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A SPECIAL MEETING REVIEW EDITION

Highlights From the 2022 Advances in Inflammatory Bowel Diseases Conference

A Review of Selected Presentations on Ulcerative Colitis From the 2022 AIBD Conference

• December 5-7, 2022 • Orlando, Florida

Special Reporting on:

- Four Studies From the True North Trial
- Anti-TNFs
- Knowing JAKs
- Leukocyte Trafficking
- Evolving Interleukins
- Positioning of Therapies—A Practical Approach

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Four Studies From the True North Trial

Ozanimod is an oral sphingosine-1-phosphate (S1P) receptor modulator that is approved in the United States and the European Union for the treatment of moderately to severely active ulcerative colitis (UC).[1,2] The phase 3 True North trial evaluated the safety and efficacy of ozanimod (0.92 mg [equivalent to ozanimod HCl 1 mg], once daily) vs placebo in patients with moderately to severely active UC.[3] The double-blind 52-week trial achieved its primary endpoint, demonstrating a significant improvement in the proportion of patients who achieved clinical remission with ozanimod vs placebo, both after 10 weeks of induction (18.4% vs 6.0%; *P*<.001) and after 42 weeks of maintenance (37.0% vs 18.5%, among patients with a response at week 10; *P*<.001).

The 2022 Advances in Inflammatory Bowel Diseases conference included 4 posters featuring studies from the True North trial.[4-7] A post hoc study evaluated the effect of ozanimod discontinuation on the time to disease relapse.[4] The study included patients who received ozanimod during induction and were then randomized to maintenance therapy through week 52 with either ozanimod (n=230) or placebo (n=227). Patients who received continuous ozanimod therapy during induction and maintenance were significantly less likely to relapse than patients who received ozanimod induction followed by placebo (nonrelapse rate at week 42 of maintenance, 86.1% with ozanimod vs 62.6% with placebo; *P*<.0001). Subgroup analysis further underscored the superior time to disease relapse achieved with ozanimod vs placebo, both in patients with a full clinical remission at week 10 (nonrelapse rate, 90.9% vs 67.9%; *P*<.001) and in patients with a clinical response without full clinical remission at week 10 (nonrelapse rate, 83.4% vs 59.7%; *P*<.0001).

A 2-year interim analysis assessed the safety and efficacy of ozanimod in True North participants who received 98 weeks of continuous ozanimod therapy.[5] The analysis included patients who demonstrated a clinical response after 52 weeks of continuous ozanimod therapy and were entered into the open-label extension (OLE) study. The results at week 46 of the OLE study showed numerically superior outcomes in patients in clinical remission vs patients with clinical response only at week 52 in terms of clinical remission (73% vs 55%), clinical response (98% vs 95%), endoscopic improvement (82% vs 58%), and corticosteroid-free remission (71% vs 50%). In the overall population of patients with a clinical response who received continuous ozanimod therapy, the mean partial Mayo score stabilized by week 18 (mean Mayo score, 1.3 points) and was maintained through OLE week 46 (mean, 0.9 points). No new safety concerns emerged from the extended observations.

A post hoc analysis evaluated the efficacy of ozanimod among True North patients who were previously exposed to vedolizumab.[6,8] The efficacy of ozanimod was evaluated at the end of induction (week 10) and maintenance (week 52). The results suggested that prior exposure to vedolizumab did not affect ozanimod efficacy. At week 10, ozanimod was superior to placebo for all endpoints examined, including symptomatic remission (15.9% vs 8.6%), clinical remission (4.8% vs 2.9%), clinical response (28.6% vs 20.0%), and endoscopic improvement (12.7% vs 5.7%). At week 52, ozanimod was again superior based on all endpoints examined, including symptomatic remission (54.5% vs 13.6%), clinical remission (39.4% vs 4.5%), clinical response (57.6% vs 22.7%), and endoscopic improvement (39.4% vs 9.1%).

A post hoc analysis of True North patient outcomes based on age group demonstrated similar efficacy with ozanimod in patients aged less than 60 years vs patients aged 60 years or greater, based on clinical remission, clinical response, endoscopic improvement, or mucosal healing at week 52 of the study.[7] Ozanimod exposure in elderly patients was not associated with new safety concerns, nor were rates of adverse events (AEs) higher in the cohort of older patients than in the cohort of younger patients.

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Anti-TNFs

The oldest biologics for IBD, anti-TNF therapies, retain a pivotal role in patient care. They remain the gold standard for specific clinical scenarios: acute severe UC, fistulizing CD, postoperative CD, and extraintestinal manifestations. Several lessons learned include that treating early is better; combination therapy is beneficial; antibodies are "bad" and adequate drug levels are "good"; we treat beyond symptoms; and anti-TNFs are relatively safe.
– Gary R. Lichtenstein, MD

Dr Remo Panaccione discussed anti–tumor necrosis factor (TNF) agents.[1] Agents that inhibit TNF activity remain the gold standard for certain populations of patients with inflammatory bowel disease (IBD), particularly patients with acute severe UC, fistulizing Crohn's disease (CD), postoperative CD, or extraintestinal manifestations (Table). In 2022, infliximab and other anti-TNF agents continue to be the standard of care for acute severe UC. However, the optimal dose remains under discussion.[2,3] The recommended dose is 5 mg/kg, and some meta-analyses have found that a dose of 10 mg/kg is not better than 5 mg/kg. Nonetheless, the higher dose should be considered in patients with a high body mass index, low level of albumin, high level of C-reactive protein, extensive disease, a Mayo score of 3, or when outside the 7- to 10-day window. A study that investigated infliximab for the prevention of recurrence in patients with CD following ileocolonic resection failed to reach its primary endpoint of clinical recurrence (P=.097).[4] However, the study demonstrated a clear improvement in terms of endoscopic recurrence favoring infliximab vs placebo (P<.001). For patients with extraintestinal manifestations, first-line anti-TNF therapy is a reasonable choice, particularly for patients with severe conditions such as pyoderma gangrenosum or uveitis.

By optimizing strategies for treating patients with anti-TNF agents, patients are more likely to experience mucosal healing and deep remission, as well as superior long-term outcomes. Despite the lack of prospective head-to-head studies, retrospective analyses suggest that superior outcomes can be achieved by administering earlier treatment with biologic therapy. As shown by the phase 3 CALM study of patients with CD, treatment can also be optimized by using biomarkers such as levels of C-reactive protein and fecal calprotectin to guide intervention.[5] Although the role of therapeutic drug monitoring (TDM) has been evaluated in several studies, its role in optimizing therapy remains unclear. A recent meta-analysis found no significant difference with proactive TDM vs conventional dose management in terms of either the primary outcome of clinical remission (relative risk [RR], 0.96) or levels of antidrug antibodies (RR, 0.84), but dose escalation was increased with TDM (RR, 1.56).[6] Patients may benefit from anti-TNF treatment that is guided by reactive TDM, whereby patient drug levels are maintained based on monitoring of drug levels during the course of therapy.

Table. Anti-TNFs Still Play a Major Role in IBD Management After Two Decades

Efficacy and Safety	Special Populations
• Highly effective • Both CD and UC • Unparalleled physician and patient experience • Can be given as SC or IV • Act rapidly • Dosing flexibility • Known and established safety profile	• Pediatrics √ • Elderly √ • Pregnancy √ • Postoperative √ • Fistulizing disease √ • Acute severe UC √ • EIMs √

CD, Crohn's disease; EIM, extraintestinal manifestation; IBD, inflammatory bowel disease; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor; UC, ulcerative colitis. Adapted from Panaccione R. Anti-TNFs. Presented at the Advances in Inflammatory Bowel Diseases Conference; Orlando, Florida; December 5-7, 2022.[1]

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Knowing JAKs

The use of JAK inhibitors for IBD patient management has favorable factors. They have a favorable route of administration orally, short plasma half-life, lack of immunogenicity, and predictable pharmacokinetics, and are fast acting for acute severe UC (within 1 or 3 days [upadacitinib and tofacitinib, respectively]). We currently have 2 approved JAK inhibitors, tofacitinib and upadacitinib, for treatment of UC patients.
– Gary R. Lichtenstein, MD

Dr Bincy P. Abraham reviewed Janus kinase (JAK) inhibitors.[1] The JAK family is comprised of several nonreceptor tyrosine kinases, including JAK1, JAK2, JAK3, and tyrosine kinase 2, and these kinases play an important role in IBD. The JAK proteins are bound to receptors that can be activated by cytokines such as interferon-α, interferon-γ, and various interleukins (ILs). After cytokine binding, the receptor activates the JAK protein, which mediates signaling through the signal transducer and activator of transcription (STAT) pathway. Inhibition of JAK activation prevents downstream phosphorylation of STAT proteins, thus preventing the production of inflammatory cytokines.

Tofacitinib and upadacitinib are JAK inhibitors currently approved for the treatment of adults with moderately to severely active UC.[2,3] The phase 3 OCTAVE studies evaluated tofacitinib vs placebo in patients with moderately to severely active UC.[4] Remission was defined by a total Mayo score of 2 or lower, with no individual subscore greater than 1, and a Mayo rectal bleeding score of 0. After 8 weeks of therapy with tofacitinib (10 mg, twice daily) vs placebo, tofacitinib yielded superior rates of remission in both OCTAVE Induction 1 (18% vs 8%) and OCTAVE Induction 2 (17% vs 4%). In the OCTAVE Sustain study, placebo yielded a remission rate of 11%, and remission rates were 34% with tofacitinib (5 mg, twice daily) and 41% with tofacitinib (10 mg, twice daily). After 8 weeks of induction or 42 weeks of maintenance with tofacitinib, patients who had previously been exposed to anti-TNF therapy had lower rates of remission and lower rates of mucosal improvement by endoscopy than anti-TNF–naive patients. Tofacitinib induced rapid responses in this patient setting.

A double-blind, multicenter, phase 2b study evaluated upadacitinib vs placebo as induction therapy in patients with moderately to severely active UC.[5] Upadacitinib was administered once daily in doses ranging from 7.5 mg to 45 mg. After 8 weeks of study therapy, the rate of clinical remission was 0% with placebo vs 9% (P=.052) with the lowest dose of upadacitinib and 20% (P=.002) with the highest dose of upadacitinib (Figure 1). The rate of clinical response was 13% with placebo and ranged from 30% to 50% with upadacitinib. The rate of endoscopic improvement at

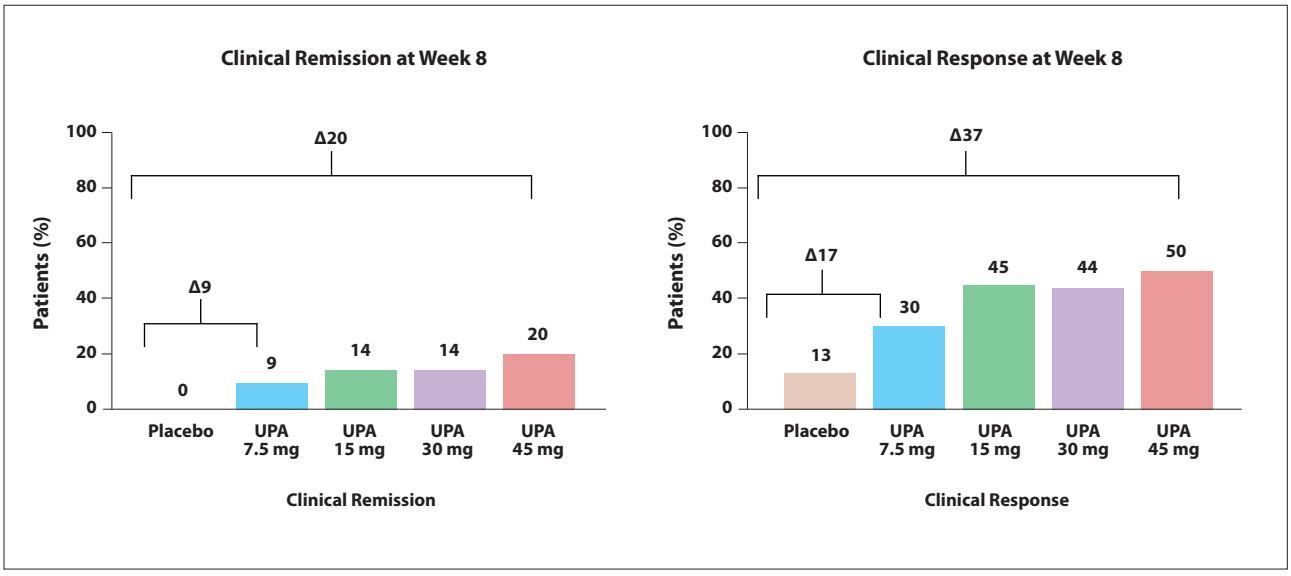

Figure 1. Upadacitinib (UPA) in ulcerative colitis. Adapted from Sandborn WJ et al. *Gastroenterology*. 2020;158(8):2139-2149.e14.[5]

week 8 was also significantly higher with all dose levels of upadacitinib than with placebo (P<.05). In the phase 3 U-ACHIEVE and U-ACCOMPLISH studies, upadacitinib also showed superior rates of clinical remission compared with placebo at week 8 and week 52 in patients with moderately to severely active UC.[6]

A postmarketing safety study of tofacitinib in patients at least 50 years of age with rheumatoid arthritis and at least 1 cardiovascular risk factor showed higher rates of cardiovascular events and malignancies with tofacitinib vs adalimumab or etanercept.[7] A systematic review and meta-analysis evaluated the rates of AEs in patients with IBD or other inflammatory disorders who were treated with tofacitinib, upadacitinib, or the JAK inhibitors filgotinib and baricitinib.[8] The analysis showed a significant increase in the risk of herpes zoster infection among patients who received treatment with a JAK inhibitor (RR, 1.57). Prior to initiating JAK inhibitor therapy, vaccination against herpes zoster is recommended. Although dose reductions may reduce the likelihood of an AE, this goal must be balanced with achieving the desired efficacy.

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Leukocyte Trafficking

Dr Uma Mahadevan explored leukocyte trafficking, which, as mediated by proinflammatory cytokines, is a key contributor to acute and chronic inflammation in IBD.[1] The integrins and S1P receptors are involved in leukocyte trafficking, and drugs against these targets have proven successful in inhibiting the inflammatory state in patients with IBD. Other potential targets related to leukocyte trafficking include endothelial cellular adhesion molecules and chemokine receptors.

Vedolizumab attacks integrin α4β7 and is approved for the treatment of adult patients with moderately to severely active UC.[2] American Gastroenterological Association guidelines provide detailed recommendations regarding how to choose vedolizumab for patients with UC, based on prior exposure and prior response to biologic agents.[3] The double-blind, multicenter, phase 4 EARNEST trial recently showed that vedolizumab was more effective than placebo across multiple endpoints in the treatment of chronic pouchitis in patients with UC.[4] Further, an observational cohort study of 135 patients with UC or CD showed that a switch from intravenous to subcutaneous vedolizumab administration was effective and safe.[5]

Ozanimod is an oral modulator of $S1P_1$ and $S1P_5$.[6] Like vedolizumab, ozanimod may be positioned as a first-line biologic agent, such as in patients with moderately to severely active UC for whom 5-aminosalicylic acid therapy has failed. In the phase 3 True North trial, ozanimod was superior to placebo in patients with moderately to severely active UC at week 10 of induction, based on clinical remission (18.4% vs 6.0%; P<.0001), clinical response (47.8% vs 25.9%; P<.0001), endoscopic improvement (27.3% vs 11.6%; P<.0001), and mucosal healing (12.6% vs 3.7%; P<.001) (Figure 2).[7] In a post hoc analysis of data from the randomized induction phase of the True North study, the ozanimod onset of action was observed as early as 2 weeks after the initial dose, based on rectal bleeding and stool frequency scores.[8] Symptom improvement was accompanied by a reduction in levels of fecal calprotectin and C-reactive protein. Early evidence of efficacy is more likely in patients without prior

Leukocyte trafficking inhibition is an effective mechanism for treatment of IBD patients. Currently, 3 approved agents inhibit leukocyte trafficking for IBD therapy: vedolizumab (α4ß7), natalizumab (α4ß7 and α4ß1), and ozanimod (S1P receptor modulator). Future novel agents in this class are in development.
– Gary R. Lichtenstein, MD

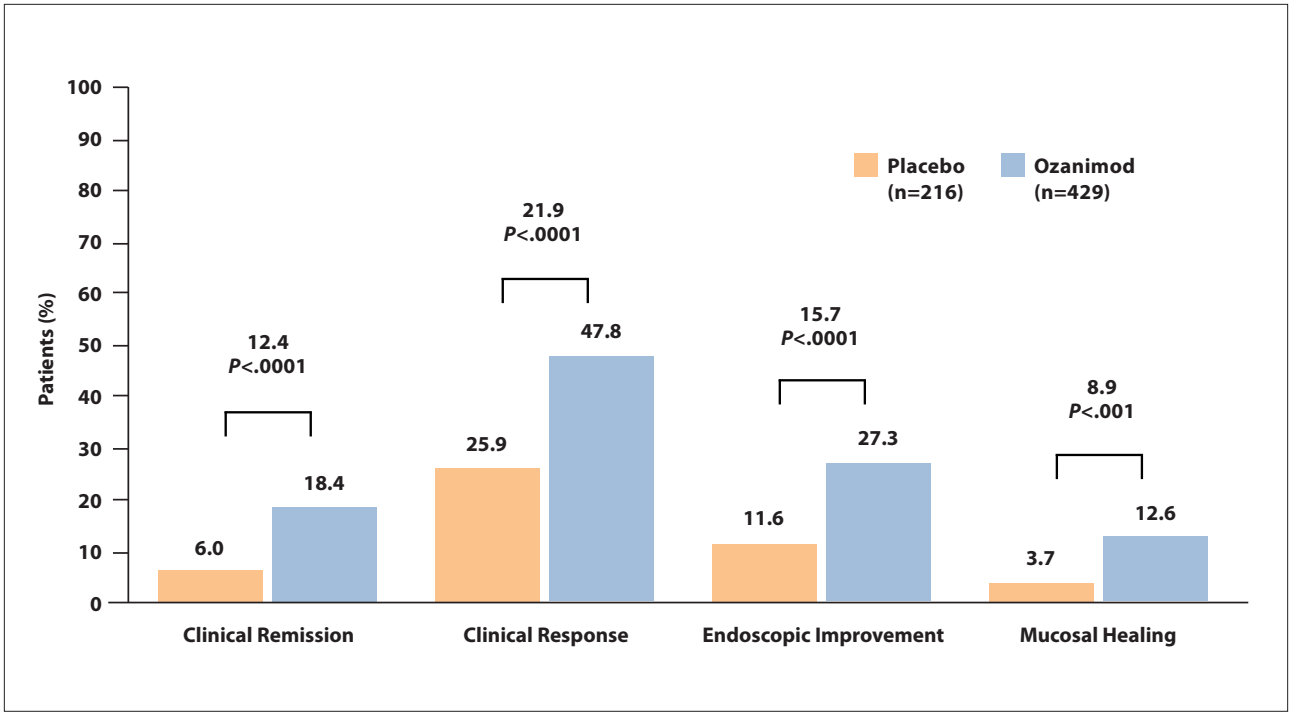

Figure 2. Efficacy of ozanimod in moderate-to-severe ulcerative colitis at week 10 (induction, intent-to-treat). Clinical remission: 3-component Mayo score results: rectal bleeding score (RBS) = 0, stool frequency score ≤1 and ≥1-point reduction from baseline, and mucosal endoscopy score (MES) ≤1 without friability. Clinical response: reduction in 3-component Mayo score of ≥2 points and ≥35%, and reduction in RBS of ≥1 point or absolute RBS of ≤1 point. Endoscopic improvement: MES ≤1 without friability. Mucosal healing: endoscopic improvement plus histologic remission (Geboes <2.0; no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue) in the same patient. Data based on all randomized patients who received ≥1 dose of study treatment (intent-to-treat population). Missing data handled using nonresponder imputation. *P* values refer to odds ratios (not shown) based on 2-sided Cochran-Mantel-Haenszel test. Adapted from Sandborn WJ et al. *N Engl J Med*. 2021;385(14):1280-1291.[7]

exposure to biologic therapies. However, patients who do not experience an early response, including those with prior anti-TNF exposure, may improve with extended ozanimod therapy. Similarly, long-term therapy can yield sustained clinical responses. No new safety signals arose in patients who received ozanimod therapy for as long as 94 weeks in the True North OLE.

A subset of patients in the True North trial received 10 weeks of ozanimod as induction therapy and were then randomized to placebo for the 42-week maintenance period. Patients who relapsed while on placebo were allowed to receive ozanimod as part of the OLE study. In a post hoc study of these 77 patients, more than one-half (58.4%) experienced a symptomatic clinical response at 10 weeks after reintroduction of ozanimod.[9] The rate of symptomatic clinical response at week 10 was 52.6% in patients without prior biologic therapy and 65.8% in patients with prior biologic exposure.

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Evolving Interleukins

Dr Bruce E. Sands discussed IL-23, a proinflammatory cytokine that regulates T helper 17 cell activity and is a promising target for treating IBD.[1] In both CD and UC, upregulation of IL-23 can lead to a chronic inflammatory state that is mediated by T helper 17 cells. Both IL-12 and IL-23 mediate their signals via the JAK-STAT pathway. In addition to being a key mediator of inflammation in IBD, IL-23 mediates molecular resistance to anti-TNF therapy in patients with CD.

Several antibodies have been developed that target the p19 subunit of IL-23, including risankizumab, brazikumab, mirikizumab, and guselkumab. Of these, risankizumab is the most advanced, with results available from the phase 3 ADVANCE, MOTIVATE, and FORTIFY studies.[2,3] The studies enrolled patients with moderately to severely active CD and inadequate response or intolerance to conventional and/or biologic therapy. The ADVANCE and MOTIVATE studies evaluated risankizumab at a dose of 1200 mg or 600 mg every 4 weeks vs placebo for a total of 3 cycles. Patients with a clinical response were randomized again to receive risankizumab at a dose of 360 mg or 180 mg

> Biologics are effective for treatment of IBD patients; however, up to 30% of patients do not respond (primary nonresponders) and another 50% of patients lose their response over time (secondary loss of response). TDM entails measurement of drug levels and antibodies to the biologic agents at various times and attempts to correlate levels and antibodies with patient outcomes. Current guidelines and consensus statements vary with regard to advocating for or against the use of TDM for patient care.
>
> – Gary R. Lichtenstein, MD

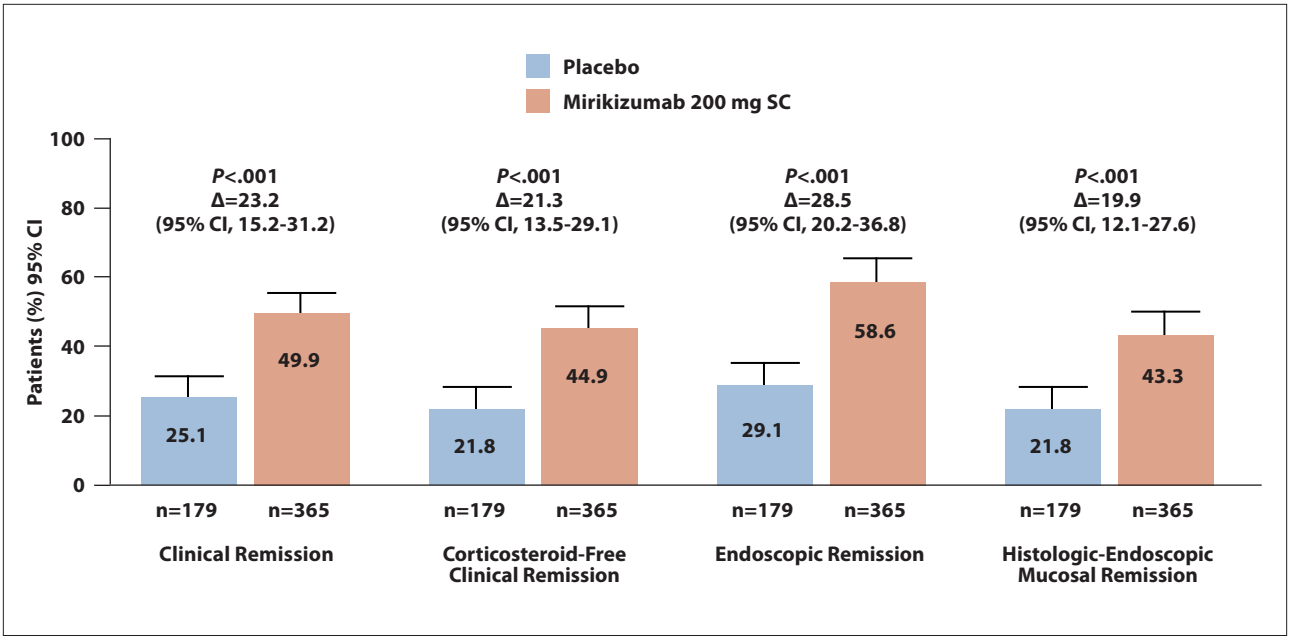

Figure 3. Outcomes after 52 weeks of treatment (week 40 of maintenance) in the LUCENT-2 study. Clinical remission: SF = 0, or SF = 1 with a ≥1-point decrease from baseline; RB = 0; ES = 0 or 1 (excluding friability). Corticosteroid-free clinical remission: clinical remission at week 40, and symptomatic remission (SF = 0, or SF = 1 with a ≥1-point decrease from induction baseline; and RB = 0) at week 28, and no corticosteroid use for ≥12 weeks prior to week 40. Endoscopic remission: ES = 0 or 1 (excluding friability). Histologic-endoscopic mucosal remission: histologic remission with resolution of mucosal neutrophils, determined by Geboes ≤2B.0 score. The Cochran-Mantel-Haenszel test was used to compare the treatment groups. Δ indicates common risk difference vs placebo. ES, endoscopic subscore; RB, rectal bleeding; SC, subcutaneous; SF, stool frequency. Adapted from Dubinsky MC et al. DDW abstract 867e. *Gastroenterology*. 2022;162(7)(suppl):S1393-S1394.[5]

every 8 weeks vs placebo for a 42-week maintenance period. At week 12, the rate of clinical remission was 24.6% with placebo vs 45.2% with risankizumab (Δ, 20.6%; *P*<.0001). The MOTIVATE study enrolled patients who were inadequate responders to prior therapy, and in these patients, the week 12 rate of clinical remission was 19.8% with placebo vs 41.9% with risankizumab (Δ, 22.1%; *P*<.0001). In the FORTIFY trial, the rate of clinical remission at 1 year was 40.9% among patients who were randomized to placebo vs 52.2% among patients who continued to receive risankizumab (Δ, 11.3%; *P*=.005). The ADVANCE, MOTIVATE, and FORTIFY trials also showed superior outcomes with risankizumab compared with placebo based on endoscopic response, endoscopic remission, and ulcer-free endoscopy. The FORTIFY trial showed a superior rate of deep remission with risankizumab vs placebo at 52 weeks. In the subgroup of patients with prior failure to ustekinumab treatment, risankizumab was also superior to placebo in terms of clinical remission and endoscopic response.

Encouraging results have emerged from the phase 3 LUCENT-1 study of mirikizumab in 1162 previously treated patients with moderately to severely active UC.[4] The trial met its primary endpoint, demonstrating a superior rate of clinical remission at week 12 with mirikizumab vs placebo (13.3% vs 24.2%; *P*=.00006). Superior rates of clinical remission were also observed in patients who were biologic-naive (15.8% vs 30.9%; *P*<.001) as well as in patients with prior failure to biologic therapy, although the difference was not significant (8.5% vs 15.2%; *P*=.065). The rate of clinical response was superior with mirikizumab vs placebo in the overall study population (*P*<.00001), in biologic-naive patients (*P*<.001), and in patients who had failed prior biologic therapy (*P*<.001). Findings from the LUCENT-2 study are shown in Figure 3.[5]

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Positioning of Therapies—A Practical Approach

Dr Miguel Regueiro discussed the positioning of therapies for IBD.[1] Physicians are commonly challenged in determining which of the many available treatments is the best for first-line intervention and how to sequence multiple therapies in individual patients with IBD. Choosing the correct therapy for induction is a key goal, and in patients with moderately to severely active IBD, advanced therapies, including biologics and small molecules, can be a reasonable choice for first-line therapy in order to achieve remission as quickly as possible and avoid further tissue damage. Approximately 40% of patients with UC have a low risk of colectomy, and these patients can be treated with 5-aminosalicylic acids plus limited steroids. The remaining 60% of patients have a high risk of colectomy and can benefit from the early application of advanced therapy to limit tissue damage.

In an effort to determine the relative efficacy of various biologic and small molecule therapies in patients who have active UC, a systematic review and network meta-analysis was conducted.[2] The study included data from 28 trials and 12,504 patients. Using a random effects model, the study found that upadacitinib and infliximab were most effective, based

> The treatment strategies for the management of patients with UC and CD are driven by the patient's potential for development of complicated disease. In UC and CD patients, there is only 1 head-to-head trial for each disease, thus making us rely on network meta-analysis. This is not perfect, but it remains the best we have currently. The SEAVUE trial (CD) and the VARSITY trial (UC) represent landmark head-to-head trials in therapeutic efficacy. Future head-to-head trials are forthcoming.
> – Gary R. Lichtenstein, MD

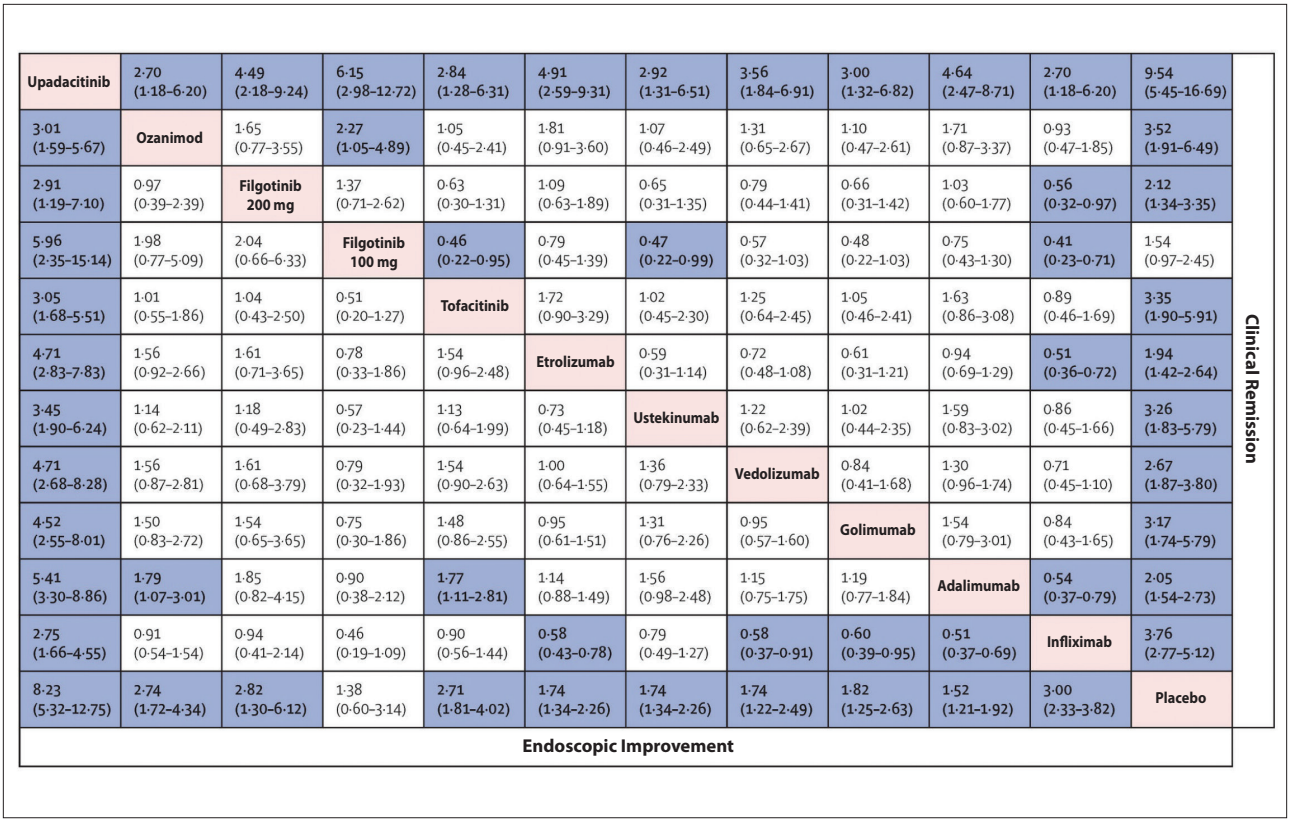

Figure 4. Network meta-analysis: ulcerative colitis. Adapted from Lasa JS et al. *Lancet Gastroenterol Hepatol.* 2022;7(2):161-170.[3]

on rates of clinical remission. In patients with prior exposure to anti-TNF therapy, the greatest efficacy was observed with upadacitinib and ustekinumab. A separate systematic review and network meta-analysis also evaluated the efficacy and safety of biologics and small molecule drugs in patients with moderately to severely active UC.[3] The analysis included 23 studies of induction therapy, representing 10,061 patients with UC. Based on the ability to induce a clinical remission, upadacitinib was most effective (Figure 4). Vedolizumab ranked lowest in terms of AEs and serious AEs.

Choosing the best treatment depends on the disease characteristics of each patient. Although biologics and small molecule drugs are often the best choice for induction, some therapies, such as JAK inhibitors, are approved for use only after treatment with a TNF inhibitor. Dr Regueiro discussed how he approaches treatment choice for patients with IBD. For patients with severe UC, first-line therapy may consist of infliximab plus azathioprine. For UC patients with moderately severe disease, patients aged 60 years or greater or with comorbid cancer or infection may be treated with vedolizumab, ustekinumab, or ozanimod (in the absence of cardiac disease), whereas younger patients without comorbidities may receive first-line ozanimod, vedolizumab, ustekinumab, or a TNF inhibitor. For most patients with CD, first-line vedolizumab, ustekinumab, or risankizumab may be chosen as first-line therapy.

References

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3. Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. 2022;7(2):161-170.

Notes


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