in UC. Anti-trafficking non-biologic therapies such as AJM300 and a phosphodiesterase (PDE) PDE4 inhibitor, apremilast, have shown benefit in terms of clinical response, clinical remission, and mucosal healing in UC. Upadacitinib and filgotinib have shown initial favorable outcomes in CD patients, with further ongoing trials. Non-biologic agents comprise a growing number of mechanisms of action with the promise of safe and effective oral therapy for patients with IBD.

**Keywords** Non-biologic · IBD · Small molecule

## Introduction

The early historical treatment of inflammatory bowel disease (IBD) consisted of small molecule agents such as corticosteroids, 5-aminosalicylates, and immunomodulators, with broad mechanisms of action. The biologic era revolutionized the medical management of IBD by achieving unsurpassed efficacy while targeting distinct molecular pathways with high specificity [1, 2]. Since the first randomized controlled trial to demonstrate the utility of infliximab, a monoclonal antibody against tumor necrosis factor α (anti-TNF) in the treatment of Crohn's disease, numerous biologic agents have been investigated in the management of IBD [3]. Approved biologics include the anti-TNF agents infliximab, adalimumab, certolizumab, and golimumab, the anti-interleukin 12/23 antibody ustekinumab, and the anti-α4β7 integrin antibody vedolizumab [4–6].

Biologic medications typically have a molecular weight > 1000 kDa and a chemical structure consisting of peptide polymer chains. These properties have important implications for the pharmacokinetics of the agent. First, the large molecular weight of biologic molecules necessitates parenteral administration, either subcutaneous or intravenous, which may be a barrier to access and adherence [7]. From a pharmacokinetic standpoint, large molecule biologics also undergo relatively slow protease-mediated degradation and thus have a long half-life. This longer half-life may be undesirable in the setting of infection, during pregnancy, and in the peri-operative period [8]. Biologic large molecules are potentially antigenic and are prone to anti-drug antibody formation. This immunogenicity may diminish long-term effectiveness through attenuation or loss of response [9, 10]. Finally, biologics are expensive to produce, as compared to small molecule agents.

These limitations have heralded significant research into the development of orally administered small molecules. These typically have a molecular weight < 1000 kDa and

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an organic chemical structure [1, 11]. This low molecular weight allows for transmembrane cellular diffusion and an intracellular site of action, in addition to obviating parenteral administration along with having a short serum half-life and rapid drug clearance [8]. Last, small molecules are not anticipated to be antigenic and should not elicit an antibody response. These features may be significant advantages in the treatment of IBD in comparison to large molecule biologics [8, 11–13].

Various classes of non-biologic molecules have been introduced in the management of IBD. These include (a) janus kinase (JAK) inhibitors, which inhibit the intracellular tyrosine kinases JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) [12, 14, 15]; (b) sphingosine-1-phosphate subtype 1 (S1P1) receptor modulators, which promote the degradation of the S1P1 cell surface receptor and ultimately inhibit lymphocyte trafficking [16–18]; (c) alpha 4-integrin antagonists, which prevent adhesion molecule and lymphocyte integrin interactions [19]; (d) intercellular adhesion molecule-1 (ICAM-1) anti-sense oligonucleotide (alicaforsen) [20]; and (e) phosphodiesterase-4 (PDE4) inhibitors which inhibit the degradation of cyclic adenosine monophosphate (cAMP) resulting in modulation of inflammatory mediators [21]. (See Table 1 for a summary of mechanisms of action, indication, and safety profile of these agents.)

The primary aim of this article is to provide a comprehensive review of the mechanisms and clinical applications of non-biologic therapies in the treatment of IBD.

## Methodology

We conducted an electronic database search of English language articles using PubMed, Web of Science, Google Scholar, and Scopus. The date range of our search included articles published up to September 2018. Keywords included "inflammatory bowel disease," "IBD," "Crohn's disease," "CD," "ulcerative colitis," "UC," "small molecules," "novel targets," "oral," and "non-biologic." Ongoing clinical trials were identified using clinicaltrials.gov. Abstracts from Digestive Diseases Week, European Crohn's and Colitis Organization Congress, Canadian Digestive Diseases Week, and United European Gastroenterology Week were also reviewed. Agents deemed to be in advanced stages of clinical development were included in this review.

**Table 1** Non-biologic agents in IBD, mechanism of action, indication, and safety profile

| Drug | Mechanism of action | Indications/status | Safety summary |
|---|---|---|---|
| Tofacitinib | JAK1 and JAK3 inhibitor | ▪ Moderate to severe UC (approved)<br>▪ Moderate to severe CD (phase 2 completed) | Herpes zoster, rare opportunistic infections, other infections, non-melanoma skin cancer, dyslipidemia, elevated liver enzymes, elevated creatinine kinase, rare neutropenia, rare lymphopenia |
| Peficitinib | JAK1 and JAK3 inhibitor | ▪ Moderate to severe UC (completed phase 2; development discontinued) | Increased creatinine kinase, anemia |
| Upadacitinib | JAK1 inhibitor | ▪ Moderate to severe CD (completed phase 2; development continues) | Limited data. One case each of herpes zoster, non-melanoma skin cancer reported |
| Filgotinib | JAK1 inhibitor | ▪ Moderate to severe CD (completed phase 2; development continues) | Urinary tract infections, nasopharyngitis, pneumonia, herpes zoster, oral candidiasis |
| TD-1473 | Pan-JAK inhibitor with limited systemic bioavailability | ▪ Moderate to severe UC (completed phase 1b; development continues)<br>▪ Moderate to severe CD (phase 2; development continues) | Limited data. No serious infections, tuberculosis, nor herpes zoster reported. |
| Ozanimod | S1P1 and S1P5 receptor modulator | ▪ Moderate to severe UC (completed phase 2)<br>▪ Moderate to severe CD (phase 3; development continues) | Asymptomatic first-degree AV block and bradycardia, elevated liver enzymes, squamous cell skin cancer (1 case) |
| Etrasimod | S1P1, S1P4, S1P5 receptor modulator | ▪ Moderate to severe UC (completed phase 2; development continues) | Limited data |
| AJM300 | α4 Integrin antagonist | ▪ Moderate to severe UC (completed phase 2a)<br>▪ Active CD (completed phase 2) | Nasopharyngitis. No PML in short-term treatment |
| PTG-100 | α4β7 Integrin antagonist | ▪ Moderate to severe UC (completed phase 2b; development continues) | Limited data |
| Alicaforscen | Anti-sense olignonucleotide against ICAM-1 | ▪ Left sided UC and pouchitis (retrospective analysis)<br>▪ Pouchitis (phase 3 enrollment completed) | Limited data |
| Apremilast | PDE4 inhibitor | ▪ Active UC (phase 2 completed) | Diarrhea, nausea, URTI, nasopharyngitis, headache |

## Janus Kinase Inhibitors

JAKs are a group of tyrosine kinase proteins that modulate the inflammatory response by facilitating intracellular processes that are the result of specific extracellular signals. The JAK family of proteins serves as a bridge which influences pro-inflammatory intracellular processes that are initiated by the binding of extracellular cytokines to cell membrane receptors. Cytokine receptor binding results in activation of associated JAKs, which allows for the phosphorylation of specific signal transducer and activator of transcription (STAT) proteins. The phosphorylated STATs migrate to the cell nucleus and ultimately influence pro-inflammatory gene transcription [14, 15]. Various inhibitors of the JAK-STAT pathway have been studied as therapeutic modalities in IBD. These include tofacitinib, filgotinib, pefictinib, upadacitinib, and TD-1473. The mechanism of action of these JAK inhibitors is outlined in Fig. 1.

### Tofacitinib

Tofacitinib is an orally bioavailable JAK inhibitor with relative specificity for JAK1 and JAK3. The efficacy of tofacitinib was studied in a phase 2 randomized, placebo-controlled, double-blind trial of 194 patients with moderate to severe UC at twice daily doses of 0.5 mg, 3 mg, 10 mg, and 15 mg for 8 weeks. The primary outcome was clinical response, and only the 15 mg tofacitinib dose was superior to placebo for this endpoint (78% versus 42%, $P < 0.001$). The secondary endpoint of clinical remission was achieved in 33%, 48%, and 41% of patients receiving tofacitinib at doses of 3 mg ($P = 0.01$), 10 mg ($P < 0.001$), and 15 mg ($P < 0.001$), respectively, compared to placebo (10%) [22].

Subsequently, three randomized placebo-controlled phase 3 trials (OCTAVE Induction 1 and 2 and OCTAVE Sustain trials) were conducted to investigate tofacitinib induction and maintenance therapy in patients with moderate to severe UC. The OCTAVE Induction 1 and 2 trials included 598 and 541 UC patients, respectively, who had failed treatment with steroids, thiopurines, infliximab, or adalimumab. Patients received induction doses of tofacitinib at 10 mg twice daily for 8 weeks. The primary end point was clinical remission at 8 weeks and was achieved in 18.5% of patients receiving tofacitinib (versus 8.2% for placebo, $P = 0.007$) in OCTAVE Induction 1 and 16.6% of patients receiving tofacitinib (versus 3.6% for placebo, $P < 0.001$) in OCTAVE Induction 2. Mucosal healing, a secondary endpoint, was achieved in 31.3% of patients receiving tofacitinib (versus 15.6% for placebo, $P < 0.001$) in OCTAVE Induction 1 and 28.4% of patients receiving tofacitinib (versus 11.6% for placebo, $P < 0.001$) in OCTAVE Induction 2. Patients who achieved clinical response during the OCTAVE Induction 1 or 2 trials were included in the OCTAVE Sustain trial. Of 593 patients included in OCTAVE Sustain, 198 received tofacitinib at 5 mg twice daily, 197 received tofacitinib at 10 mg twice daily, and 198 received placebo. The primary endpoint was clinical remission at 52 weeks, and secondary endpoints included mucosal healing at 52 weeks and sustained clinical (at 24 and

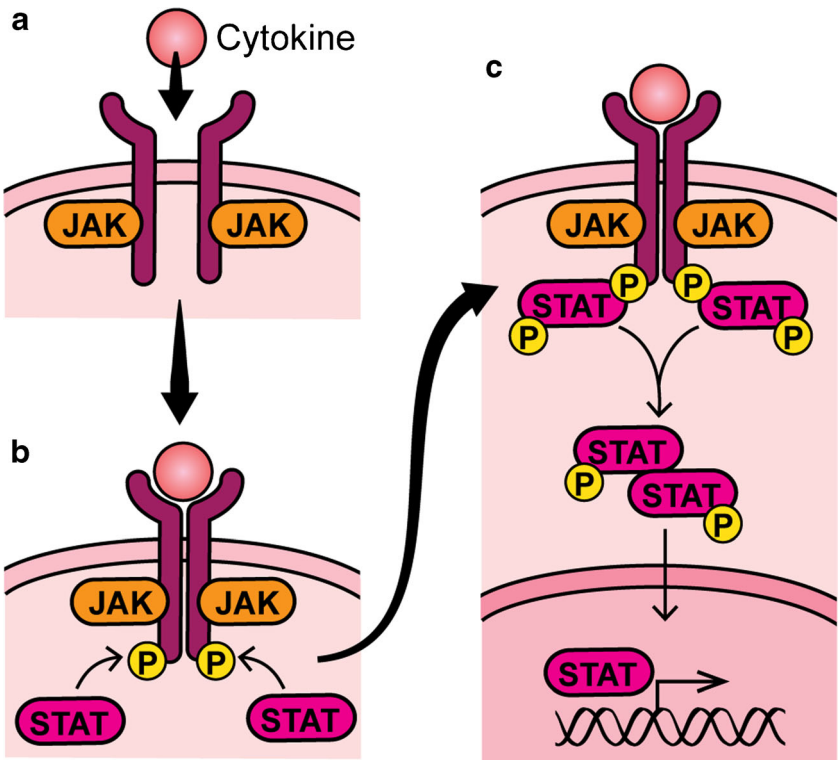


**Fig. 1** JAK-STAT pathway. **a** Cytokine binding to cell surface receptors leads to **b** dimerization of the cell surface receptor and activation of JAKs, which results in the phosphorylation of receptor chains that act as STAT-binding sites. **c** Activated JAKs facilitate the phosphorylation of STATs, which are subsequently released from the receptor chains and dimerize. These dimerized STATs then translocate to the cell nucleus where they modulate gene transcription. This pathway is inhibited by the JAK inhibitor molecules. Printed with permission from Mount Sinai Health

52 weeks) and steroid-free remission. The primary endpoint of clinical remission at 52 weeks was achieved in 34.3% of patients receiving tofacitinib at 5 mg twice daily and 40.6% of patients receiving tofacitinib at 10 mg twice daily (compared to 11.1% in the placebo group, $P < 0.001$ for both doses). The secondary endpoint of mucosal healing was achieved in 37.4% of patients receiving tofacitinib at 5 mg twice daily and 45.7% of patients receiving tofacitinib at 10 mg twice daily (compared with 13.1% in placebo, $P < 0.001$ for both doses). Steroid-free sustained clinical remission was achieved in 35.4% (5 mg group) and 47.3% (10 mg group) of tofacitinib-treated patients, compared with 5.1% in placebo ($P < 0.001$ for both dosage comparisons) [23•]. Subsequent analysis also suggests that patients maintained on tofacitinib 5 mg BID who experience flare may be rescued by resuming the 10 mg BID dose used for induction therapy [24].

In regard to safety outcomes, a greater percentage of patients sustained infections of any severity in the tofacitinib 10 mg induction period (23.3% in OCTAVE Induction 1 and 18.2% in OCTAVE Induction 2) compared to placebo (15.6% in OCTAVE Induction 1 and 15.2% in OCTAVE Induction 2). In OCTAVE Sustain, infectious complications were also greater in the tofacitinib 5 mg group (35.9%) and the tofacitinib 10 mg group (39.8%) compared to placebo (24.2%) [23•]. Across the three trials, most infections were mild to moderate in severity; serious infections happened in the tofacitinib 10 mg group in 1.3% of patients in OCTAVE Induction 1, 0.2% of patients in OCTAVE Induction 2, and 0.5% of patients in OCTAVE Sustain (1% serious infections in the 5 mg group in OCTAVE Sustain). Herpes zoster (HZ) infection occurred in the tofacitinib 10 mg group in 0.6% and 0.5% in OCTAVE Induction 1 and 2 trials, respectively, while occurring in 5.1% of patients in OCTAVE Sustain (1.5% herpes zoster occurrence in 5 mg group in OCTAVE Sustain). One patient in OCTAVE Induction 2 had cytomegalovirus-associated colitis, and there were no cases of tuberculosis in any of the three trials. Non-melanoma skin cancer was also observed, and the risk seemed to be higher among patients treated with 10 mg BID as the predominant dose. As has been seen in other indications, some patients treated with tofacitinib experienced increased total cholesterol; HDL and LDL cholesterol elevated in proportion. No increase in major adverse cardiovascular events was noted. Creatinine kinase levels were also observed to be higher in the tofacitinib treatment groups compared to placebo across all three trials; however, there were no associated incidences of rhabdomyolysis or myopathy [23•].

In regard to HZ risk, an increased risk has been associated with various tofacitinib indications, including UC, psoriasis, and rheumatoid arthritis. This increased risk appears to be dose dependent, with an observed increased risk with higher doses of tofacitinib [25]. In fact, in the OCTAVE Sustain trial, HZ occurred at a higher rate among patients treated with tofacitinib 10 mg bid (5.1%) compared with 5 mg bid (1.5%) [23•]. Additionally, a retrospective analysis of all identified HZ cases in the UC tofacitinib development program showed a higher incidence rate (IR) among individuals treated with the 10 mg BID dose compared to those treated with the lower 5 mg bid dose. In this analysis, IRs were also higher among patients over the age of 65 years, with a history of diabetes mellitus, with oral steroid therapy at baseline, with prior TNF inhibitor failure, and those of Asian ethnicity [26]. Given this dose-dependent HZ risk, vaccination against varicella zoster is recommended prior to JAK inhibitor therapy with tofacitinib. Furthermore, identified cases of HZ while on therapy with JAK inhibitors for IBD require immediate anti-viral treatment and assessment by an infectious disease specialist [25].

The positioning of tofacitinib in the treatment algorithm for UC is a crucial clinical issue. The OCTAVE program has shown tofacitinib to be efficacious and safe for both induction and maintenance. Interestingly, in the OCTAVE Induction 1 and 2 trials, the treatment effect was observed to be similar among anti-TNF exposed and unexposed patients. Furthermore, tofacitinib may be considered as an induction agent among steroid intolerant UC patients and may be more desirable than thiopurines for maintenance therapy among those who are steroid dependent given its rapid onset of action. Additionally, the OCTAVE Open trial suggests that tofacitinib represents a more flexible treatment modality, which can effectively recapture patients who have had treatment interruptions [24]. The small molecule structure of tofacitinib, and lack of anti-drug antibody formation, may lend this agent well to dose interruption, dose reduction, and dose escalation without concern for loss of response due to anti-drug antibodies.

In the OCTAVE program, patients included in the induction trials had failed treatment with steroids, thiopurines, infliximab, or adalimumab. A greater percentage of tofacitinib-treated patients compared to placebo achieved remission and mucosal healing during induction, regardless of anti-TNF exposure status [23•]. However, a more recent multicenter retrospective analysis of the real-world effectiveness of tofacitinib showed that a larger proportion of bio-naive tofacitinib-treated patients achieved clinical response and endoscopic healing, in comparison to those with exposure to either one or two classes of biologics (Ungaro et al., unpublished data, accepted to ECCO 2019). These real-world data would suggest that tofacitinib should potentially be positioned earlier in the treatment algorithm of UC, perhaps prior to currently approved biologic therapy.

The role of tofacitinib in Crohn's disease was evaluated in a phase 2 randomized placebo-controlled trial of 139 patients with moderate to severe Crohn's disease. Neither the primary end point of clinical response at week 4 nor the secondary end point of clinical remission at week 4 was achieved [27•].

Similar findings were reported in one other sequential and integrated phase 2b randomized placebo-controlled trial investigating tofacitinib for induction and maintenance therapy in moderate to severe CD. In these studies, there was no statistically significant difference in the primary outcome of clinical remission between tofacitinib-treated patients versus placebo neither during induction nor maintenance [28]. The results of these analyses would suggest that tofacitinib has a limited role in treating CD.

## Upadacitinib

Upadacitinib is a selective JAK1 inhibitor which has been studied in patients with IBD [29]. The efficacy of upadacitinib as an induction agent has been investigated in the CELEST study, a randomized placebo-controlled trial of 220 moderate to severe CD patients with prior inadequate response to anti-TNF agents. Patients were randomized to either placebo, 3, 6, 12, 24 mg twice daily, or 24 mg once daily of upadacitinib for a 16-week period. Primary endpoints were clinical remission at week 16 and endoscopic remission at weeks 12 or 16. Clinical remission was achieved in 27% of patients receiving upadacitinib 6 mg twice daily versus 11% in placebo ($P < 0.1$). No other doses achieved statistical significance for the clinical remission endpoint. Significantly more patients in the 3 mg twice daily (10%, $P < 0.1$), 12 mg twice daily (8%, $P < 0.1$), 24 mg twice daily (22%, $P < 0.01$), and 24 mg once daily (14%, $P < 0.05$) achieved endoscopic remission compared to placebo. Serious adverse events were reported to be similar across all study groups, with the exception of the 12 mg twice daily upadacitinib group which had numerically higher serious adverse events compared to others [30•]. Additional analysis from the CELEST cohort has also demonstrated that upadacitinib induction results in significantly decreased mean C-reactive protein (CRP) by week 2 of treatment (12 mg twice daily, 24 mg twice daily, and 24 mg once daily doses) and significantly decreased mean fecal calprotectin by week 4 (12 mg twice daily, 24 mg twice daily doses) [31]. Overall, these analyses demonstrate that upadacitinib is an efficacious induction agent for patients with CD who failed prior therapy with anti-TNF agents. The JAK1 specificity of upadacitinib may also lead to a more favorable safety profile compared to other agents in this class, a property that may be beneficial in patients at an otherwise high risk for infection. The role of upadacitinib in moderate to severe UC is currently being investigated in an ongoing phase 3 multicentered placebo-controlled randomized trial [32].

## Filgotinib

Filgotinib is another selective JAK1 inhibitor which has been studied in moderate to severe CD patients as part of the FITZROY study [29]. In this randomized placebo-controlled phase 2 trial, 174 CD patients with moderate to severe disease were randomized to placebo or filgotinib 200 mg once daily for a 10-week induction period. Primary endpoint was clinical remission at week 10, and overall more patients in the filgotinib group (47%) compared to placebo (23%) achieved this outcome ($P = 0.0077$). This analysis also included an observational maintenance phase in which patients were assigned, based on treatment response during induction, to receive either filgotinib 100 mg once daily, 200 mg once daily, or placebo for an additional 10 weeks beyond the induction period. Between 50 and 71% of initial responders to filgotinib during induction maintained clinical remission at week 20. Filgotinib was found to have an adequate safety profile, with serious adverse events occurring in 9% in the filgotinib group and 4% of the placebo group [33•]. This analysis positions filgotinib as a potentially useful agent in the induction of clinical remission in patients with CD. Further trials investigating filgotinib in CD and UC are currently in progress [34–39].

## Other JAK Inhibitors

Peficitinib is a JAK1/3 inhibitor that has been investigated in UC patients. A phase IIb randomized placebo-controlled trial had completed enrollment of 219 moderate to severe UC patients to assess the utility of this agent; however, the parent company discontinued drug development due to a lack of efficacy [15, 40].

TD-1473 is a pan-JAK inhibitor that showed similar JAK inhibition potential as tofacitinib in in vitro models. Also, TD-1473 has low systemic bioavailability with oral dosing, with systemic levels of TD-1473 (at a dose of 1 mg/kg oral) found to be 1000-fold lower compared to tofacitinib (15 mg/kg oral). It is conceivable that this pharmacokinetic profile may yield similar treatment efficacy with a lower potential for systemic side effects [41]. A phase 1B randomized placebo-controlled trial assessing the safety, tolerability, pharmacodynamics, and plasma exposure of TD-1473 in moderate to severe UC was recently reported. This trial included 40 total patients, with 9 receiving placebo, 10 receiving TD-1473 at 20 mg per day, 10 receiving 80 mg per day, and 11 receiving 270 mg per day. Endoscopic improvement occurred in 20%, 30%, 18%, and 0% of patients in the TD-1473 20 mg, 80 mg, 270 mg, and placebo groups, respectively. TD-1473 also showed evidence of gut selectivity in this study, with minimal systemic exposure based on measurement of plasma drug levels and higher drug colonic tissue concentrations compared to plasma at 80 mg and 270 mg doses. In regard to safety and tolerability, two hospitalizations for UC flare occurred in the TD-1473 group (20 mg and 80 mg cohorts). No serious infections, tuberculosis, or herpes zoster cases were reported [42]. A phase 2 randomized trial assessing the efficacy and safety of TD-1473 in moderate to severe CD is also currently underway [43].

## Sphingosine Receptor Modulators

Sphingosine-1-phosphate (S1P), a sphingolipid produced through the metabolism of sphingomyelin, binds to a family of five G protein-coupled receptors (subtypes S1P1–S1P5). The S1P1–S1P5 receptor family is involved in modulating lymphocyte trafficking from lymphoid organs. Internalization and degradation of the S1P receptor are instigated by S1P receptor agonists, thereby reducing the number of lymphocytes in the systemic circulation [18]. The first agent in this class to be used in the treatment of inflammatory conditions was fingolimod, a non-selective S1P modulator which was approved for multiple sclerosis (MS) in 2010 [44–46]. Fingolimod has high affinity for the S1P1, S1P3, S1P4, and S1P5 receptors. The non-selective mechanism of fingolimod is likely responsible for its various safety issues, such as an association with bradyarrhythmia and heart block, hypertension, hepatic injury, basal cell carcinoma, and infections [16]. Progressive multifocal leukoencephalopathy (PML) has also been reported in nine patients treated with fingolimod, both with and without prior exposure to natalizumab [47, 48]. Another sphingosine receptor modulating agent which has been studied in UC is ozanimod, a S1P1 and S1P5 receptor agonist (Fig. 2). The TOUCHSTONE study was a randomized placebo-controlled trial investigating the utility of ozanimod in 197 patients with moderate to severe UC. Patients were randomized to receive ozanimod at doses of 0.5 mg or 1 mg daily or placebo for 32 weeks. The primary outcome was clinical remission and was achieved in 16% of patients in the 1 mg arm and 14% of those in the 0.5 mg arm, versus 6% in placebo ($P = 0.048$ and $P = 0.14$, respectively, against placebo). No significant difference in regard to the primary outcome was found at week 32 between the ozanimod 0.5 mg group and placebo [50•]. Histologic remission occurred in 11% of patients in the placebo group, 14% of patients in the group receiving 0.5 mg ozanimod, and 22% of patients receiving 1 mg of ozanimod ($P = 0.63$ for 0.5 mg and $P = 0.07$ for 1 mg versus placebo). Mucosal healing occurred in 12% of patients in the placebo group, 28% of patients receiving 0.5 mg ozanimod, and 34% of patients receiving 1 mg ozanimod ($P = 0.03$ for 0.5 mg and $P = 0.002$ for 1 mg). In regard to safety data, one patient in the 0.5 mg ozanimod group had asymptomatic first-degree atrioventricular block and sinus bradycardia at day 8 (this patient had a history of bradycardia prior to treatment), however did not require intervention. Four other patients in the ozanimod treatment groups (one in 0.5 mg group and three in 1 mg group) had elevated alanine aminotransferase > 3× upper limit of normal. Squamous cell carcinoma occurred in one patient in the 1 mg ozanimod group [50•]. A 2-year open-label extension analysis of the TOUCHSTONE cohort was undertaken and involved 170 of the initial 197 enrolled patients. These patients received ozanimod 1 mg daily, and at week 92 follow-up 91% had no active disease based on

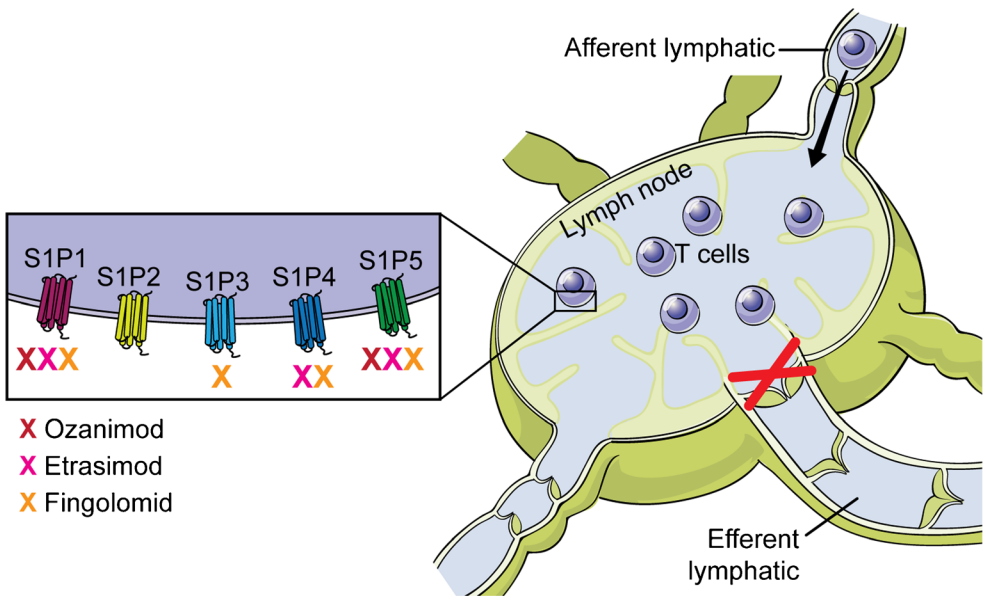


**Fig. 2** Mechanism of action of sphingosine receptor modulators. Ozanimod is an S1P1/S1P5 receptor modulator; etrasimod is an S1P1/S1P4–S1P5 receptor modulator; fingolomid is an S1P1/S1P3–S1P5 receptor modulator. S1P receptor modulator binding to S1P receptors results in receptor internalization and degradation, thereby inhibiting the recruitment of lymphocytes. Printed with permission from Mount Sinai Health. Physiologic functions of S1P receptors [49]: S1P1-control of heart rate, angiogenesis, lymphocyte recruitment from lymphoid organs, neuron cell function. S1P2-regulation of vascular tone. S1P3-control of heart rate, vasoconstriction, neuron cell function. S1P4-vasoconstriction, expression of lymphoid tissue, modulation of TH17 cell differentiation. S1P5-migration of natural killer cells

physician global assessment, 97% had Mayo rectal bleeding subscore of 0 or 1, and 86% had a Mayo rectal bleeding subscore of 0. Adverse events (i.e., nausea, upper respiratory tract infection, nasopharyngitis, and back pain) were reported in 85 patients, and serious adverse events (i.e., UC flare and anemia) were reported in 20 patients [51]. The total number of patients in TOUCHSTONE was insufficient to determine if there is a true risk of PML with ozanimod. Overall, the TOUCHSTONE study demonstrated that ozanimod may be a viable induction and maintenance agent for UC patients with an acceptable safety profile. Further phase III trials in UC are ongoing, and it is possible that ozanimod may become another small molecule therapeutic agent for this patient population in the future [52, 53].

The efficacy of ozanimod at a dose of 1 mg daily in moderate to severe CD was recently investigated in a phase 2 open-label study of 69 patients. In this analysis, reductions in the simple endoscopic score for Crohn's disease (SES-CD) of ≥ 25% and ≥ 50% from baseline by week 12 were observed in 43.3% and 26.7% of patients, respectively. Crohn's disease activity index (CDAI) remission (defined as CDAI < 150) occurred in 46% of patients, with CDAI score reductions occurring by week 4 [54]. Other randomized trials are ongoing to study the utility of ozanimod in CD as an induction [55, 56] and maintenance agent [57, 58].

If ozanimod proves to have minimal or no risk of PML, this agent may be a worthwhile addition for mild to moderate CD for which we have no ideal maintenance agent. It could assume the same position in UC as an early therapy. In UC, it would likely not achieve a position before 5-ASA unless it proved to be more effective then these agents, and if concerns about cardiac conduction abnormalities are minimal, along with PML not being an issue.

Etrasimod is a selective S1P1, S1P4, and S1P5 receptor modulator which has been shown to induce lymphopenia in in vitro models [59]. It has recently been studied in a 12-week phase 2 induction study of moderate to severe UC patients. In this trial, patients received etrasimod at 1 mg daily, 2 mg daily, or placebo. Primary endpoint was a change from baseline in the three-component Mayo score at week 12. The etrasimod 2 mg cohort showed statistically significant improvement from baseline in the three-component Mayo score versus placebo (difference of 0.99 points, $P = 0.009$). The etrasimod 2 mg group also showed a statistically significant improvement in endoscopic scores versus placebo (41.8% versus 17.8%, $P = 0.003$). Adverse events occurred at a similar rate across all groups in the study. Serious adverse events occurred in 11.1% of patients in placebo, 0% of patients treated with etrasimod 2 mg, and 5.8% of patients treated with etrasimod 1 mg. No cases of atrioventricular block nor bradycardia occurred [60].

## Anti-trafficking Therapies

The migration of inflammatory cells, such as lymphocytes, into the gastrointestinal tract is a multistep process that facilitates the tethering, activation, adhesion, and migration of these cells. Cell membrane bound integrin molecules, like the gut-specific α4β7 integrin, are involved in this leukocyte migration process. α4β7 integrin binds with mucosal addressin-cell adhesion molecule 1 (MAdCAM-1), which is expressed on the endothelium within the gastrointestinal tract, and this interaction facilitates lymphocyte migration. While vedolizumab inhibits this process through an anti-α4β7 antibody, other approaches seek to do so by small molecule mechanisms [19].

### AJM300

AJM300 is small molecule antagonist of α4 integrin which inhibits integrin-adhesion molecule interactions, thus attenuating lymphocyte migration to the gastrointestinal system [61]. A phase 2a randomized placebo-controlled trial investigated the efficacy and safety of AJM300 in 102 patients with moderate UC. Patients were randomized to either AJM300 or placebo for 8 weeks. The primary endpoint was clinical response, and overall 62.7% of patients in the AJM300 group and 25.5% of patients in the placebo group (OR 5.35, CI 2.23–12.82, $P = 0.0002$) achieved this outcome at week 8. Clinical remission occurred in 23.5% of patients in the AJM300 group and 3.9% in placebo (OR 7.81, CI 1.64–37.24, $P = 0.0099$). Mucosal healing occurred in 58.8% AJM300-treated patients and 29.4% in placebo (OR 4.65, CI 1.81–11.90, $P = 0.0014$). Adverse event rates were similar between AJM300 and placebo groups (49% and 56.9%, respectively).

Of note, natalizumab is a monoclonal IgG4 antibody against the integrin α4 subunit. It was the first anti-trafficking agent developed for treatment of IBD and MS, preventing the interaction between α4β7/MAdCAM-1 and α4β1/vascular cell adhesion molecule-1 (VCAM-1). Blockage of α4β1/VCAM-1 interaction is associated with reduction in lymphocytic trafficking into the central nervous system, thus having a beneficial impact in the treatment of MS. Natalizumab has been associated with the development of PML, an opportunistic infection of the brain that results from reactivation of the John Cunningham virus (JC virus). Natalizumab reduces the migration of T lymphocytes which specifically target the JC virus, thus interfering with the immune response to this infection. Fortunately, no cases of PML have thus far been reported with other non-biologic anti-trafficking agents used for the treatment of IBD [61]. No serious adverse events such as PML, which has previously been observed with α4 integrin inhibition by the monoclonal IgG4 antibody natalizumab, were seen in the AJM300-treated group nor placebo [62•]. However, the total number of patients

investigated and the duration of therapy in this phase 2a trial of AJM300 were not sufficient to determine if there is a true risk of PML.

A randomized placebo-controlled trial assessing the efficacy of AJM300 in CD was conducted by Takazoe et al. This study included 71 CD patients, who were randomized to placebo or AJM300 at doses of 40 mg, 120 mg, or 240 mg for 8 weeks. This study did not show a statistically significant difference in CDAI reduction (primary study endpoint) from baseline at week 4 [63]. A phase 3 study is currently underway to further assess the safety and efficacy of AJM300 in UC patients [64].

### PTG-100

PTG-100 is an orally administered α4β7 integrin antagonist that has been recently studied in a phase 2b randomized placebo-controlled trial of 240 patients with moderate to severe UC. Patients received PTG-100 at 150 mg daily, 300 mg daily, 900 mg daily, or placebo. The trial met futility criteria after randomization of the first 65 patients due to a high placebo remission rate (24%). This was thought to be secondary to a systemic error in endoscopy reading, and thus, all endoscopic images were re-read. Nonetheless, in the re-read dataset, maximal benefit was observed in patients treated with 900 mg daily of PTG-100 for 12 weeks, showing higher rates of clinical remission (15.8%), endoscopic response (15.8%), and histologic remission (44%) compared to placebo (4.8%, 4.8%, and 0% for clinical remission, endoscopic response, and histologic remission, respectively). Further clinical trials of PTG-100 in this patient population are required in order to adequately draw conclusions about its efficacy in IBD [65].

### Alicaforscen

Intercellular adhesion molecule-1 (ICAM-1) is an important ligand of leukocyte β2 integrins and is distributed throughout the systemic vasculature. Blockade of ICAM-1 in the gut could in theory inhibit inflammation in IBD. Alicaforsen is an anti-sense oligonucleotide that inhibits the production of ICAM-1 by interfering with translation [61]. Alicaforscen has thus far not been shown to be efficacious in the CD population, and enema administration of this agent in ulcerative colitis has shown a possible long-term disease response without any short-term improvement in disease activity [66–69]. A recent retrospective case series analyzed the efficacy of enema formulations of alicaforsen in left-sided UC and proctitis. This series reported improvement in clinical disease activity in 10/12 patients with a 6-week course of alicaforsen; however, relapses occurred in 7/10 of these patients [20]. The efficacy of alicaforsen in chronic refractory pouchitis after proctocolectomy for UC has been investigated in a retrospective case series of 13 patients. Eleven of 13 patients showed clinical improvement based on reductions in stool frequency or pouchitis disease activity index (PDAI), and 10/13 patients showed improvement in endoscopic disease activity [70]. Overall, the available evidence is conflicting regarding the utility of alicaforsen in IBD. Efficacy in CD appears to be lacking; however, there may be a role for this agent in the management of UC and pouchitis. A phase 3 placebo-controlled randomized controlled trial of alicaforsen in refractory pouchitis is currently underway [71].

## PDE4 Inhibitors

The PDE4 enzyme is an important inflammatory mediator that facilitates the breakdown of intracellular cAMP which regulates a variety of immunologic processes [21]. Apremilast is a PDE4 inhibitor that has shown favorable efficacy outcomes in ulcerative colitis patients. A phase 2 randomized placebo-controlled trial of 170 ulcerative colitis patients showed a significantly higher proportion of patients achieved total Mayo score clinical remission at week 12 with apremilast 30 mg twice daily compared to placebo (31.6% for apremilast 30 mg versus 13.8% for placebo, $P < 0.05$). A significantly greater number of patients treated with apremilast 30 mg twice daily also achieved a ≥ 1 point decrease in Mayo endoscopic subscore (73.7% versus 41.4% for placebo, $P < 0.05$) and mucosal healing (33.3% versus 15.5% for placebo, $P < 0.05$) [72•]. These initial favorable outcomes will need to be confirmed in additional studies [73]. PDE4 inhibitors have not yet been studied in patients with Crohn's disease.

Apremilast was generally well tolerated with a favorable safety profile among patients with psoriasis or psoriatic arthritis. Adverse events were generally mild to moderate in intensity and included diarrhea, nausea, upper respiratory tract infection (URTI), nasopharyngitis, and headache [74].

## Other Small Molecules

Various other small molecule therapies have been studied in IBD; however, many of these agents have shown inconsistent efficacy outcomes.

*Mongersen* is an anti-sense oligonucleotide molecule that degrades mRNA for the intracellular protein SMAD7, thereby allowing for increased activity of the anti-inflammatory cytokine transforming growth factor (TGF)-β1. An initial phase 1 study showed this agent to be safe and well tolerated in CD, and a subsequent phase 2 trial showed favorable results in terms of clinical remission and response [75, 76]. However, a subsequent phase 3 trial was terminated due to a lack of efficacy.

*CCX282-B* is an antagonist of the C-C chemokine receptor 9 (CCR9), thereby inhibiting the migration of inflammatory lymphocytes to the intestine [61]. PROTECT-1 was the first randomized placebo-controlled trial to investigate the efficacy of the CCX282-B in Crohn's disease patients. The primary efficacy endpoint of clinical response was not achieved in the 8-week induction period nor in the 36-week maintenance period [77]. A subsequent phase 3 randomized placebo-controlled trial studying CCX282-B as an induction agent in Crohn's disease failed to show efficacy in comparison to placebo [78].

*Laquinimod* is an oral small molecule agent that dampens the inflammatory response through an inhibitory effect on inflammatory cytokines via downregulation of T cells and antigen-presenting cells. A randomized placebo-controlled study of laquinimod in Crohn's disease did not show benefit [79], and further trials are not planned.

*LT-02* (phosphatidylcholine) works by improving gut barrier function and thus may have a role in the treatment of inflammatory bowel disease. Despite earlier studies suggesting benefit in UC, a more recent study failed to achieve its primary endpoint [80]. The current status of LT-02 is unknown.

## Conclusions

A wide variety of non-biologic agents are under investigation in IBD. These agents have diverse intracellular mechanisms of action, avoid the need for parenteral administration, and are not immunogenic. Clearly, not all such agents will live up to their early promise, however.

Thus far, the small molecule JAK inhibitors have the most robust evidence supporting their use in IBD. In particular, tofacitinib has shown efficacy and safety in the treatment of UC [23•]. In our experience, tofacitinib fulfills an important position in the armamentarium of agents available for the management of UC. It represents a convenient orally administered medical option that is devoid of the risk of antibody formation and has an acceptable safety profile. Specific potential safety concerns with tofacitinib include infectious complications (i.e., herpes zoster infection), non-melanoma skin cancers, and dyslipidemia. Other JAK inhibitors such as upadacitinib and filgotinib are still in investigative stages but show promising results in CD. Whether these agents will be advantageous compared to tofacitinib in efficacy or safety due to greater JAK1 specificity remains to be seen in clinical trials. Additionally, the S1P receptor modulators ozanimod and etrasimod show promise. It is clear that after a 20-year span in which biologic agents dominated, a return to small molecules, with superior safety and efficacy compared to older conventional agents, is at hand.

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## Compliance with Ethical Standards

**Conflict of Interest** Bruce Sands discloses consulting fees from 4D Pharma, Abbvie, Allergan Sales, Amgen, Arena Pharmaceuticals, BoehringerIngelheim, Capella Biosciences, Celgene, EnGene, Ferring, Gilead, Janssen, Lilly, Lyndra, MedImmune, Oppilan Pharma, Otsuka, Palatin Technologies, Pfizer, Progenity, Rheos Medicines, Seres Therapeutics, Synergy Pharmaceuticals, Takeda, Target PharmaSolutions, Theravance Biopharma R&D, TiGenix, Vivelix Pharmaceuticals, and WebMD and research funding from Celgene, Pfizer, Takeda, and Janssen.

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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