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Highlights From the 2023 Advances in Inflammatory Bowel Disease Conference

A Review of Selected Presentations on Inflammatory Bowel Disease From the 2023 AIBD Conference

December 14-16, 2023 • Orlando, Florida

Special Reporting on:

- Anti-TNF
- JAKs
- IL-23
- Leukocyte Trafficking
- Comparative Effectiveness in Positioning Therapies

PLUS Meeting Abstract Summaries

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Anti-TNF

Therapy for inflammatory bowel disease (IBD) requires the consideration of numerous treatment parameters, including safety vs efficacy; the dose, timing, interval, and duration of administration of multiple drugs; and the costs associated with ongoing treatment.[1] With so many variables to consider, optimizing therapy for patients with IBD can be challenging. Currently, 4 anti–tumor necrosis factor (TNF) biologic therapies are available for the treatment of Crohn's disease (CD) and ulcerative colitis (UC), including certolizumab pegol, adalimumab, golimumab, and infliximab (Figure 1). Despite the availability of traditional drugs and newer biologics, primary and secondary nonresponse remains a problem, as disease duration is associated with increased failure to respond to therapy.[2,3] One approach to improve outcomes is prioritizing early initiation of anti-TNF therapy.[4] When a patient presents with moderately to severely active CD, starting anti-TNF therapy as soon as possible yields superior disease control compared with initial treatment comprising 5-aminosalicylates, corticosteroids, and/or immunosuppressive therapy. Similarly, induction therapy with an anti-TNF biologic is more likely to achieve clinical remission in patients with early IBD than in patients with late IBD.[5]

The development of antidrug antibodies presents a challenge to the use of biologic therapy. Episodic therapy increases the risk of developing antidrug antibodies and may be unintentional, owing to a loss of insurance coverage or the development of complications. Patients who achieve subtherapeutic serum levels of drugs and patients who experience complete drug clearance between doses are also at risk. Further, patients who have already developed anti-TNF antibodies are more likely to develop antibodies to a second anti-TNF therapy, and patients with a specific haplotype may be at higher risk as well.[6,7] Other risk factors for the development of antidrug antibodies to monoclonal antibody therapy include male sex, increased body mass index, a high baseline level of C-reactive protein (CRP), smoking, and others.[8-10]

Patients with IBD and a high amount of visceral adipose tissue (VAT) have shown a reduced response to anti-TNF therapy.[11,12] A prospective study evaluated 141 patients with IBD who were starting therapy with infliximab, vedolizumab, or ustekinumab vs 51 healthy controls.[13] Patients with higher intra-abdominal VAT as a percentage of total body weight were less likely to achieve corticosteroid-free deep remission (P<.001) or endoscopic remission (P=.02) compared with patients who had a lower proportion of intra-abdominal VAT. Patients with a higher proportion of intra-abdominal VAT who failed to respond to treatment demonstrated a higher level of serum interleukin-6 (IL-6) and TNF at baseline compared with patients who exhibited a response or patients with a low proportion of intra-abdominal VAT. Increasing the dose level may improve outcomes; however, the data are equivocal.

Patients' disease status should be routinely assessed by ultrasound, endoscopy, levels of CRP and fecal calprotectin, as well as serum levels of anti-TNF drug and antidrug antibodies.[14] For patients who exhibit a

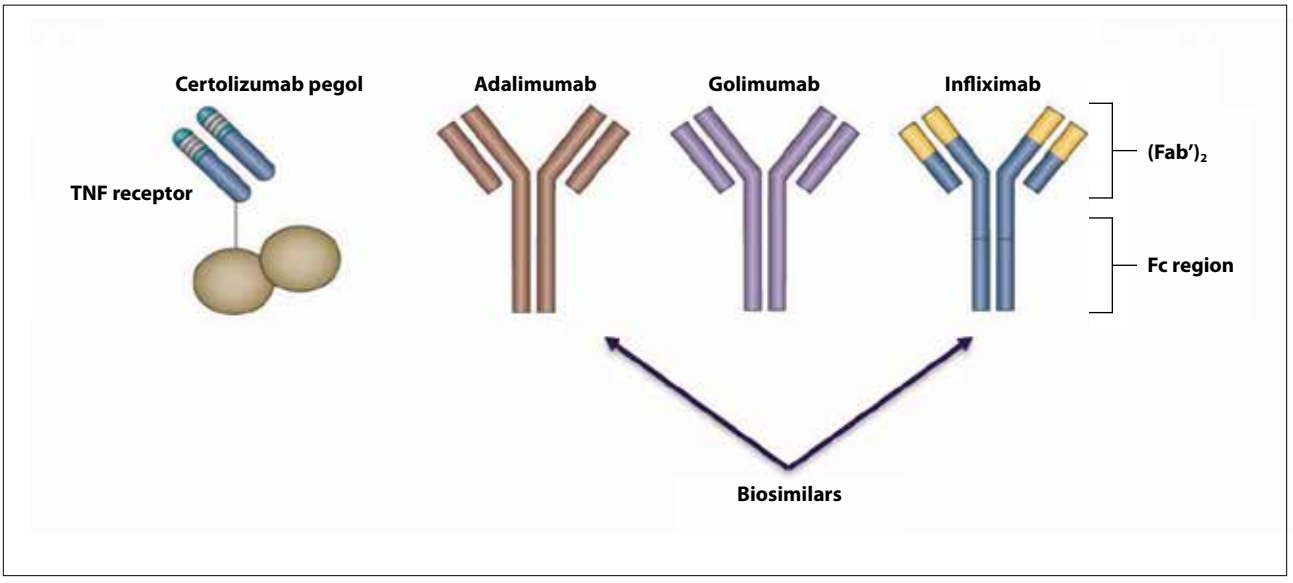

Figure 1. The 4 anti-TNF biologic therapies available for the treatment of Crohn's disease and ulcerative colitis.

Fab, fragment, antigen binding; Fc, fragment, crystallizable; TNF, tumor necrosis factor.
Adapted from Rubin et al. Anti-TNF. Presented at the Advances in Inflammatory Bowel Disease Conference; Orlando, Florida; December 14-16, 2023.[1]

Targeting TNF remains a mainstay of treatment for CD and UC, in particular for patients with fistulizing disease or extraintestinal manifestations. Advances in anti-TNF therapy include the availability of subcutaneous infliximab, which affords higher and more stable blood levels and another option for therapeutic delivery. Biosimilars to infliximab and adalimumab should eventually improve the pharmacoeconomics of advanced therapy for IBD.
– Stephen B. Hanauer, MD

partial or limited response to therapy, recapture of response may be possible by administration of a small loading dose, followed by decreasing the interval or increasing the drug dose. Other parameters to check include the presence of antidrug antibodies and the level of drug in the patient's serum. Patients with a poor response and a therapeutic level of drug in the serum most likely require a different therapy, which may comprise changing to a different drug within the same class or switching to a drug with a different mechanism of action.

Therapeutic drug monitoring (TDM) is an active area of research for optimizing anti-TNF biologic therapy for patients with IBD. Some studies have suggested that proactive TDM and the associated dose adjustments may improve outcomes. For example, a retrospective observational study evaluated proactive TDM and adjusting the dose of infliximab to a target concentration in 48 patients with IBD who were in clinical remission.[15] The initial trough concentration was undetectable in 15% of patients. After the first proactive measurement of drug level, the dose of infliximab was escalated in 12 patients (25%) and was decreased in 7 patients (15%) throughout the study. Patients with proactive dose adjustments based on proactive TDM were more likely to remain on infliximab compared with controls (HR, 0.3; 95% CI, 0.1-0.6; *P*=.0006). More recently, the NOR-DRUM B study evaluated the use of proactive TDM with infliximab during maintenance therapy.[16] The parallel-group, open-label trial included 458 patients with CD, UC, and other diseases such as rheumatoid arthritis and psoriasis. Patients were evenly randomized to receive infliximab based on standard dosing or with dose adjustments based on proactive TDM. Patients had a mean age of 44.8 years and nearly one-half of patients were female. The trial met its primary endpoint, demonstrating sustained disease control without disease worsening in 167 patients (64%) in the proactive TDM arm vs 127 patients (56%) in the standard therapy arm, with an adjusted difference of 17.6% (95% CI, 9.0-26.2; *P*<.001) that favored proactive TDM and dose adjustment. The study showed a benefit with proactive TDM among patients with UC but not among patients with CD.

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JAKs

Janus kinase (JAK) inhibitors reduce inflammation by preventing intracellular signaling that would otherwise activate inflammatory genes.[1] By targeting different JAK proteins, therapies may have different levels of efficacy, preferred patient populations, and safety profiles. Three JAK inhibitors are approved for the treatment of IBD: upadacitinib is approved for both CD and UC, whereas tofacitinib and filgotinib are approved only for UC, and filgotinib has yet to receive approval from the US Food and Drug Administration for the treatment of patients with IBD.

JAK inhibitors provide oral, once-daily options that are fast acting and highly efficacious for both biologic-naive and biologic-experienced patients with UC and CD (such as upadacitinib). MACE events seen in rheumatoid arthritis trials were not observed at increased risk in IBD trials. The rapid onset of action of JAKs may afford opportunities to treat acute severe UC, including in hospitalized patients.
– Stephen B. Hanauer, MD

The phase 3 OCTAVE Sustain trial investigated twice-daily tofacitinib 5 mg and tofacitinib 10 mg vs placebo in patients with UC who had failed prior therapy.[2] The study enrolled 593 patients who had demonstrated a clinical response to induction therapy in the OCTAVE Induction 1 and 2 trials for randomization into the 3 arms (Figure 2). At week 52, the proportion of patients in remission was 11.1% in the placebo arm, 34.3% in the tofacitinib 5 mg arm (P<.001), and 40.6% in the tofacitinib 10 mg arm (P<.001), thus achieving the primary endpoint. Both doses of tofacitinib were significantly superior to placebo based on numerous other endpoints, including response, remission, sustained mucosal healing, and sustained steroid-free remission. The ORAL Surveillance study investigated safety events associated with administration of tofacitinib, with a specific focus on major adverse cardiovascular events (MACE) and malignancy, excluding nonmelanoma skin cancer, in patients over 50 years of age with rheumatoid arthritis.[3] Patients were randomized to tofacitinib 5 mg or tofacitinib 10 mg, administered twice daily, vs anti-TNF therapy. The study demonstrated a higher incidence of MACE with the combined tofacitinib arms vs the anti-TNF arm (3.4% vs 2.5%; HR, 1.33; 95% CI, 0.91-1.94), as well as an increase in malignancy (4.2% vs 2.9%; HR, 1.48; 95% CI, 1.04-2.09). Subsequent analyses suggested that patients who did not smoke and were less than 65 years of age did not have an increased risk of MACE or malignancy.

Upadacitinib was investigated

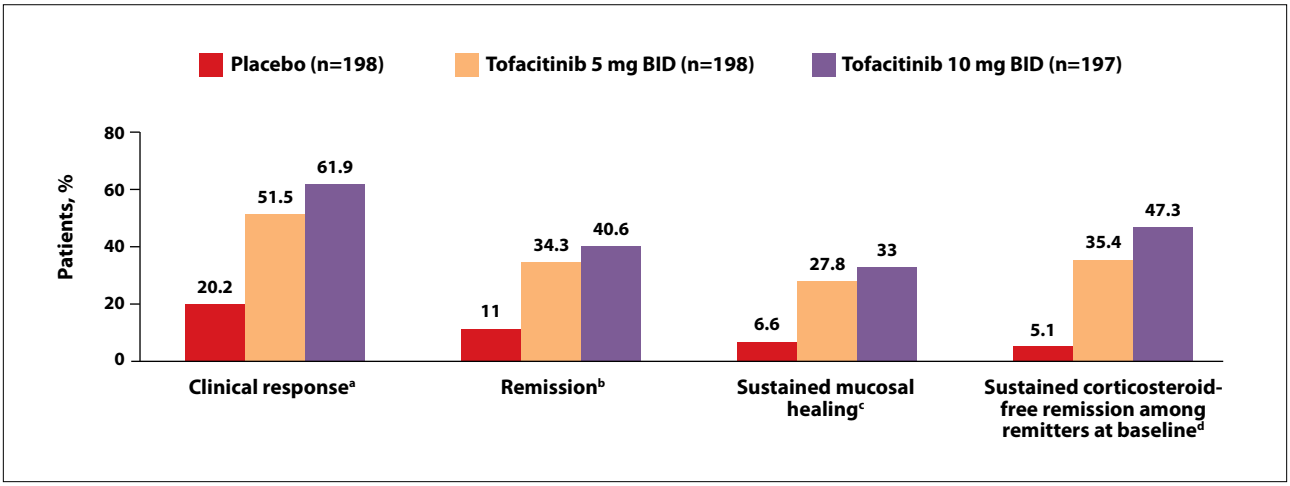

Figure 2. Clinical response and remission at 52 weeks in patients with ulcerative colitis from the OCTAVE Sustain trial.

[a]Decrease in total Mayo score of ≥3 points and ≥30%, with decrease in RBS of ≥1 or absolute RBS ≤1.
[b]Total Mayo score of ≤2, with no subscore >1 and RBS of 0.
[c]Mayo endoscopic subscore of ≤1 at both 24 and 52 weeks.
[d]Corticosteroid-free defined as not requiring corticosteroids for ≥4 weeks before each visit.
BID, twice daily; RBS, rectal bleeding subscore.
Adapted from Loftus et al. JAKs. Presented at the Advances in Inflammatory Bowel Disease Conference; Orlando, Florida; December 14-16, 2023.[1]

in patients with UC in the phase 3 U-ACHIEVE and U-ACCOMPLISH studies.[4,5] A total of 474 patients with moderately to severely active UC were randomized to receive daily upadacitinib 45 mg vs placebo for 8 weeks of induction therapy. Patients with a response were then randomized to daily upadacitinib 15 mg, upadacitinib 30 mg, or placebo for the maintenance portion of the study. Based on the ability to induce or maintain clinical remission, upadacitinib was superior to placebo in the induction trials (P<.001) and in the maintenance trial (P<.001). Upadacitinib induced responses in patients as early as week 2 of therapy, with improvements observed as early as day 1.[6,7] Based on the common adverse events (AEs) of anemia and leukopenia, a complete blood count and hepatic enzymes should be evaluated every 3 months for patients receiving JAK inhibitor therapy for UC.

Daily upadacitinib 45 mg was also investigated as induction therapy in the U-EXCEL trial, which enrolled patients with CD with an inadequate response or intolerance to conventional or biologic therapy.[8] A notable finding of the study was the superior rate of steroid-free clinical remission at week 12 with upadacitinib vs placebo (22.2% vs 50.7%; P<.0001). The trial also showed a significantly higher rate of early responses and clinical remissions, including steroid-free remissions, with upadacitinib vs placebo. Rates of any AE, severe AEs, and serious AEs were similar between upadacitinib and placebo. However, placebo treatment was associated with a greater likelihood of worsening of CD symptoms (10.2% vs 3.7%). Anemia was more common with upadacitinib therapy vs placebo (6.3% vs 4.5%), as was acne (6.9% vs 0.6%). Herpes zoster was more common with upadacitinib vs placebo (2.9% vs 0%) and can be prevented with vaccination. Patients who achieved a clinical response at week 24 were randomized to U-ENDURE maintenance therapy with upadacitinib vs placebo. This trial achieved both primary endpoints, demonstrating a superior rate of clinical remission and endoscopic response with the JAK inhibitor, administered at 15 mg or 30 mg daily, compared with placebo (P<.0001 for all comparisons vs placebo). Rates of any AE, severe AEs, and serious AEs were numerically higher in the placebo arm vs either upadacitinib arm. Upadacitinib 30 mg daily is the preferred dose; however, the dose can be reduced to 15 mg in patients with anemia, leukopenia, or liver function abnormalities.

Filgotinib has been investigated in patients with UC in the phase 2b/3 SELECTION trial.[9] The higher dose of 200 mg yielded significantly better outcomes vs placebo, demonstrating a superior rate of clinical remission at week 10 of induction therapy in biologic-naive patients (26.1% vs 15.3%; P=.0157) and in biologic-experienced patients (11.5% vs 4.2%; P=.0103). Filgotinib 200 mg also yielded a significantly higher rate of clinical remission at week 58 of maintenance therapy (37.2% vs 11.2%; P<.0001). Filgotinib has an acceptable safety profile. Rates of any AE and serious AEs were similar between the placebo and filgotinib arms.

ABSTRACT SUMMARY Efficacy of Upadacitinib in Patients With One or More Prior Surgical Procedures for Crohn's Disease: A Post Hoc Analysis of U-EXCEL, U-EXCEED, and U-ENDURE Phase 3 Trials

A post hoc analysis of data from the U-EXCEL and U-EXCEED induction trials and the U-ENDURE maintenance trial to assess the efficacy of upadacitinib vs placebo in patients with CD who had undergone at least 1 surgical procedure for their CD (Abstract S7). In the induction cohort, the rate of CDAI clinical remission was similar with upadacitinib (45 mg) vs placebo (P<.05), but upadacitinib was superior to placebo based on the rate of steroid-free/abdominal pain score remission (P<.05), endoscopic response (P=.0001), and endoscopic remission (P<.01). In the maintenance cohort, the higher dose of upadacitinib (30 mg) but not the lower dose (15 mg) yielded a superior rate of CDAI clinical remission (P<.05), steroid-free/abdominal pain score clinical remission (P<.05), and endoscopic remission (P<.01) vs placebo, whereas endoscopic remission rates were similar with either dose of upadacitinib vs placebo. No new safety signals were observed.

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IL-23

IL-23 is a key mediator of inflammation in IBD via the JAK-STAT pathway. The monoclonal antibodies risankizumab, mirikizumab, and guselkumab were developed to target the p19 subunit of IL-23.[1] Risankizumab was evaluated in patients with moderately to severely active CD in the phase 3 ADVANCE and MOTIVATE induction studies followed by the FORTIFY maintenance study.[2,3] The induction studies demonstrated a superior rate of clinical remission and endoscopic response with 12 weeks of risankizumab vs placebo in previously treated patients. Importantly, the trials showed similar rates of clinical remission and endoscopic response with risankizumab in patients who had failed prior conventional therapy and in patients who had failed prior biologic therapy. In the FORTIFY study, patients with a response from the induction studies were randomized to 52 weeks of therapy with risankizumab or matched placebo. The study showed a clear superiority with risankizumab vs placebo. The endoscopic response rate was 47% with risankizumab—more than double the rate achieved with placebo. Furthermore, risankizumab yielded high rates of clinical remission and deep remission compared with placebo. In a subsequent data analysis, risankizumab elicited a numerically higher rate of clinical remission and endoscopic response among patients who had failed therapy with ustekinumab.[4]

The SEQUENCE study compared risankizumab with ustekinumab in patients with moderately to severely active CD who had failed therapy with at least 1 TNF inhibitor.[5] A total of 520 patients were evenly randomized into the 2 arms. The first primary endpoint was demonstration of noninferiority of risankizumab vs ustekinumab based on clinical remission at week 24, assessed by the CD activity index (CDAI) score. The second primary endpoint was the superiority of risankizumab vs ustekinumab based on endoscopic remission at week 48. The trial successfully met its first endpoint, showing a CDAI clinical remission rate of 58.6% with risankizumab vs 39.5% with ustekinumab (P<.01) (Figure 3). The trial also met its secondary endpoint by showing a superior endoscopic

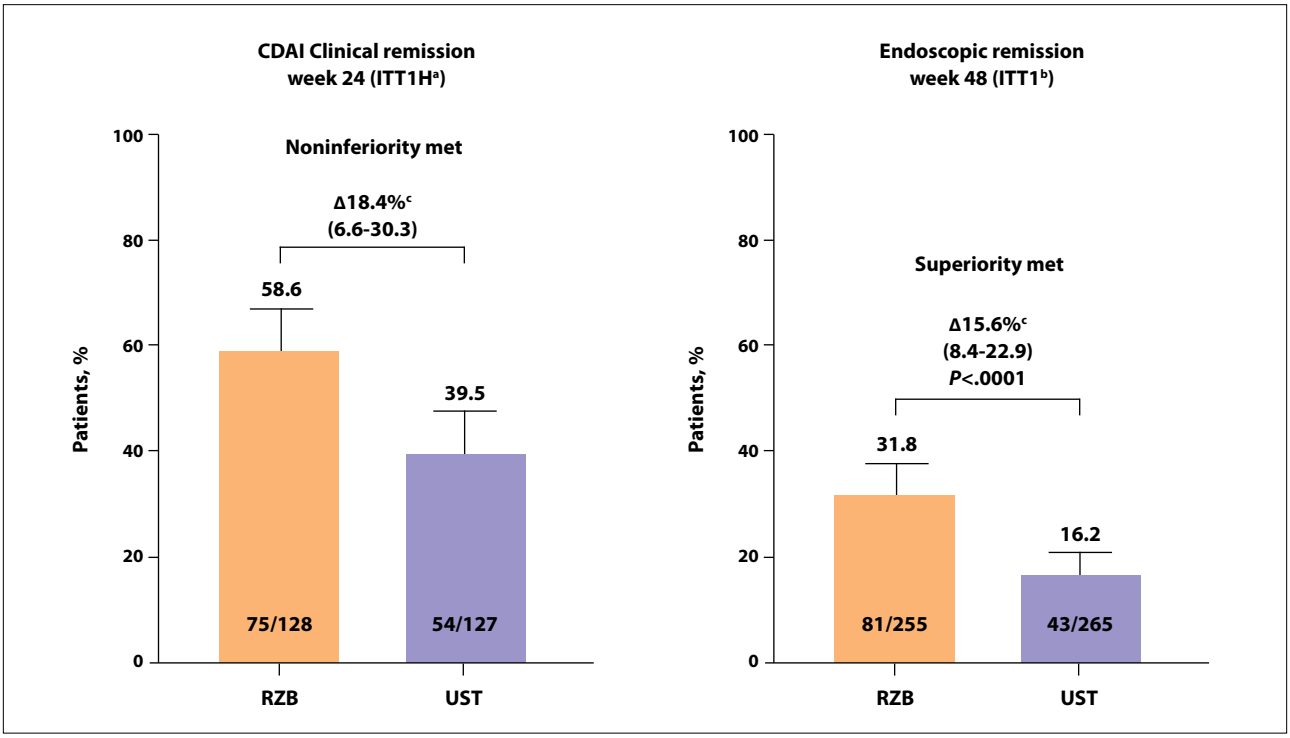

Figure 3. Clinical remission at week 24 (noninferiority) and endoscopic remission at week 48 (superiority) for risankizumab vs ustekinumab in patients with moderately to severely active Crohn's disease from the SEQUENCE study.

[a]ITT1H population includes the first ~50% of ITT1 patients.
[b]ITT1 population includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least 1 dose of study drug.
[c]Differences adjusted by the stratification factors (number of times the subject failed prior anti-TNF therapy [≤1, >1] and steroid use at baseline [yes, no]).
CDAI, Crohn's disease activity index; ITT, intention-to-treat; IV, intravenous; RZB, risankizumab; SC, subcutaneous; TNF, tumor necrosis factor; UST, ustekinumab.
Adapted from Sands et al. IL-23. Presented at the Advances in Inflammatory Bowel Disease Conference; Orlando, Florida; December 14-16, 2023.[1]

remission rate with risankizumab vs ustekinumab (31.8% vs 16.2%; *P*<.0001). Moreover, all secondary endpoints showed that risankizumab was superior to ustekinumab, and publication of these trial results in a peer-reviewed journal is expected. Further, a welcome feature of the IL-23 inhibitors is their record of tolerability. In the SEQUENCE trial, the rate of severe treatment-emergent AEs was 16.0% with risankizumab and 19.2% with ustekinumab, and the rate of serious treatment-emergent AEs was 10.3% vs 17.4%, respectively, with no deaths in either arm.

The phase 2 GALAXI-1 induction study investigated guselkumab, administered at 3 dose levels, vs placebo in 309 patients with moderately to severely active CD.[6] Patients in a fifth arm were treated with ustekinumab. Based on clinical remission, the study showed the superiority of guselkumab vs placebo, with similar rates of remission observed at week 12 regardless of the dose of guselkumab. The anti-p19 antibody yielded a significant improvement in the rate of clinical remission vs placebo in the overall population, in patients who had failed prior biologic therapy, and in patients who had failed prior conventional therapy (*P*<.05).

The phase 2 SERENITY trial evaluated 12 weeks of induction therapy with mirikizumab, administered at 3 dose levels, vs placebo in 291 patients with moderately to severely active CD.[7] A dose response was observed with the 3 dose levels of mirikizumab based on Simple Endoscopic Score–CD (SES-CD) response and SES-CD remission. The rate of SES-CD response was 43.8% with the highest dose of mirikizumab vs 10.9% with placebo (*P*<.001), and the rate of SES-CD remission was 20.3% vs 1.3%, respectively (*P*=.009). The rate of CDAI response was 42.2% with the highest dose of mirikizumab vs 23.4% with placebo (*P*=.034), and the rate of CDAI remission was also significantly higher with mirikizumab vs with placebo (26.6% vs 9.4%; *P*=.023).

Anti-p19 therapy has also proven efficacious in the treatment of patients with UC. In the phase 3 LUCENT-1 trial of patients with moderately to severely active UC, the trial met its primary endpoint, demonstrating a rate of clinical remission of 24.2% with mirikizumab vs 13.3% with placebo at week 12 (*P*=.00006).[8] Mirikizumab was superior to placebo among patients who were biologic-naive (*P*<.001) but did not achieve significance among patients who had failed prior biologic therapy (*P*=.065). However, mirikizumab was superior to placebo as maintenance therapy in both biologic-/tofacitinib-naive patients (51.5% vs 30.7%; *P*<.001) and in patients who had failed biologic therapy or tofacitinib (46.1% vs 15.6%; *P*<.001). Guselkumab and risankizumab have also demonstrated superior efficacy as induction monotherapy vs placebo in patients with UC, based on results from the phase 2b QUASAR study and preliminary results from the phase 3 INSPIRE study.[9,10]

Intriguingly, the proof-of-concept VEGA study investigated induction therapy with golimumab vs guselkumab monotherapy compared with golimumab plus guselkumab in 214 patients with moderately to severely active UC.[11] The combination provides simultaneous targeting of TNF

> IL-23 mediates inflammation in the gut, skin, and entheses, and genome-wide associations identify IL-23 receptor genes as protective in IBD. Inhibition of IL-23 is highly efficacious for patients with CD and UC, and risankizumab was more effective than ustekinumab for biologic-exposed CD. The efficacy and safety profiles of IL-23 blockers make them excellent first-line treatment options for moderate-to-severe IBD.
>
> – Stephen B. Hanauer, MD

ABSTRACT SUMMARY Risankizumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Efficacy and Safety in the Randomized Phase 3 INSPIRE Study

The phase 3 INSPIRE study evaluated induction therapy with risankizumab 1200 mg vs placebo in patients with moderately to severely active UC (Abstract S4). The trial met its primary endpoint, demonstrating a superior rate of clinical remission with risankizumab vs placebo at week 12 (20.3% vs 6.2%; *P*<.00001) in the overall study population. Risankizumab was superior to placebo in all ranked secondary endpoints at week 12, including clinical response based on adapted Mayo score (*P*<.00001), endoscopic remission (*P*<.00001), and other secondary endpoints encompassing endoscopic, histologic-endoscopic, and patient-reported outcomes. Risankizumab treatment was generally well tolerated, with safety outcomes that were generally favorable compared with the placebo group.

and IL-23. Eligible patients had not received prior therapy with an anti-TNF agent and were refractory or intolerant to conventional therapy. Rates of clinical response were generally similar in all 3 arms, with the exception of golimumab monotherapy vs the combination at week 12 (61% vs 83%; *P*=.0032). At week 12, golimumab or guselkumab monotherapy yielded similar rates of clinical remission (24%-25%); however, the rate of clinical remission with the 2 drugs combined was 47%—nearly double that of either monotherapy. At week 38, the rate of clinical remission was 21% with golimumab and 31% with guselkumab, whereas the combination of both drugs yielded a clinical remission rate of 38%.

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Leukocyte Trafficking

Inhibition of leukocyte trafficking to the gut can also reduce the inflammation associated with IBD.[1] Vedolizumab binds to the α4β7 integrin, reducing the recruitment of leukocytes to the intestine. The efficacy of vedolizumab in patients with UC has been demonstrated as both induction therapy and maintenance therapy in the GEMINI 1 trial.[2] The VARSITY study then demonstrated the superiority of vedolizumab vs adalimumab as maintenance therapy in patients with moderately to severely active UC, for both clinical remission (31.3% vs 22.5%; *P*=.0061) and mucosal healing (39.7% vs 27.7%; *P*=.0005) at week 52.

Using data from the GEMINI 2 trial, which evaluated vedolizumab in patients with CD, the Clinical Decision Support Tool (CDST) was developed to predict which patients with CD are more likely to respond to therapy with vedolizumab.[3,4] The findings were validated using data from the VICTORY cohort of patients who were treated with vedolizumab for 26 weeks. Factors associated with a greater likelihood of response to vedolizumab treatment included prior treatment with a TNF inhibitor, prior bowel surgery, prior fistulizing disease, baseline albumin level, and baseline level of CRP. The CDST showed a high sensitivity in predicting clinical remission (92%), corticosteroid-free remission (94%), mucosal healing (98%), clinical remission and mucosal healing (100%), and corticosteroid-free remission with mucosal healing (100%). However, the CDST did not successfully predict outcomes to ustekinumab therapy in patients with refractory CD.[5] A prospective study examining T-cell populations and transcriptional profiles in patients with IBD found that the best predictors of response were use of thiopurines at baseline, the metabolic state of regulatory T cells in the ileum, and the gene signature of regulatory T cells in the peripheral blood.[6]

Gene expression in macrophages, neutrophils, and dendritic cells was examined in biopsy specimens of the ileum and colon prospectively collected from 54 patients with UC or CD.[7]

Inhibition of leukocyte trafficking provides therapeutic targets by inhibiting either egress out of lymph nodes (S1P modulators) or ingress into the gut mucosa from the bloodstream (vedolizumab). S1P modulators are safe, effective, once-daily oral therapies for UC and are being evaluated in CD. Vedolizumab can now be administered intravenously or subcutaneously.

– Stephen B. Hanauer, MD

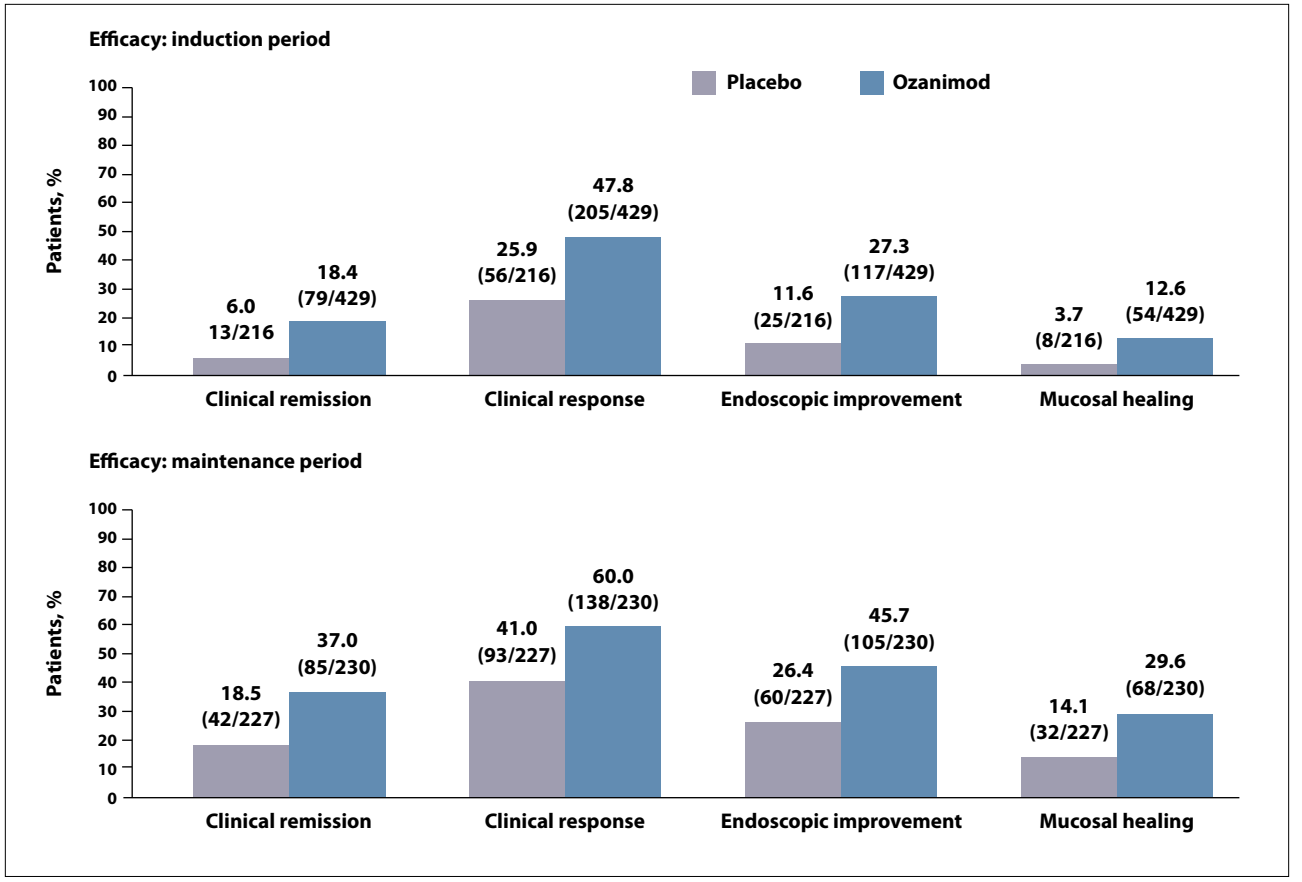

Figure 4. Induction period at week 10 and maintenance period at week 52 of ozanimod vs placebo for patients with moderately to severely active ulcerative colitis from the True North study.

Adapted from Abreu et al. Leukocyte trafficking. Presented at the Advances in Inflammatory Bowel Disease Conference; Orlando, Florida; December 14-16, 2023.[1]

Principal component analysis based on the transcriptional profiles yielded distinct groups that reflected the location of the tissue. The expression of genes associated with inflammation was higher in the colon, and ileum samples showed higher levels of expression of metabolic genes. The study identified specific pathways that were upregulated in the colon vs the ileum. For example, pathways related to innate immune system function were upregulated in the colon, whereas upregulation of metabolic pathways was observed more often in the ileum. The study identified genes and pathways that could be targeted as therapy for IBD.

Ozanimod and etrasimod are sphingosine 1-phosphate (S1P) receptor modulators that have been evaluated in phase 3 trials of patients with UC. The True North study evaluated ozanimod vs placebo in 1012 patients with moderately to severely active UC.[8] At week 10 of induction therapy, the rate of clinical remission was 18.4% with ozanimod vs 6.0% with placebo (P<.001), thus meeting its primary endpoint (Figure 4). Ozanimod therapy also yielded a superior rate of clinical response (47.8% vs 25.9%; P<.001), endoscopic improvement (27.3% vs 11.6%; P<.001), and mucosal healing (12.6% vs 3.7%; P<.001). Patients who exhibited a response in the induction phase of the trial were randomized to ozanimod or placebo for the maintenance phase of the trial. At week 52, the rate of clinical remission was 37.0% with ozanimod vs 18.5% with placebo (P<.001), meeting the primary endpoint for maintenance. All secondary endpoints also showed a superior benefit with ozanimod vs placebo, including clinical response (60.0% vs 41.0%; P<.001), endoscopic improvement (45.7% vs 26.4%; P<.001), and mucosal healing (29.6% vs 14.1%; P<.001). The True North trial included an open-label extension (OLE) study.[9] In an interim analysis of the OLE, a large proportion of patients who demonstrated a response to ozanimod after 1 year of therapy continued to maintain endoscopic improvement, histologic remission, and mucosal healing after an additional 2 years of ozanimod therapy. Safety data from the True North OLE reflected a favorable long-term safety profile with ozanimod in patients with UC.[10]

Etrasimod maintenance therapy was evaluated in patients with moderately to severely active UC in the ELEVATE UC 12 and ELEVATE UC 52

trials.[11] Approximately 38% of patients had previously been exposed to JAK inhibitors or other advanced therapies. The studies met their primary endpoints, demonstrating a superior rate of clinical remission with etrasimod vs placebo after 12 weeks of induction (27.0% vs 7.4%; *P*<.001) and at week 52 of maintenance (32.1% vs 6.7%; *P*<.001). In both the induction and maintenance portions of the trials, the superiority of etrasimod vs placebo was underscored by secondary endpoints, including endoscopic improvement, symptomatic remission, endoscopic improvement combined with histologic remission, and clinical response (*P*<.001).

ABSTRACT SUMMARY Outcomes of Early vs Delayed Advanced Therapy Among Patients With Moderate Ulcerative Colitis in the United States: TARGET-IBD

The rates of endoscopic remission were compared in 179 patients from the TARGET-IBD study based on early vs delayed initiation of advanced therapy for their moderately active UC (Abstract S10). Early treatment was defined as occurring within 2 years of the UC diagnosis. The median time from initiating advanced therapy to endoscopic remission was 10.8 months (IQR, 8.4-19.0) among early initiators vs 15.4 months (IQR, 10.6-21.7) among delayed initiators. In multivariable analysis, the likelihood of endoscopic remission was nearly twice as likely among early initiators as with late initiators (hazard ratio, 2.44; 95% CI, 1.19-4.97). The likelihood of endoscopic remission was further increased among patients who initiated treatment with an advanced therapy within 1 year of diagnosis compared with patients who initiated treatment with an advanced therapy more than 2 years after diagnosis (hazard ratio, 3.44; 95% CI, 1.45-8.15).

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Comparative Effectiveness in Positioning Therapies

With the development of new therapies with new mechanisms of action, it is important to understand how drugs compare in terms of safety, efficacy, and patient preference.[1] Various approaches can be used to compare efficacy and safety outcomes in IBD subpopulations. Randomized controlled trials are the mainstay of comparative research, but they may be limited by several factors, such as a small study population that limits the power to detect a difference between therapies; a follow-up time that is too short; the expense associated with managing large numbers of patients, often at different treatment centers; and the difficulty of recruiting patients with IBD. Observational studies can offer access to a larger patient population, which may be particularly valuable for evaluating rare safety events, but such studies do not contain randomized patient populations and can be limited by confounding variables or selection bias. Alternatively, a network meta-analysis can compare 3 or more treatments in a single analysis. Evidence is gathered from several clinical trials and may have the advantage of including large patient populations. A network meta-analysis relies on the concept of transitivity, such that the only difference between comparisons lies in the treatments. In other words, studies being compared should have a similar patient population, median age, disease duration, concomitant medication use, and other factors.

Only a few randomized controlled trials that directly compare 2 or more advanced therapies have been conducted in patients with IBD. The phase 3 VARSITY trial was the first study to compare 2 biologic therapies in patients with moderately to severely active UC.[2] The study randomized 769 patients for treatment with adalimumab vs vedolizumab. VARSITY showed a significant improvement in clinical remission rate at 52 weeks with

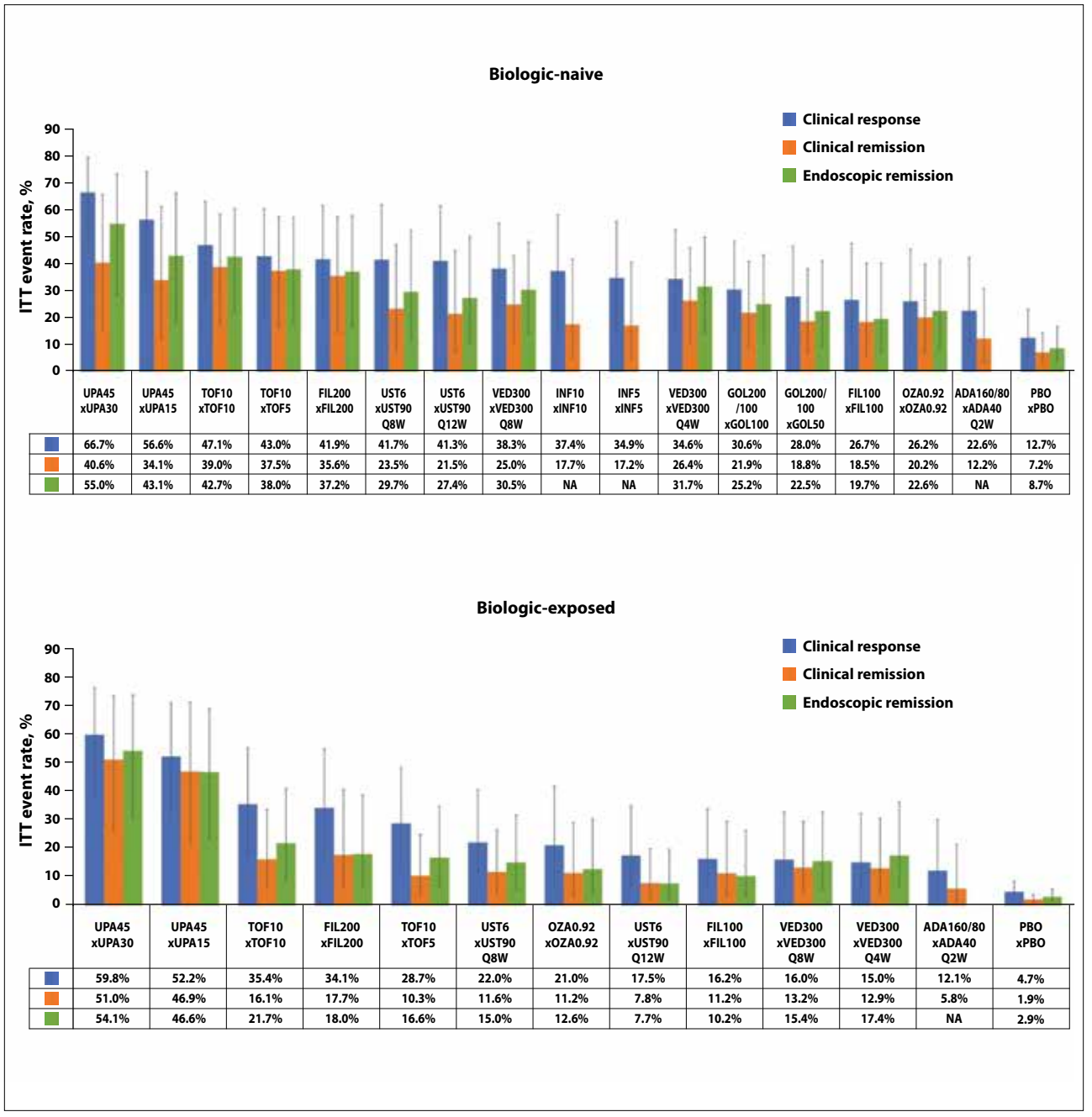

Figure 5. Comparative effectiveness via a Bayesian network meta-analysis for patients with UC.

ADA, adalimumab; FIL, filgotinib; GOL, golimumab; INF, infliximab; ITT, intention-to-treat; NA, not available; OZA, ozanimod; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.
Adapted from Long et al. Comparative effectiveness in positioning therapies. Presented at the Advances in Inflammatory Bowel Disease Conference; Orlando, Florida; December 14-16, 2023.[1]

vedolizumab compared with adalimumab in the overall study population (*P*=.006). However, no difference in therapeutic outcome was observed between groups that were taking steroid medication or immunomodulators. Moreover, no dose escalation was permitted, and drug levels were not assessed; thus, drug levels may not have been optimized.

Recent network meta-analyses have attempted to derive data to help prioritize the positioning of therapies in patients with UC.[3-5] A Bayesian network meta-analysis compared the efficacy and safety of targeted therapies in patients with moderately to severely active UC (Figure 5).[5] Efficacy outcomes were evaluated in the intention-to-treat populations from 23 clinical trials. Although induction

Levels of evidence vary across comparative effectiveness studies in IBD, necessitating an understanding of which study best informs clinical decision-making in each clinical scenario. Although each mechanism of action carries therapy-specific safety concerns, the safest agent is the one that best controls the IBD. Positioning and sequencing decisions should be patient-centric and informed by shared decision-making.

– Stephen B. Hanauer, MD

and maintenance data were initially evaluated separately, they were later combined to provide a single overview of targeted therapy efficacy in UC, and the maintenance data were adjusted with the induction response data. In the biologic-naive population, the analysis showed the highest efficacy with upadacitinib (45 mg for induction and 30 mg for maintenance), based on the rates of clinical response (66.7%), clinical remission (40.6%), and endoscopic improvement (55.0%). Upadacitinib at the same doses for induction and maintenance also showed the best efficacy in the biologic-exposed population, based on the rates of clinical response (59.8%), clinical remission (51.0%), and endoscopic improvement (54.1%). Network meta-analyses have also been performed in CD populations.[6-8]

Optimal therapeutic decision-making includes several considerations beyond drug efficacy. Patient characteristics to consider include age, comorbidities, and personal preferences. Advanced therapy choices in IBD must take individual patient characteristics into consideration, including pregnancy, pharmacokinetics, combination with existing therapies, and perianal disease. Disease characteristics include the extent of disease, complications, early vs late, and prior outcomes from therapy. Safety concerns vary with drug class and sometimes among drugs that have the same target or a similar mechanism of action.[9,10] Common safety concerns associated with drugs for IBD include infection, cancer, and cardiovascular events.

An observational study evaluated the efficacy and safety outcomes in patients with CD initiating a new biologic therapy at 5 health systems in California.[11] Using propensity score matching, the study evaluated the risk of infection, hospitalization, or surgery in patients treated with ustekinumab, vedolizumab, or anti-TNF agents. Ustekinumab was associated with the lowest risk of infection, and no differences between agents emerged for risk of hospitalization or surgery. Vedolizumab and anti-TNF agents were associated with a similar risk of infection. Although safety outcomes should be considered, the best therapy is the one that controls the disease.

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Notes

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