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# New Therapeutics for Ulcerative Colitis

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## Keywords

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## Abstract

Ulcerative colitis (UC) is a relapsing and remitting inflammatory disease of the colon with a variable course. Despite advances in treatment, only approximately 40% of patients achieve clinical remission at the end of a year, prompting the exploration of new treatment modalities. This review explores novel therapeutic approaches to UC, including promising drugs in various stages of development, efforts to maximize the efficacy of currently available treatment options, and non-medication-based modalities. Treatment approaches which show promise in impacting the future of UC management are highlighted.

## INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing and remitting inflammatory disease of the colon, with inflammation confined to the mucosa, involving the rectum and extending proximally (1, 2). Over time, the emergence of agents with increasing therapeutic efficacy has shifted treatment strategies toward a treat-to-target approach. Growing evidence demonstrates superior outcomes when deep remission or a combination of clinical remission and endoscopic healing is achieved (3, 4). However, despite therapeutic advances, a treatment gap still exists, with only approximately 40% of patients who have short-term response to therapy remaining in clinical remission at the end of a year (5, 6). This has prompted efforts to develop novel treatment modalities and approaches (6, 7). The goal of this review is to provide an overview of promising new therapeutic agents (**Table 1**) under development and novel therapeutic approaches for the management of UC.

**Table 1 Novel medications for the treatment of ulcerative colitis**

| Medication | Mechanism | Drug stage | Efficacy summary in ulcerative colitis | Safety summary in ulcerative colitis | References |
|---|---|---|---|---|---|
| Tofacitinib | Pan-active JAK inhibitor | Approved | Clinical remission:<br>8 weeks: 16.6–18.5%<br>52 weeks: 34.3–40.6% | Herpes zoster (5.6%)<br>Increased nonmelanoma skin cancer | 13–19 |
| Upadacitinib | JAK 1 inhibitor | Phase III, enrolling | Clinical remission:<br>8 weeks: 13.5%–19.6% | Only 1 case of herpes zoster | 20, 21 |
| Filgotinib | JAK 1 inhibitor | Phase III, enrolling | ND | ND | 22 |
| TD-1473 | Local pan-active JAK inhibitor | Phase IIb/III, enrolling | Day 28: Numerically higher clinical and endoscopic response versus placebo | No impact on hematologic and lipid levels | 23, 24 |
| Apremilast | PDE4 inhibitor | Phase II, complete | Clinical remission:<br>12 weeks: 21.8–31.6%<br>52 weeks: 32.7–40.3% | ≥1 AE 49.1–63.5% versus 53.4% placebo<br>Serious AEs: 1.8–3.4%<br>Headaches: 21.1–25.5% | 25–30 |
| Ozanimod | S1P1 and S1P5 receptor agonist | Phase III, enrolling | Clinical remission:<br>8 weeks: 14–16%<br>32 weeks: 21–26%<br>PGA: 92 weeks: 91% PGA 0 or 1 | 1 first-degree heart-block<br>3 elevated liver tests<br>1 squamous cell carcinoma<br>Large lymphocyte reductions | 31, 32, 34, 37, 38 |
| Etrasimod | S1P1, S1P4 and S1P5 receptor agonist | Phase III, enrolling | Modified Mayo clinic scores:<br>12 weeks: 0.43–0.99-point increase versus placebo<br>Endoscopic:<br>12 weeks: 41.8% improved | TEAEs in 7.7% subjects<br>1 with decreased heart rate and 2nd-degree atrioventricular block type 1 | 31–34 |
| Etrolizumab | Anti-β7 subunit of α4β7 and αEβ7 | Phase III, enrolling | Clinical remission:<br>10 weeks: 10–21%<br>Mucosal healing:<br>10 weeks: 21–26% | Similar AE rates to placebo<br>No cases of PML | 44–47 |
| PF-00547659 | Blocks MAdCAM | Phase II, complete | Clinical remission:<br>12 weeks: 11.3–16.7%<br>Response rates:<br>12 weeks: 45.1–54.2% | Similar AE rates to placebo<br>No dose effect for AEs<br>Headache most common AE (~10%) | 48, 49 |

(*Continued*)

**Table 1** (*Continued*)

| Medication | Mechanism | Drug stage | Efficacy summary in ulcerative colitis | Safety summary in ulcerative colitis | References |
|---|---|---|---|---|---|
| Ustekinumab | Anti-p40 subunit of IL-12/23 | Approved | Clinical remission:<br>8 weeks: 15.5–15.6%<br>44 weeks: 38.4–43.8% | Similar AE rates to placebo at week 8 and week 44<br>7 subjects developed cancer (3 nonmelanoma skin cancer) | 53, 57, 58 |
| Mirikizumab | Anti-p19 subunit of IL-23 | Phase III, enrolling | Clinical remission:<br>12 weeks: 11.5–22.6%<br>52 weeks: 37–46.8%<br>Response rates:<br>12 weeks: 41.3–59.7% | TEAEs similar to placebo, not dose dependent<br>Common AEs: worsening UC (3.2–9.5%), nasopharyngitis (4.8–9.5%) | 60 |
| Risankizumab | Anti-p19 subunit of IL-23 | Phase II/III, enrolling | ND | ND | 61, 62 |
| Brazikumab | Anti-p19 subunit of IL-23 | Phase II, enrolling | ND | ND | 63 |
| Guselkumab | Anti-p19 subunit of IL-23 | Phase IIa/IIb/III, enrolling | ND | ND | ND |

Abbreviations: AE, adverse event; JAK, Janus kinase; ND, no data; PDE, phosphodiesterase; PGA, physician global assessment; PML, progressive multifocal leukoencephalopathy; TEAE, treatment-emergent adverse event; S1P1, sphingosine 1 phosphate 1; UC, ulcerative colitis.

## NEW THERAPEUTIC AGENTS

### Janus Kinase Inhibitors

Biologic agents have enhanced targeted efficacy in the treatment of UC, but several limitations have prompted the development of small-molecular agents. Biologics, contrasted with small molecules, are costly to produce; have molecular weights >1,000 kDa, necessitating a parenteral route of delivery; have a long half-life; and have antigenic properties which diminish long-term effectiveness (8–10). Janus kinase (JAK) inhibitors are the first family of novel small molecules approved in many countries for the treatment of inflammatory bowel disease (IBD). JAK, composed of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), is a group of tyrosine kinase proteins which mediate the inflammatory response. They are activated when cytokines bind to cell surface receptors, thereby phosphorylating signal transducer and activator of transcription (STAT) proteins. This results in STAT protein release from the receptor, followed by dimerization and translocation to the nucleus, resulting in gene transcription of a broad range of proinflammatory mediators (11, 12).

**Tofacitinib.** Tofacitinib is an oral pan-active JAK inhibitor with relative specificity for JAK1 and JAK3. It attenuates interleukin (IL)-2-dependent differentiation of helper T cells and inhibition of proinflammatory cytokine signaling, including IL-6 and interferon-γ (13). Tofacitinib is the first approved medication in this class for the treatment of IBD, and in a phase II study, it demonstrated significantly higher rates of clinical remission and response compared to placebo (14). These promising results were followed up in three phase III studies: OCTAVE Induction 1,

OCTAVE Induction 2, and OCTAVE Sustain (maintenance). The OCTAVE 1 and OCTAVE 2 trials randomized 598 and 541 patients with moderately to severely active UC, who failed conventional therapy or an anti–tumor necrosis factor (TNF) agent, to tofacitinib 10 mg twice daily or placebo for 8 weeks. In OCTAVE 1 and OCTAVE 2, 18.5% and 16.6% of subjects in the tofacitinib group, compared to 8.2% ($p = 0.007$) and 3.6% ($p < 0.001$) of subjects in the placebo groups, were in remission at 8 weeks, respectively. In the OCTAVE Sustain trial, of those with response to induction, 40.6% of subjects on the 10 mg dose and 34.3% of subjects on the 5 mg dose, compared to 11.1% in the placebo group ($p < 0.001$), were in remission at 52 weeks. There was a significantly increased rate of mucosal healing (Mayo Sigmoidoscopy Subscore = 0 or 1) in the tofacitinib group at week 52 (5 mg dose, 37.4%; 10 mg dose, 45.7%) compared to placebo (13.1%; $p < 0.001$). Greater efficacy was noted in TNF-naïve patients than in those with prior treatment failure (15).

Several safety signatures were noted with tofacitinib. Higher rates of infection and serious infection were observed (1.3% in OCTAVE 1; 0.2% in OCTAVE 2). A dose-dependent increase in herpes zoster was found, occurring in 5.1% of subjects in the 10 mg group and 0.5% of subjects in the placebo group (15). A pooled assessment of zoster risk across all UC trials found that 5.6% of subjects developed this complication [incident rate (IR) 4.07, 95% confidence interval (CI) 3.14–5.19] (16). Additionally, rates of nonmelanoma skin cancers were higher, particularly in subjects receiving 10 mg twice-daily dosing.

In 2019, tofacitinib received a black box warning based on post-marketing studies in diseases other than IBD, showing an increased risk of thrombosis in patients who were taking 10 mg twice daily and had at least one cardiovascular risk factor (17). However, evaluation of 1,157 patients and 2,404 patient-years of exposure in the UC clinical trial data found only one patient with a deep vein thrombosis (IR 0.04, 95% CI 0.00–0.23) and four with a pulmonary embolism (IR 0.16, 95% CI 0.04–0.41). All had thromboembolic risk factors other than UC (18). Further evaluation of this risk is needed in subjects in UC trials, though caution should be maintained in subjects with risk factors for thromboembolism. Additionally, tofacitinib has been shown to alter lipid profiles; treatment groups show a greater increase in total cholesterol, high-density lipoprotein, low-density lipoprotein, and very-low-density lipoprotein cholesterol compared to placebo, with a correlation between reduced C-reactive protein and increased lipid concentrations ($p < 0.001$) (19).

**Upadacitinib.** Upadacitinib is a JAK inhibitor which selectively binds to JAK1 rather than JAK2, JAK3, and TYK2 (20). The U-Achieve program comprises three studies evaluating upadacitinib's efficacy and safety in UC. The first study, a phase IIb dose-ranging induction study, has been published, while the phase III dose-confirming study and maintenance study are under way (21). This multicenter double-blind study randomized 250 adults with moderately to severely active UC to once-daily placebo or four doses of upadacitinib (7.5 mg, 15 mg, 30 mg, or 45 mg) for 8 weeks. Patients receiving 15 mg (14.3%; $p = 0.013$), 30 mg (13.5%; $p = 0.011$), and 45 mg (19.6%; $p = 0.002$) achieved clinical remission, while no patients receiving placebo achieved clinical remission. Endoscopic improvement at week 8 was achieved in 14.9% (7.5 mg), 30.6% (15 mg), 26.9% (30 mg), and 35.7% (45 mg) of patients receiving upadacitinib compared with 2.2% receiving placebo ($p = 0.033$, $p < 0.001$, $p < 0.001$, $p < 0.001$), respectively. Only one case of herpes zoster was noted; this occurred in a subject receiving upadacitinib 45 mg daily (21).

**Other JAK inhibitors.** Filgotinib is a selective JAK1 inhibitor which has been studied in Crohn's disease (CD). Early results from the phase III induction and maintenance study in moderately to severely active UC demonstrates that among biologic-naïve subjects receiving filgotinib 200 mg, 26.1% achieved clinical remission at week 10, compared to 15.3% on placebo; and among

biologic-experienced subjects on the same dosage, 11.5% achieved clinical remission at week 10 versus 4.2% on placebo ($p = 0.0157$). At week 58, 37.2% of subjects receiving filgotinib 200 mg achieved clinical remission, compared with 11.2% receiving placebo ($p < 0.0001$) (22). Evaluation of the data, once published, is needed, but these early results are promising.

Given the safety signals with systemically active JAK inhibitors, locally delivered formulations are being evaluated. TD-1473 is an oral, locally active pan-JAK inhibitor that, when dosed at 1 mg/kg, inhibits local proinflammatory cytokine pathways in IBD with systemic levels 1,000-fold lower than oral tofacinitib 15 mg/kg (23). A phase I study in healthy subjects and phase Ib study in subjects with moderately to severely active UC was performed (24). The drug was found to be well tolerated. Pharmacokinetic studies demonstrated low or undetectable drug levels, with little to no serum accumulation after multiple doses. At all doses, numerically higher clinical and endoscopic response and endoscopic improvement compared to placebo were observed at day 28 (24). An 8-week phase IIb dose-finding study, an 8-week phase III induction study, a 44-week phase III maintenance study, and a long-term extension study in moderately to severely active UC are under way to further evaluate these findings (NCT03758443).

## Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors target intracellular signaling pathways to modulate inflammatory mediators. Phosphodiesterase-4 (PDE4) inhibitors result in an elevation of cellular levels of cyclic adenosine monophosphate (cAMP), thereby inhibiting production of inflammatory mediators, such as TNF-α and IL-23, while also increasing production of anti-inflammatory mediators, such as IL-10 (25).

Apremilast is an oral small molecule which targets PDE4 and in IBD inhibits TNF and matrix metalloproteinase-3 in mononuclear cells (26). A double-blind phase II trial was performed in 170 adults with moderately to severely active UC. Subjects were randomized to receive apremilast 30 mg, apremilast 40 mg, or placebo twice daily for 12 weeks and then randomized to 30 mg or 40 mg twice daily for an additional 40 weeks (27). Total Mayo score clinical remission was achieved at week 12 in 31.6% ($p = 0.01$) of subjects receiving 30 mg and 21.8% of patients receiving 40 mg ($p = 0.27$) compared to 12.1% of subjects receiving placebo. At week 52, 40.3% of subjects randomized to 30 mg and 32.7% randomized to 40 mg were in clinical remission.

Trials in psoriatic arthritis and psoriasis revealed diarrhea, nausea, nasopharyngitis, upper respiratory tract infections, and headaches to be the most common adverse events (AEs) (28–30). In the phase II UC trial, 49.1% of subjects receiving apremilast 30 mg, 63.6% receiving apremilast 40 mg, and 53.4% receiving placebo experienced ≥1 AE. Serious AEs occurred in 3.4% of patients receiving placebo compared to 1.8% receiving apremilast 40 mg. Headaches were the most commonly reported AE, occurring in 25.5% of subjects on the 40 mg dose, 21.1% of subjects on the 30 mg dose, and 6.9% of subjects on placebo (27).

## Sphingosine Receptor Modulators

Sphingosine 1 phosphate (S1P) receptors are a family of five G protein–coupled cell surface receptors, $S_1P_1$–$S_1P_5$, that are broadly expressed in tissues and bind lysophospholipid S1P (31). This family of proteins plays an integral role in multiple immunologic and cardiovascular functions. $S_1P_1$ is one of the most widely expressed members of this family of receptors, particularly on endothelial cells, and plays a key role in lymphocyte trafficking from lymphatic tissue (32, 33). $S_1P_1$ agonists result in $S_1P_1$ internalization and inhibit migration of B and T lymphocytes from lymph tissue, reducing their numbers in the blood (32, 34).

Fingolimod was the first agent approved for the treatment of multiple sclerosis. It exhibited nonselective activation of $S_1P_1$, $S_1P_3$, $S_1P_4$, and $S_1P_5$ receptors. Its safety issues pertain to its relative lack of specificity and include heart block, bradyarrhythmia, elevated liver enzymes, and infections (35, 36). Ozanimod is an oral $S_1P_1$ and $S_1P_5$ receptor agonist studied in a phase II trial in 197 subjects with moderately to severely active UC (37). Patients were randomized to receive ozanimod 0.5 mg, ozanimod 1 mg, or placebo daily for 32 weeks. Clinical remission at week 8 occurred in 16% of subjects on 1 mg ($p = 0.14$) and 14% of subjects on 0.5 mg ($p = 0.048$), compared to 6% on placebo. Mucosal healing was achieved at week 8 in 12% of patients in the placebo group, compared to 28% receiving 0.5 mg and 34% receiving 1 mg ($p = 0.002$). Clinical remission at week 32 was 21% in the 1 mg ozanimod group, 26% in the 0.5 mg ozanimod group, and 6% in the placebo group. One patient had first-degree atrioventricular block and bradycardia, three subjects had elevated liver enzymes (>3 times the upper limit of normal), and one patient developed squamous cell carcinoma, though the latter patient had had previous treatment with thiopurines. Large lymphocyte reductions were seen, with a mean decrease of 32% at week 8 in those receiving ozanimod 0.5 mg and 49% in those receiving 1 mg (37).

At week 92 in the open-label trial of ozanimod, 91% of subjects had a physician global assessment score of 0 or 1, demonstrating little to no activity, and little to no blood in their stool. AEs were reported in 50% of subjects, while serious AEs were reported in 11.1% of subjects (38). Ozanimod is being further evaluated in a phase III induction and maintenance study in patients with moderately to severely active UC followed by an optional open-label extension (NCT02531126, NCT02435992).

Etrasimod is a selective $S_1P_1$, $S_1P_4$, and $S_1P_5$ receptor agonist which has been evaluated in a phase II randomized double-blind placebo-controlled trial in moderately to severely active UC. The primary endpoint was the change in mean modified Mayo scores from baseline to 12 weeks. Subjects were randomized to once-daily etrasimod 1 mg, etrasimod 2 mg, or placebo for 12 weeks. The etrasimod 2 mg group demonstrated a significantly greater increase (0.99 points; $p = 0.009$) in modified Mayo clinic scores compared to placebo, while etrasimod 1 mg led to an increase of 0.43 points compared to placebo ($p = 0.15$). Endoscopic improvement was seen in 41.8% of subjects receiving etrasimod 2 mg compared to 17.8% in the placebo group ($p = 0.003$). At least one treatment-emergent AE was deemed to be related to the drug in 7.7% of subjects. One patient developed decreased heart rate and second-degree atrioventricular block type 1, while two patients had first-degree atrioventricular block (33). Etrasimod is being further evaluated in a phase III randomized double-blind placebo-controlled trial in moderately to severely active UC (NCT04176588).

## Anti-Adhesion Molecules

Active IBD attracts granulocytes, lymphocytes, and macrophages to the gastrointestinal tract, resulting in leukocyte tethering, rolling, activation, adhesion, and migration through the blood vessel walls. These mechanisms propagate inflammation through cytokine release, increase of adhesion molecules, and further recruitment of proinflammatory cells (39–41). This infiltration process is controlled by the interaction between cell surface receptors on leukocytes, such as integrins, and adhesion molecules on endothelial cells, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1, and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) (42, 43). Natalizumab was the first monoclonal antibody to target the α4 integrin subunit and is approved in many countries to treat multiple sclerosis and CD. However, this agent is associated with the development of progressive multifocal leukoencephalopathy (PML), thought to be related to its inhibition of α4β1, preventing binding to ICAM-1 and immune surveillance of the central nervous system for the John Cunningham virus (23). Vedolizumab, currently approved for

the treatment of UC in numerous countries, specifically targets α4β7 integrin, with no observed increase in risk of PML. Other medications, including both small molecules and biologics, are under investigation to disrupt leukocyte trafficking.

**Etrolizumab.** Etrolizumab is a monoclonal antibody that targets the β7 subunit of both the α4β7 and αEβ7 integrin. By preventing their binding to MAdCAM-1 and E-cadherin, respectively, etrolizumab inhibits leukocyte homing to mucosal tissue and localization of intraepithelial lymphocytes (44–46). Etrolizumab was evaluated in a double-blind placebo-controlled phase II trial of moderately to severely active UC that randomized 127 patients to receive subcutaneous etrolizumab 100 mg at weeks 0, 4, and 8; etrolizumab 420 mg at week 0 followed by 300 mg at weeks 2, 4, and 8; or placebo. At week 10, 21% of the subjects in the 100 mg group ($p = 0.0040$) and 10% of the subjects in the 300 mg group ($p = 0.048$) were in clinical remission, versus no patients in the placebo group. Week 10 rates of mucosal healing were 15% for the placebo group, 26% for the 100 mg group ($p = 0.32$), and 21% for the 300 mg group ($p = 0.82$) (47).

AEs occurred with similar frequency in all three groups (61%, etrolizumab 100 mg; 48%, etrolizumab 300 mg; 72%, placebo). The most common AEs reported were worsening UC (23%, etrolizumab 300 mg; 19%, placebo) and nasopharyngitis (15%, etrolizumab 300 mg; 19%, placebo). There were no cases of PML (47). Etrolizumab is being further studied in several phase III randomized double-blind placebo-controlled studies in UC, including the HICKORY and LAUREL trials (NCT02100696, NCT02165215). It is uncertain if the mechanistic differences between etrolizumab and vedolizumab will translate into distinct efficacy profiles.

**PF-00547659.** PF-00547659 (ontamalimab) is a monoclonal antibody that blocks MAdCAM, the endothelial receptor for α4β7 integrin, representing the first such agent studied in IBD (48). The TURANDOT study is a 12-week phase II randomized placebo-controlled clinical trial assessing PF-00547659 in patients with moderately to severely active UC. TURANDOT randomized 357 subjects to receive subcutaneous injections of 7.5 mg, 22.5 mg, 75 mg, or 225 mg of PF-00547659 or placebo at baseline and every 4 weeks. Remission rates at week 12 significantly differed from placebo (2.7%) for the 7.5 mg (11.3%; $p = 0.0425$), 22.5 mg (16.7%; $p = 0.0099$), and 75 mg (15.5%; $p = 0.0119$) groups. Response rates significantly differed from placebo (28.8%) for the 22.5 mg group (54.2%; $p = 0.0044$), 75 mg group (45.1%; $p = 0.0479$), and 225 mg group (50.0%; $p = 0.0157$). Overall, across groups, rates of remission in anti-TNF-naïve patients (ranging from 16.7% to 23.3%) were higher than in those previously exposed (7.3–9.8%). There was no large difference between the rates of AEs between placebo and any of the active treatment groups. The most common AE was headache, occurring in approximately 10% of patients, followed by UC exacerbation, though follow-up was limited to 12 weeks (49).

## Anti-Interleukin Antibodies

IL-12, a heterodimer composed of the p35 and p40 subunits, is produced by phagocytic and dendritic cells and activates natural killer cells and T lymphocytes, particularly Th1 cells (50, 51). This leads to production of proinflammatory cytokines, including interferon-γ (52). IL-23, a heterodimer consisting of the IL-12 p40 subunit and a p19 subunit, is important for Th17 differentiation, which produces inflammatory cytokines including TNF-α and interferon-γ. Engagement of IL-12 with its receptor results in intracellular JAK activation and downstream gene transcription (53, 54). It has been implicated in several immune disorders (55, 56).

**Ustekinumab.** Ustekinumab is a monoclonal antibody that targets the p40 subunit shared by IL-12 and IL-23, inhibiting its interaction with its cell surface receptor, as well as its downstream

effects (53). It is a first-in-class medication approved for the treatment of CD, with recent extension of approval to UC in the United States and other countries (57). The UNIFI trial was an 8-week randomized induction trial and 44-week randomized maintenance trial in subjects with moderately to severely active UC who failed or were intolerant of another biologic agent or conventional therapy (58). UNIFI randomized 961 patients to receive a single dose of ustekinumab 130 mg intravenously, a weight-based dose of 6 mg/kg, or placebo. Those with clinical response at 8 weeks were randomized to subcutaneous injections of ustekinumab 90 mg every 12 weeks or 8 weeks or placebo as part of the maintenance trial. Rates of clinical remission at 8 weeks were significantly higher ($p < 0.001$) in both the 130 mg (15.6%) and 6 mg/kg (15.5%) treatment groups compared to placebo (5.3%). The rate of clinical remission among responders who were randomized to maintenance therapy was higher at week 44 in those receiving ustekinumab 90 mg every 12 weeks (38.4%; $p = 0.002$) or every 8 weeks (43.8%; $p < 0.001$) than in those receiving placebo (24.0%) (58).

Similar rates of AEs were reported between ustekinumab 130 mg (41.4%), ustekinumab 6 mg/kg (50.6%), and placebo (48.0%) at the end of 8 weeks. Through week 44, similar rates of AEs were also reported across the groups, ranging from 69.2% to 78.9%. While potential opportunistic infections were reported in four patients receiving ustekinumab, cancer developed in seven patients receiving ustekinumab (including three nonmelanoma skin cancers) and in one patient receiving placebo (58).

**Mirikizumab.** Studies in psoriasis have proposed that targeting IL-23 through the p19 subunit, not found in IL-12, is more effective than ustekinumab's targeting through the p40 subunit (59). Mirikizumab is a humanized immunoglobulin that binds selectively to the p19 subunit of IL-23. It was evaluated in a phase II multicenter randomized placebo-controlled trial in patients with moderately to severely active UC. Investigators randomized 249 patients to intravenous placebo, mirikizumab 50 mg or 200 mg with exposure-based dosing, or mirikizumab 600 mg with fixed dosing at weeks 0, 4, and 8. Clinical responders at week 12 were randomized to mirikizumab 200 mg subcutaneously every 4 or 12 weeks (60).

Clinical remission at week 12 was achieved in 15.9% of patients in the 50 mg group ($p = 0.066$), 22.6% of patients in the 200 mg group ($p = 0.004$), and 11.5% of patients in the 600 mg group ($p = 0.142$) compared to 4.8% of those in the placebo group. Clinical response occurred in 41.3% of the 50 mg group ($p = 0.014$), 59.7% of the 200 mg group ($p < 0.001$), and 49.2% of the 600 mg group ($p = 0.001$), compared to 20.6% of the placebo group. Clinical remission rates at week 52 were 46.8% in patients randomized to mirikizumab 200 mg every 4 weeks, and 37% in those given mirikizumab 200 mg every 12 weeks (60).

Treatment-emergent AEs were not dose dependent, occurring in 50.8% of subjects receiving placebo and 51.6–57.1% of subjects receiving mirikizumab. The most common AEs were worsening of UC (3.2–9.5%) and nasopharyngitis (4.8–9.5%). AEs were comparable across treatment groups, though worsening UC was more frequent in the placebo group (60). Mirikizumab is being further studied in UC in two phase III trials and a long-term extension trial. The LUCENT 1 trial (NCT03518086) is a 12-week induction study in moderately to severely active UC, while LUCENT 2 (NCT03524092) is a 40-week maintenance trial for subjects completing induction.

**Other anti-IL-23 antibodies.** Several other anti-p19 antibodies are currently under investigation in UC. Risankizumab was effective in a phase II study in CD, with safety similar to placebo (61, 62). Phase II and III randomized double-blind placebo-controlled trials are under way in subjects with moderately to severely active UC (NCT03398148, NCT03398135). Brazikumab

similarly demonstrated no safety concerns and probable efficacy in a phase IIa study in CD (63). Two phase II studies are under way in moderately to severely active UC, one with vedolizumab as an active comparator (NCT03616821; EXPEDITION). Guselkumab is currently approved for the treatment of severe plaque psoriasis; a phase IIa randomized trial is under way in moderately to severely active UC combining this agent with the anti-TNF antibody golimumab (NCT03662542), while a phase IIb/III placebo-controlled trial evaluating its efficacy and safety in moderately to severely active UC has also started (NCT04033445).

## EVOLVING THERAPEUTIC CONCEPTS

### Optimization of Therapy

Advances in medical therapy for the treatment of UC have focused on the expansion of novel therapies, as discussed above. However, there are also growing efforts to maximize the efficacy of currently approved agents. While reactive patient monitoring and optimization are largely the standard of care, proactive therapeutic drug monitoring may reduce the likelihood of disease exacerbation and loss of drug response. A retrospective study by Vaughn et al. (64) demonstrated that achieving serum infliximab drug levels greater than 5 μg/ml, by means of proactive drug monitoring, made patients more likely to remain on infliximab than those who did not undergo proactive monitoring. This was supported by a multicenter retrospective study finding that subjects with IBD who received proactive monitoring had better clinical outcomes, including lower rates of surgery and hospitalization and a lower risk of antidrug antibodies (65). However, the TAXIT trial, a randomized controlled trial in 251 subjects with IBD, did not demonstrate the efficacy of therapeutic drug monitoring after initial optimization of infliximab levels at 3–7 μg/ml. While initial optimization resulted in a significantly greater percentage of patients in clinical remission (88% versus 64% preoptimization; $p = 0.02$), subsequent concentration-based dosing was not superior to clinically based dosing in achieving remission after 1 year (66). In light of these findings, additional studies are needed to better support the effectiveness of this treatment paradigm and to guide clinicians on its best practice. Furthermore, the utility of this paradigm with agents other than TNF inhibitors needs further evaluation.

Combining different classes of agents has also been explored. Randomized controlled trial data demonstrate the superiority of the combination of infliximab (an anti-TNF antibody) and immunomodulators in achieving corticosteroid-free remission; however, post hoc analysis of trials in CD demonstrated that patients with similar serum infliximab levels, whether on monotherapy or on combination therapy, had similar rates of remission. This suggests that combination therapy appears to improve efficacy by enhancing the pharmacokinetics of infliximab (67, 68). Such analyses suggest that proactive optimization of biologic monotherapy may be as effective as combination therapy, while minimizing medication exposure. Retrospective evaluation of this approach demonstrates that biologic durability does not differ between proactive therapeutic drug monitoring and combination therapy, particularly with infliximab (69). However, further studies and prospective randomized controlled trials are needed to fully determine whether this approach is as effective as combination therapy.

Beyond monitoring strategies, there is growing interest in the combination of biologic agents and small molecules. The rationale for this therapeutic approach is that inhibiting different, and sometimes complementary, pathways may enhance efficacy with minimization of side effects. This approach has been evaluated in multiple randomized controlled trials in immune-mediated diseases, with variable efficacy and safety outcomes (6). While improved outcomes in several large randomized controlled trials have been reported, particularly in the rheumatologic literature,

safety signals were noted; several studies reported higher rates of AEs, serious AEs, malignancy, and death in the combination therapy groups (70, 71). This cautionary message necessitates the study of this approach in IBD prior to its widespread adoption.

Several case reports and series, as well as a double-blind placebo-controlled trial combining natalizumab with infliximab for 8 weeks, demonstrate generally favorable efficacy and safety of combination therapy in IBD (6, 72–75). However, unique to IBD are medications with gut-specific mechanisms and favorable safety profiles, such as vedolizumab and the other antitrafficking agents. These are being evaluated in a phase IV open-label trial (the EXPLORER trial) combining adalimumab with vedolizumab and methotrexate for the treatment of moderately to severely active CD (NCT02764762). The VEGA trial is also evaluating combination therapy in a phase IIa randomized double-blind trial, evaluating guselkumab and golimumab in moderately to severely active UC (NCT03662542). The results from both trials will inform the use of this approach in both UC and IBD.

## Fecal Transplant

Fecal microbiota transplant (FMT), approved for the treatment of recurrent or refractory *Clostridioides difficile* in the United States and other countries, entails the transfer of the intestinal microbiome and correction of dysbiosis associated with UC (76). While the precise mechanism of FMT is unknown, several randomized controlled studies have evaluated its efficacy in UC. Rossen and colleagues (77) performed a phase II randomized controlled trial in 50 subjects with moderately to severely active UC who received either an FMT from a healthy donor or an autologous FMT via nasoduodenal tube at baseline and at 3 weeks. In their intention-to-treat analysis, they found that 30.4% of subjects receiving FMT from healthy donors and 20.0% of controls ($p = 0.51$) achieved clinical remission. No treatment-related AEs were reported (77). Moayyedi and colleagues performed a randomized controlled study of 75 subjects with active UC who received FMT via an enema from a healthy donor or a placebo water enema once weekly for 6 weeks. While the trial was stopped by the data safety monitoring committee for futility at the interim analysis, 24% of subjects who received FMT and 5% who received placebo were in clinical remission at 7 weeks ($p = 0.03$). There was no difference in serious AEs between the two groups ($p = 1.0$) (78).

In contrast to the two prior randomized studies, in which one donor was used for every patient, the FOCUS trial utilized a multidonor protocol. Eighty-five subjects were randomized to receive FMT or placebo via colonoscopic infusion followed by enemas 5 days/week for 8 weeks. Steroid-free clinical remission was achieved in 27% of subjects allocated to FMT compared to 8% in the placebo group. AEs were reported in 78% of patients receiving FMT compared to 83% of those assigned to placebo, and the majority were self-limited gastrointestinal complaints (79).

Overall, FMT appears effective in achieving clinical remission in approximately one-third of patients with active UC, but further work is needed to optimize its efficacy. This will include comparing anaerobic and aerobic stool preparation, identifying the characteristics of effective donors, and determining the benefit of treating patients with antibiotics prior to FMT. Furthermore, optimization of the dose, route, frequency, and duration of FMT is needed (80). Ultimately, an improved understanding of the necessary beneficial components of FMT may lead to the development of agents that do not require derivation from stool, thereby improving safety and standardization of the approach.

## Hyperbaric Oxygen

Hyperbaric oxygen, a therapy in which subjects breathe 100% oxygen under increased pressure, results in increased physiological oxygen concentrations. It targets the abnormal response to tissue

hypoxia, enhances barrier function, reduces inflammatory cytokines, shifts the gut microbiome, and diminishes intestinal Th17 activation that underlies UC (81, 82). A phase IIa double-blind randomized controlled trial was performed in subjects hospitalized with moderately to severely active UC. Subjects were randomized to daily hyperbaric oxygen plus steroids or sham hyperbaric air and steroids. While only 18 of the planned 70 subjects were enrolled, clinical remission rates at study day 5 were 50% in the hyperbaric oxygen group and 0% in the sham group ($p = 0.04$). Interestingly, a lower proportion of hyperbaric oxygen patients (10%) progressed to second-line therapy compared to the control group (63%) ($p = 0.04$). Treatment was well tolerated overall (83). While this study is promising, larger studies are needed to verify these results.

## CONCLUSION

The management of UC is rapidly evolving, with a growing number of medications and therapeutic approaches being developed and evaluated. In the near future, clinicians will have an increasing number of agents with diverse mechanisms of action that can be used in the management of UC. Furthermore, evaluation of novel, non-medication-based modalities, such as FMT and hyperbaric oxygen, may provide useful adjuvant therapies. Advances in therapeutic drug monitoring and more strategic utilization of approved agents will continue to enhance the effectiveness of available options. The management of UC should be improved over the coming years, offering multiple new options for our patients.

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