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# MIRIKIZUMAB AS INDUCTION AND MAINTENANCE THERAPY FOR ULCERATIVE COLITIS

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**Abstract**
A monoclonal antibody called mirikizumab is used to treat ulcerative colitis. It is marketed under the Omvoh brand. It is intended to bind to interleukin-23 (IL-23) and obstruct its function. Upper respiratory tract (nose and throat) infections, headaches, rashes, and injection site responses (when administered by subcutaneous injection) are the most frequent adverse effects. In the United States in October 2023 and the European Union in May 2023, mirikizumab was authorized for medicinal use. For the treatment of people with moderately to highly active ulcerative colitis who have not responded well to, have lost responsiveness to, or are intolerant to either biologic therapy or conventional therapy, mirikizumab is suggested. A subset of people with ulcerative colitis (UC) do not react to currently available medications, despite advancements in UC medical therapy. Many innovative medications have recently acquired regulatory approval for use in UC, or are in the latter stages of development. The novel antibody mirikizumab, which is given intravenously (IV), binds to the inflammatory protein interleukin 23 and inhibits its function, preventing inflammation from being triggered. For individuals with moderately to highly active UC, mirikizumab would therefore provide an additional therapy choice if legalized.

***Keywords:*** Mirikizumab, ulcerative colitis, monoclonal antibodies, inflammatory disease.



## Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by contiguous chronic mucosal inflammation of the colon with a relapsing-remitting course, resulting in Treatment goals in UC are stepwise: symptomatic response is the immediate treatment goal, symptomatic remission the intermediate goal, while endoscopic and even histologic remission in conjunction with symptomatic remission is the long-term target.

- Histologic remission is considered a potential adjunct to endoscopic remission representing a deeper level of healing. Molecular remission is currently being investigated. Tumor necrosis factor (TNF) antagonists were the key therapeutic agent for moderate-to-severe UC for more than a decade with vedolizumab, a gut-selective anti-integrin antibody.
- Tofacitinib, a pan-Janus kinase (JAK) inhibitor and ustekinumab, an antibody against the p40 subunit of interleukin (IL)-12/ 23
- Entering clinical practice in recent years. Despite their proven efficacy, some patients either do not respond to treatment or lose response after initial improvement Furthermore, particularly anti-TNF agents and tofacitinib are associated with potentially serious adverse effects.
- Underscoring the necessity for further drug development in UC. Management of moderate-to-severe UC in recent years has shifted from hospital- or practice-based infusion units to patients' homes by reformulating existing biologics for subcutaneous use (infliximab, vedolizumab).
- Development of subcutaneously administered monoclonal antibodies (ustekinumab, adalimumab, golimumab). And the use of orally administered small molecules Beyond convenience, small molecules also have the advantage of avoiding immunogenicity, a somewhat limiting factor in the efficacy of monoclonal antibodies, particularly TNFantagonists.
- It should be noted, however, that novel biologics have lower immunogenicity. A number of novel agents have entered late stages of clinical development or have recently been approved for UC. In this review, we provide an overview of the efficacy and safety of emerging therapeutic agents for UC that have entered or completed Phase 3 trials: anti-IL-23

antibodies, sphingosine-1-phosphate receptor (S1PR) modulators, and selective JAK inhibitors. We also outline clinical dilemmas surrounding their optimal use in practice and identify research priorities. Body of review: -Anti-IL-23 agents**:**

- The IL-23 axis is an emerging treatment target in IBD (both Crohn's disease [CD] and UC), with ustekinumab, a human monoclonal antibody targeting the shared p40 subunit of IL12 and IL-23 already in clinical use in in many countries.
- IL-23 is a heterodimeric cytokine with a unique p19 subunit and p40 subunit which it shares with IL-12. IL-23 exerts its effect by binding to the IL-23 receptor and activating intracellular.
- JAKs (predominantly TYK2 and JAK2) . IL-23 is mainly synthesized by dendritic cells and macrophages and is one of the key mediators in the T helper 17 (Th17) cell pathway
- These helper cells are characterized by the production of IL-17, IL-21, IL-22, and IL-26. IL-17 producing cells are increased in the serum and mucosa of patients with IBD.
- Together with T cell receptor activation, IL-6 and transforming growth factor-β (TGF-β) induce the expression of retinoid-related orphan receptor-γt (ROR-γt), a transcription factor that promotes expression of IL17 and IL-23 receptors on the surface of The17 cells.
- IL-23 can thus establish a positive feedback loop leading to the expansion of The17 cells. IL-17 also stimulates innate lymphoid cells-3, natural killer T cells, and γδ T cells.
- There is considerable cross-regulation between the IL-23 Th 17 and IL-12 Th1 pathway.
- Broadly speaking, IL-12 may mediate more systemic effects, while IL-23 is implicated in mucosal immunology, although these notions remain unsubstantiated in humans.
- Selective IL-23 inhibitors are approved for psoriasis (guselkumab, risankizumab, tildrakizumab) and psoriatic arthritis (guselkumab).
- It is uncertain how IL-23-specific monoclonal antibodies targeting the p19 subunit compare to agents targeting both IL-12 and IL-23 through the p40 subunit. Drugs currently in development for UC all target IL-23 in isolation.

**MIRIKIZUMAB**

Efficacy: -

- Mirikizumab (LY3074828; Eli Lilly) is a humanized monoclonal antibody against the p19 subunit of IL-23, administered as three intravenous doses (every 4 weeks) during a 12-week induction period followed by subcutaneous maintenance dosing every 4 to 12 weeks.
- A Phase 3 trial is ongoing (NCT03926130). The drug has not yet been approved for any indication. The LUCENT-1 study (NCT03518086) assessed the efficacy and safety of mirikizumab as induction therapy in patients with moderate-to-severe UC.
- The primary endpoint of the induction study was clinical remission at week 12, defined by the modified Mayo score: rectal bleeding subscore of 0; stool-frequency subscore of ≤1, with a decrease of ≥1 point from baseline; and Mayo endoscopy subscore of ≤1. Clinical remission was significantly higher among patients receiving mirikizumab compared to placebo (24.2% [210/868] vs. 13.3% [39/294], P < 0.001).
- Bionaïve patients achieved clinical remission in 30.9%, while patients with previous biologic failure achieved clinical remission in 15.2%. Mirikizumab was superior to placebo in achieving endoscopic improvement and histo-endoscopic mucosal improvement. Results of the maintenance trial are expected to be reported in the very near future.

Safety:-

The overall incidence of adverse events (44.5% [426/958] vs. 46.1% [148/321]) and serious adverse events (2.8% [27/958] vs. 5.3% [17/321]) was comparable between the mirikizumab and placebo group. The most common adverse events included nasopharyngitis, anemia, headache, and worsening of UC. There was no concerning signal for infections (serious, opportunistic, or total), cardiovascular events, or hepatic events.

Other anti-IL-23 agents: -

Three additional p19 antibodies, risankizumab, brazikumab, and guselkumab, are being investigated for use in UC, with guselkumab having the first Phase 2 results available. Risankizumab (BI655066/ABBV066, Abbvie) is a humanized monoclonal antibody against the p19 subunit of IL-23. It has been approved for moderate to severe plaque psoriasis, and has been submitted for approval to regulatory authorities for CD. In UC, a Phase 2/3 induction trial (NCT03398148) and Phase 3 maintenance trial (NCT03398135) are ongoing. Brazikumab (MEDI2070, previously known as AMG139, Astra Zeneca) is a human monoclonal antibody against the p19 subunit of IL-23. It has not yet been approved for any indication. It was studied in a Phase 2a study in CD, with an ongoing Phase 2/3 trial (NCT03759288). In UC, a Phase 2 trial is ongoing (NCT03616821). Guselkumab (CNTO1959, Janssen) is a human monoclonal antibody against the p19 subunit of IL-23, approved for moderate-to-severe plaque psoriasis. A Phase 2/3 trial is recruiting in CD (NCT03466411, GALAXI). In UC, a Phase 2b randomized, double-blind, placebo-controlled trial demonstrated superiority of guselkumab to placebo for clinical response during induction at week12 (61.1% pooled for guselkumab at 200 mg and 400 mg doses vs. 27.6% for placebo; P < 0.001) (integrated

Phase 2b/3 study; NCT04033445, QUASAR). The efficacy of the 200 mg and 400 mg doses was comparable. Combination therapy was significantly more effective than either drug alone.

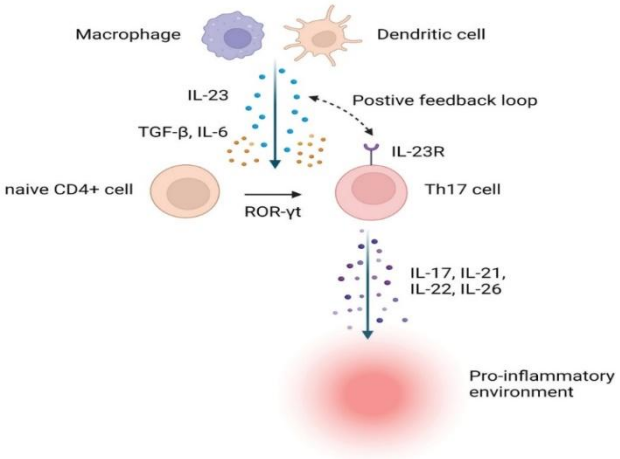


Figure 1 The biology of interleukin-23 signaling. Abbreviations: IL – interleukin; R – receptor; ROR-γt – retinoid-related orphan receptor- γt; TGF-β – transform in growth factor beta. Created with BioRender.com

Sphingosine-1-phosphate receptor modulators: -

- S1P is a multifunctional molecule, synthesized from sphingosine, an endogenous cellular sphingolipid, through phosphorylation by sphingosine kinases.

S1P is secreted from cells, thereby establishing a concentration gradient: concentrations are high in the blood and lymph, but low in the interstitial fluid. S1P signals through five subtypes of G-protein coupled receptors (S1PR1-5). The expression of these receptors varies by tissue, and the function of each receptor is highly dependent on the cell type on which it is expressed. Under physiological conditions, the S1P receptor on lymphocytes responds to an S1P gradient, which drives lymphocyte egress from lymphoid tissues into the systemic circulation toward the site of inflammation. This is mediated by S1PR1, which also has a role in angiogenesis, heart rate regulation

- It has been associated with fibrosis. S1PR2/3 is involved in regulation of endothelial barrier function, fibrosis, and vasoconstriction. S1PR4 have more limited expression in the hematopoietic and lymphoid tissue, while S1PR5 are mainly expressed in the central nervous system. S1PR4 influence T cell differentiation and modulate cytokine expression, S1PR5.Mediate natural killer cell and monocyte trafficking, and maintain endothelial barrier integrity.

  S1P receptor modulators bind to one of the S1PR on activated lymphocytes, which leads to internalization of the receptor and subsequent loss of responsiveness to the S1P gradient.
- This results in retention of lymphocytes within the lymph nodes and thus inhibition of lymphocyte trafficking to inflammatory sites with potentially preserved immune surveillance as circulating monocytes, natural killer cells, and natural killer T cells were affected only minimally in a study of patients with multiple sclerosis.
- The majority of patients develop peripheral lymphopenia during treatment with these agents, but this pharmacodynamic effect does not seem to correlate with effica Ozanimo

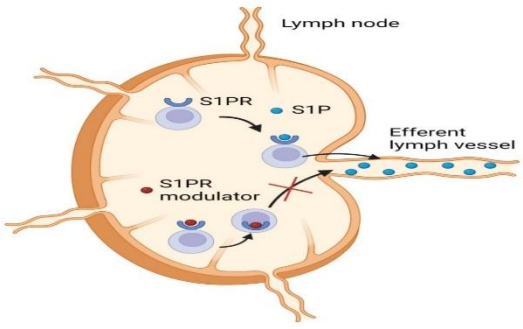


Fig2: The biology of sphingosine-1-phosphate signaling. Abbreviations: S1P – sphingosine-1-phosphate; S1PR – sphingosine-1-phosphate receptor. Created with BioRender.com

Safety:

The overall incidence of adverse events was comparable between the ozanimod and placebo group during induction (39.9% [318/796] pooled over both ozanimod cohorts vs. 38.0 [82/216] for placebo). During maintenance the incidence of adverse events was higher in the ozanimod group than in the placebo group (49.1% [113/230] vs. 36.6% [83/227]).

However, the rate of serious adverse events was comparable across all groups both in induction and maintenance (ozanimod: 5.0% [40/796] for induction, 5.2% [12/230] for maintenance; placebo: 3.2% [7/216] for induction, 7.9% [18/227] for maintenance). Based on previous associations with S1PR modulation, the following adverse events of special interest were examined in the True North study: bradycardia, cardiac conduction abnormalities (second-degree and higher atrioventricular block), macular edema, cancer, serious or opportunistic infection, pulmonary toxicity, and hepatotoxicity.

Etrasimod: -

- Etrasimod (Arena Pharmaceuticals) is a S1PR1, S1PR4, and S1PR5 modulator, which demonstrated superiority over placebo in a Phase 2 study in UC at the 2 mg dose (clinical remission: 33% vs. 8.1%; endoscopic improvement: 41.8% vs. 17.8%), but not at the 1 mg dose.
- No adverse events, unexpected for an S1P modulator were observed. The Phase 3 studies induction and maintenance completed enrollment in 2021 (NCT03945188, NCT03996369), however the results have not yet been reported. Etrasimod has not yet been approved for any indication.

Janus kinase inhibitors**:**

- JAKs are tyrosine kinases that bind different intracellular cytokine receptors and regulate immune responses, wound healing, and hematopoietic differentiation. The JAK family consists of four intracellular proteins: JAK1, JAK2, JAK3, and TYK2. Their activation requires homo- or heterodimerization with subsequent autophosphorylation.
- Different combinations of JAKs are associated with different cytokine receptors. From a mechanistic viewpoint, JAK1 is the molecule involved in IL2, IL-4, IL-6, IL-15, and interferon signaling, whereas JAK2 is more involved in signaling of hematopoietic cytokines, prolactin, and growth hormone, which underscores that JAK1 is the most likely therapeutic target of JAK inhibitors in inflammatory bowel disease, although the end effect of selective JAK inhibition is difficult to predict due to cytokine pleiotropism and dose-dependent selectivity.
- Despite sound in vitro data on the selectivity of JAK inhibitors, its clinical impact is probably dependent not only on the agent itself, but also its dose, cell type, tissue penetration, and individual genetic background. The clinical consequences of JAK-1 selectivity (as claimed for filgotinib and upadacitinib) in IBD remain unknown – both in terms of efficacy and safety. A meta-analysis of JAK inhibition across other immunemediated diseases in addition to IBD showed a numerically higher rate of herpes zoster with nonselective JAK inhibitors (tofacitinib, baricitinib) compared to selective JAK1 inhibitors (upadacitinib, filgotinib). Further analyses based on Phase 3 data in IBD are still pending.

Safety:

Both during induction and maintenance, the rate of adverse events was similar for the 200 mg arm (53.6% during induction, 66.8% during maintenance), the 100 mg arm (50.4% during induction, 60.3% during maintenance), and placebo (56.3% during induction, 62.2% during maintenance). Serious adverse events occurred in 5.0% (28/562) of patients given filgotinib 100 mg, 4.3% (22/507) of patients given EXPERT REVIEW OF CLINICAL IMMUNOLOGY 519 filgotinib 200 mg, and 4.7% (13/279) of patients given placebo during induction. In the maintenance study, serious adverse events were reported in 4.5% (8/179) of patients given filgotinib 100 mg and 7.7% (7/91) of patients in the respective placebo group, by 4.5% (9/202) of patients in the filgotinib 200 mg group, and no patients in the respective placebo group.

- The incidence of infections and serious infections, even when adjusted for duration of previous drug exposure, was similar between the filgotinib and placebo groups in both the induction and maintenance studies. Six patients from all studies had herpes zoster infections, none of which were serious or prompted discontinuation of the study drug. One patient who received filgotinib 200 mg in the induction study had pulmonary embolism.
- No patients who receiving filgotinib had venous thromboses or pulmonary embolisms in the maintenance study. Two patients who received placebo both in the induction study and in the maintenance, study had venous thromboses. Non-melanoma skin cancers occurred in three patients in the induction studies and one patient in the maintenance study all had previously been treated with thiopurines.
- Other malignancies were reported in three patients (colon cancer, breast cancer, and malignant melanoma; all in patients who received filgotinib). In the induction studies, a small increase in serum lipid concentrations was observed in the filgotinib groups, which remained stable during maintenance. The proportion of patients with abnormal creatine kinase increase was higher in the filgotinib groups than in the placebo groups in all three studies, without clinical rhabdomyolysis. No new safety concerns were observed in a 4-year follow-up study of filgotinib in patients with rheumatoid arthritis.
- Findings from animal studies suggested potential issues with male reproductivity.
- Two targeted clinical studies are addressing this concern in humans, which both have completed recruitment. Full results have not been published as of yet, but a press release reported numerically higher rates of decreases in sperm count with placebo rather than filgotinib.
- The Food and Drug Administration's (FDA) black box warning against thromboembolic events based on data for tofacitinib was extended to baricitinib and upadacitinib in 2021 and would probably have included filgotinib if the sponsor had not abandoned the pursuit of approval of the agent for rheumatoid arthritis in the United States.

Upadacitinib:-

Efficacy:

- Upadacitinib (Rinvoq ®, Abbvie) is an oral JAK1 preferential inhibitor. It has been approved in the United States for UC and submitted for regulatory approval in Europe. A Phase 2 trial in CD has been successfully completed.
- and two Phase 3 trials for this indication have completed recruitment. The efficacy and safety of upadacitinib for the treatment of moderate-to-severe UC was evaluated in two Phase 3 induction trials (U-ACCOMPLISH [NCT03653026], U-ACHIEVE [NCT02819635]) and one maintenance trial (U-ACHIEVE Maintenance.
- In the twoinduction studies, patients with moderate-to-severe UC who had inadequate response, loss of response, or intolerance to aminosalicylates, immunosuppressants, corticosteroids and/or biologics were randomized 2:1 to receive upadacitinib 45 mg daily or placebo for 8 weeks. Randomization was stratified for baseline corticosteroid use, inadequate response to biologics, and adapted Mayo score at baseline (≤7 vs. >7). The primary endpoint was again clinical remission at week 8, defined by the components of the Mayo score: rectal bleeding subscore of 0; a stool-frequency subscore of ≤1, and not greater than at baseline; and an endoscopy subscore ≤1. In U-ACCOMPLISH, 33.5% of 341 patients in the upadacitinib group and 4.1% of 174 patients in the placebo group achieved clinical remission ($P < 0.001$).
- Treatment with upadacitinib was also significantly more likely than placebo to result in endoscopic improvement, endoscopic remission, and histologic-endoscopic mucosal improvement. In U-ACHIEVE, 26.1% of 319 patients in the upadacitinib group and 4.8% of 154 patients in the placebo group achieved clinical remission ($P < 0.001$). Upadacitinib was superior to placebo in endoscopic, endoscopic remission, and histologicendoscopic mucosal improvement. Although upadacitinib was superior to placebo both in patients with and without previous inadequate response to biologics, the difference versus placebo was numerically greater among patients who had not had inadequate response to biologics.
- At week 8, responders to upadacitinib were re-randomized 1:1:1 at to receive upadacitinib 30 mg (n = 154), 15 mg (n = 148), or placebo (n = 149) through week 52.
- Re-randomization was stratified by previous biologic failure status, induction clinical remission status and baseline corticosteroid use. Both the 30 mg dose (51.7%; $P < 0.001$) and the 15 mg dose (42.3%; $P < 0.001$) were superior to placebo (12.1%) in achieving clinical remission at week 52. Upadacitinib also met all the secondary endpoints: endoscopic improvement, endoscopic remission and histologic-endoscopic mucosal improvement. Both doses of upadacitinib were superior to placebo in maintenance of clinical remission (subset of patients in clinical remission at the end of induction) (30 mg: 69.7%; 15 mg: 59.2%; placebo: 22.2%; $P < 0.001$) and maintenance of endoscopic improvement (subset of patients with endoscopic improvement at the end of induction) (30 mg: 69.5%; 15 mg: 61.6%; placebo: 18.9%; $P < 0.001$).

Safety:

- With the exception of the U-ACCOMPLISH induction study (52.9% for upadacitinib vs. 39.5% for placebo) the rate of adverse events was comparable between upadacitinib (U-ACHIEVE induction: 56.4%; maintenance: 30 mg 78.6%, 15 mg 77.7%) and placebo (U-ACHIEVE induction: 60.0%; maintenance: 75.8%).
- The rate of serious adverse events was lower with upadacitinib (U-ACHIEVE induction 2.5%, 30 mg maintenance 5.8%, 15 mg maintenance 6.8%; U-ACCOMPLISH induction 3.2%) than with placebo (U-ACHIEVE induction 5.8%, maintenance 12.8%; U-ACCOMPLISH induction 4.5%). The rate of serious infections was low and comparable across all groups throughout the whole study. Herpes zoster was only observed in upadacitinib-treated patients with an incidence around 4%. Two venous thromboembolisms occurred in the 30 mg maintenance arm and one in the placebo arm during induction.
- One major cardiovascular 520 J. HANZEL ET AL. event occurred in the placebo arm, none occurred in the upadacitinib arms. Nonmelanoma skin cancer occurred in two patients receiving upadacitinib 30 mg, but not in other groups. Other malignancies were found at similar rates across all groups (0.7–1.3%). In terms of laboratory abnormalities, elevations in creatine kinase, elevations in liver enzymes, and neutropenia were more commonly recorded with upadacitinib, but this was not the case for anemia and lymphopenia. With low numbers of adverse events of special interest, a potential dose-dependency is difficult to evaluate.

**Conclusion:**

In Phase 3 trials in UC, several medications from various classes have lately demonstrated efficacy; some of these medications have even received regulatory approval. S1PR modulators, selective JAK-1 inhibitors, and anti-IL-23 antibodies are a few of these. The placement of therapeutic agents in treatment algorithms has grown more difficult as more of them become available. S1PR modulators and selective JAK inhibitors both have a slightly increased risk of cardiovascular and infectious side events, but out of the three types, IL-23 inhibitors have the best safety profile. If targeted JAK1 inhibition can reduce this risk, that is yet to be determined. Comparison of efficacy is challenging in the lack of head-to-head studies; nevertheless, network meta-analyses indicate that upadacitinib may be the most effective medication in isolation. It looks promising to further break the treatment ceiling in UC when anti-TNF medicines and anti-IL-23 antibodies are combined.

**Author contributions**

All authors are contributed equally.

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**Declaration of Competing Interest**
The authors have no conflicts of interest to declare.

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