GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

January 2025 Volume 21, Issue 1, Supplement 1

A SPECIAL MEETING REVIEW EDITION

Highlights From the 2024 Advances in Inflammatory Bowel Disease Conference

A Review of Selected Presentations on Inflammatory Bowel Disease From the 2024 AIBD Conference

December 9-11, 2024 • Orlando, Florida

Special Reporting on:

- Management of Uncomplicated Luminal Crohn's Disease
- Management of Complicated Crohn's Disease
- Progression of Disease When Mesalamine Fails
- When the First Advanced Therapy Fails

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Management of Uncomplicated Luminal Crohn's Disease

Dr Uma Mahadevan, from the UCSF Colitis and Crohn's Disease Center, first presented studies focused on advances in the management of patients with mild Crohn's disease (CD) and then followed with a summary of studies that evaluated the role of biologics in the management of patients with moderate-to-severe CD.[1]

Management of Mild Uncomplicated CD

Management approaches for patients with mild CD include budesonide induction therapy for 8 to 12 weeks with tapering, or alternatively a tapering course of prednisone, or sulfasalazine (for colonic cases of CD).[2] Patient monitoring should include objective laboratory and biomarker assessments during periods of active CD activity; while in remission, patients can be monitored with annual endoscopy to assess mucosal healing. Patients who respond to induction therapy can be maintained with supportive care, antidiarrheal agents, and dietary modifications. In patients who do not respond to corticosteroid induction therapy, or who quickly relapse after corticosteroid tapering, disease activity level should be reassessed and CD diagnosis confirmed prior to discussing moving to biologic therapies if objective evidence of CD activity persists.

One important recent advancement in the management of mild CD is an increasing understanding that 5-aminosalicylates (5-ASA) are not beneficial as maintenance therapy for patients with mild CD. This was demonstrated in an Israeli nationwide study using the epi-IIRN cohort, which included all patients with CD who were diagnosed in Israel between 2005 and 2020.[3] Included were 8610 newly diagnosed patients who had received either 5-ASA as maintenance therapy (n=3027) or no maintenance therapy (n=5583). Propensity score matching, used to compare outcomes in the 2 groups, revealed comparable findings across multiple outcomes, including time to biologic used (P=.24), time to corticosteroid dependency (P=.91), time to hospitalization (P=.5), and time to CD-related surgery (P=.096). Although rates of both acute kidney injury (5.2% vs 3.3%; P<.001) and pancreatitis (2.4% vs 1.8%; P=.03) were higher in the 5-ASA maintenance group compared with the no-treatment maintenance group, the rates of adverse events were similar after propensity score matching.

For patients with mild CD who do not wish to receive pharmacologic therapy despite being symptomatic, particularly patients with ileal disease, a surgical intervention may be appropriate. A recent study investigated the use of ileocecal resection, normally reserved for patients with complicated CD or in cases of treatment failure, as a surgical treatment for patients with uncomplicated ileocecal CD.[4] This study used cross-linked nationwide registers to identify 1279 patients diagnosed with ileal or ileocecal CD between 2003 and 2018 and treated with either ileocecal resection (45.4%) or anti–tumor necrosis factor α (TNFα) agents (54.6%) within their first year of diagnosis. The risk of the primary outcome (a composite of 1 or more of the following: CD-related hospitalization, systemic corticosteroid exposure, CD-related surgery, and perianal CD) was 33% lower among patients who received ileocecal resection as intervention compared with patients who received an anti-TNFα

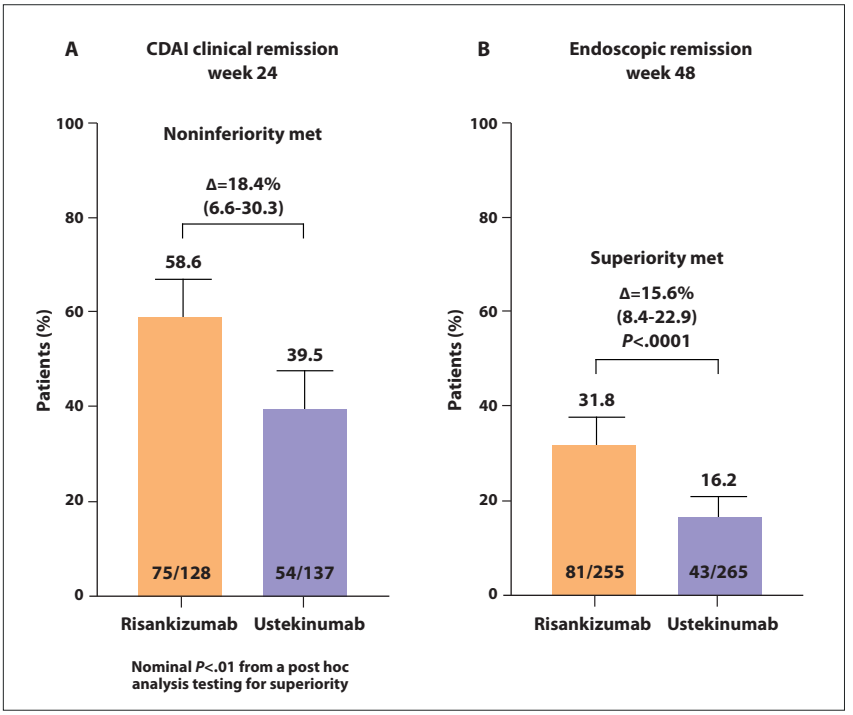

Figure 1. SEQUENCE primary endpoints: **(A)** clinical remission at week 24 (noninferiority) and **(B)** endoscopic remission at week 48 (superiority).[8] CDAI clinical remission: CDAI <150. Endoscopic remission: SES-CD ≤4 and at least a 2-point reduction vs baseline and no subscore >1 in any individual variable, as scored by a central reviewer. CDAI, Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease. Adapted from Mahadevan U. Management of uncomplicated luminal Crohn's disease. Presented at: 2024 Advances in Inflammatory Bowel Disease Conference; December 9-11, 2024; Orlando, Florida.[1]

agent (adjusted hazard ratio [HR], 0.67; 95% CI, 0.54-0.83). Further, ileocecal resection was associated with a reduced risk of systemic corticosteroid exposure and CD-related surgery. Approximately one-half of the patients (49.7%) in the ileocecal resection group were receiving no therapy after 5 years.

Management of Moderate-to-Severe Luminal CD

The PROFILE study was a multicenter, open-label, randomized controlled trial that used biomarker stratification to assess outcomes in patients with newly diagnosed active CD.[5] Patients were stratified by a previously validated biomarker to IBDhi or IBDlo cohorts and then were randomized to top-down (early combined immunosuppression with infliximab and an immunomodulator) or conventional accelerated step-up treatment. A total of 193 patients were randomized to each group after a median of 12 days from diagnosis (range, 0-191). For the primary endpoint, which was sustained corticosteroid-free and surgery-free remission to week 48, there was no biomarker-treatment interaction effect (absolute difference of 1%; 95% CI, -15 to 15; *P*=.944). However, although the biomarker did not show clinical utility for treatment decisions, the primary endpoint showed a clear benefit with the very early use of combination treatment with infliximab plus thiopurine compared with conventional accelerated step-up therapy (79% vs 15%, absolute difference of 64%; 95% CI, 57-72; *P*<.0001). There was also a lower incidence of adverse events (including CD flares) and fewer complications requiring abdominal surgery (1 vs 10). These data confirmed that patients with newly diagnosed CD benefit from proceeding straight to effective therapy (eg, infliximab plus an immunomodulator) instead of first moving through conventional treatment with corticosteroids and mesalamine.

> Meeting a patient with uncomplicated CD presents an opportunity to effectively treat the disease before irreversible complications develop. Although there are some patients at low risk for progression, most patients with CD will develop complications over time without effective therapy. Therapy choice should be made based on whether the patient is naive to biologics and if they have any coexisting extraintestinal manifestations to guide use of a specific drug class.
>
> — Corey A. Siegel, MD, MS

LIBERTY-CD was a randomized, double-blind, phase 3 trial in patients with moderate-to-severe CD that demonstrated the superiority of subcutaneous infliximab (CT-P13 SC) vs placebo when administered as maintenance therapy after intravenous infliximab induction therapy.[6] Patients already receiving intravenous infliximab as a maintenance therapy could switch to subcutaneous infliximab at any point, but the dosing was only comparable for patients receiving the recommended dosage every 8 weeks. A post hoc analysis was conducted to evaluate the impact of the patient's body mass index on the efficacy of subcutaneous infliximab.[7] Among the 231 patients included in this analysis, trough infliximab levels decreased as body mass index increased; this change was accompanied by a numerical trend for lower rates of clinical remission and endoscopic response.

The SEQUENCE phase 3b study was a head-to-head comparison of the anti-p40 (interleukin [IL]-12/23) agent ustekinumab vs the anti-p19 (IL-23) agent risankizumab.[8] This multicenter, open-label, randomized controlled trial enrolled patients with moderate-to-severe CD with an inadequate response to or unacceptable side effects with anti-TNFα therapy; these patients were randomized to receive risankizumab or ustekinumab at standard dosages for 48 weeks. The study's 2 primary endpoints, tested sequentially, were clinical remission at week 24 (analyzed for noninferiority in the first 50% of patients to complete the week 24 visit) and endoscopic remission at week 48 (analyzed for superiority in 100% of the patients). Both primary endpoints were met. Risankizumab was noninferior to ustekinumab in week 24 clinical remission (58.6% vs 39.5%; adjusted difference, 18.4%; 95% CI, 6.6-30.3) and superior to ustekinumab in week 48 endoscopic remission (31.8% vs 16.2%; adjusted difference, 15.6%; 95% CI, 8.4-22.9; *P*<.0001) (Figure 1). The incidence of adverse events was similar with the 2 treatments.

Two phase 3 induction trials, U-EXCEL (n=526) and U-EXCEED (n=495), evaluated the efficacy of upadacitinib in patients with moderate-to-severe CD.[9] Patients were randomized in a 2-to-1 fashion to induction therapy with upadacitinib (45 mg once daily) or placebo for 12 weeks; those with a clinical response to upadacitinib induction therapy were randomized in the 52-week U-ENDURE (n=502) maintenance trial to receive upadacitinib (15 mg or 30 mg once daily) or placebo. The primary endpoints were clinical remission and endoscopic response, both assessed at week 12 and week 52. At week 12, induction

therapy with upadacitinib was significantly superior to placebo both for clinical remission (U-EXCEL: 49.5% vs 29.1%; U-EXCEED: 38.9% vs 21.1%; *P*<.001 for both comparisons) and for the other primary endpoint of endoscopic response (U-EXCEL: 45.5% vs 13.1%; U-EXCEED: 34.6% vs 3.5%; *P*<.001 for both comparisons). At week 52, both doses of upadacitinib maintenance therapy were significantly superior to placebo for both endpoints. Week 52 clinical remission rates were 37.3% (upadacitinib 15 mg) and 47.6% (upadacitinib 30 mg) compared with 15.1% with placebo (*P*<.001 for both comparisons). The rates of endoscopic response at week 52 were 27.6% (upadacitinib 15 mg) and 40.1% (upadacitinib 30 mg) compared with 7.3% with placebo (*P*<.001 for both comparisons). Herpes zoster infections were more common with upadacitinib (45 mg and 30 mg) than with placebo, and hepatic disorders and neutropenia were also more common with upadacitinib 30 mg. Gastrointestinal perforations occurred in 4 patients treated with upadacitinib 45 mg, 1 patient treated with upadacitinib 30 mg, and 1 patient treated with upadacitinib 15 mg.

A systematic review and meta-analysis performed a robust comparison of several advanced therapies to determine their relative risk of serious infections using data from 20 active comparator studies conducted in patients with inflammatory bowel disease.[10] In patients with CD, there was no significant difference in the risk of serious infections between vedolizumab vs anti-TNFα agents in patients with CD (odds ratio [OR], 1.03; 95% CI, 0.78-1.35). In patients with CD, ustekinumab was associated with a lower risk of serious infections compared with both anti-TNFα agents (OR, 0.49; 95% CI, 0.25-0.93) and vedolizumab (OR, 0.40; 95% CI, 0.17-0.93).

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Management of Complicated Crohn's Disease

Dr Miguel Regueiro, from the Cleveland Clinic, covered advances in the management of fistulizing CD, including perianal fistulas and intra-abdominal fistulas, as well as the management of stricturing CD.[1]

Perianal Fistulas

There are 2 major types of perianal fistulas, simple and complex, the latter of which comprises the vast majority of cases in CD.[2] Features of complex fistulas include the presence of multiple tracks and multiple internal and external openings, and a high location in the anovaginal or rectovaginal areas. Additionally, these fistulas tend to be associated with abscesses or strictures and are often recurrent. Despite a litany of medications that have been evaluated as treatments for perianal fistulizing CD, most have been largely ineffective until the use of biologic therapies.

Infliximab has been studied most extensively in perianal fistula cases of CD. A post hoc analysis of the ACCENT-II trial evaluated patients with fistulizing CD treated with induction (n=282) and maintenance (n=139) infliximab therapy.[3] This analysis demonstrated that, at week 14, higher trough levels of infliximab were independently associated with fistula response (OR, 1.16; 95% CI, 1.02-1.32; *P*=.019) and with a composite remission endpoint of combined complete fistula response and C-reactive protein normalization (OR, 2.32; 95% CI, 1.55-3.49; *P*<.001) (Figure 2). This association was also shown in a cross-sectional study of 117 patients with CD who had perianal fistulas and were treated with infliximab for at least 24 weeks.[4] Patients who experienced fistula healing had significantly higher median serum infliximab levels vs those with persistently active fistulas (15.8 vs 4.4 μg/mL; *P*<.0001). Additionally, there was a continuous gain in fistula healing as infliximab levels increased (area under the curve for the association between fistula healing and infliximab levels was 0.82 [*P*<.0001]).

Other biologics have since been evaluated in perianal fistulizing CD, with varying results. An exploratory analysis of the GEMINI 2 trial was

conducted in patients who had responded to vedolizumab induction therapy and then received maintenance treatment with either vedolizumab (n=308) or placebo (n=153).[5] Fistula closure rates, assessed at weeks 14 and 52, were higher among patients who received maintenance vedolizumab (28% and 31%) compared with maintenance placebo (11% and 11%). Additionally, patients who received maintenance vedolizumab experienced a faster time to fistula closure and were more likely to have fistula closure at week 52 (33% vs 11%; HR, 2.54; 95% CI, 0.54-11.96).

A post hoc pooled analysis of the CERTIFI, UNITI-1, and UNITI-2 trials of ustekinumab-treated patients (n=150) reported that 26.0% had a fistula response at week 8 compared with 16.9% of 71 patients treated with placebo (*P*=.14).[6] Complete fistula resolution was achieved in 24.7% of ustekinumab-treated patients compared with 14.1% of placebo-treated patients (*P*=.073). Neither of these comparisons was considered clinically significant.

More recently, a post hoc analysis of 3 upadacitinib trials (the U-EXCEL and U-EXCEED induction studies, and the U-ENDURE maintenance study) was reported.[7] Resolution of perianal fistula drainage at the completion of induction therapy was more frequent in the upadacitinib groups compared with the placebo group (44.7% vs 5.6%; *P*=.003). The benefit with upadacitinib in drainage resolution was also observed with maintenance treatment (28.6% with upadacitinib 15 mg and 23.1% with upadacitinib 30 mg, vs 0% with placebo).

As established several years ago, some of the most robust outcomes in patients with perianal fistulizing CD remain with a combination of infliximab plus the surgical placement of setons.[8] In that study, receipt of infliximab alone was compared with the combination of infliximab plus seton placement. The combination proved superior in terms of initial response (100% vs 82.6%; *P*=.014), lower recurrence rate (44% vs 79%; *P*=.001), and longer time to recurrence (13.5 vs 3.6 months; *P*=.0001).

Darvadstrocel, a dispersion of expanded allogeneic adipose-derived mesenchymal stem cells, has garnered much interest over the years for its role in the treatment of complex perianal fistulas in CD.[9] Darvadstrocel was previously evaluated in the phase 3 ADMIRE-CD study, where it was associated with a significant improvement in fistula remission.[10] However, the follow-up ADMIRE-CD II trial did not meet its primary endpoint of combined remission at 24 weeks.[11] The study authors noted a higher-than-expected placebo response rate in the ADMIRE-CD II study, which may have been attributed to the use of a surgical approach (curettage and ligation of internal fistula procedure) in both the placebo and treatment arms.

Intra-abdominal Fistulas

The initial management of a patient with an intra-abdominal abscess typically involves drainage (percutaneous if possible, or open if the abscess is larger or septic).[12] Patients should avoid corticosteroids and narcotics, if possible, and antibiotic therapy can be administered either intravenously or orally.[13] In the short term, immunosuppressants and biologic therapies should be held (particularly if the patient is septic), and the patient should be placed on bowel rest initially.

Most intra-abdominal abscesses in CD require surgery at some point, as was shown in a retrospective study of 121 patients with CD who were hospitalized for imaging-confirmed abscess between 2008 and 2016.[14] Of this group, only 36.4% avoided surgery after 2 years of follow-up. Among patients who did not immediately require surgery, bowel wall thickness greater than 6 mm (HR, 3.08; 95% CI, 1.20-6.21), disease length greater than 15 cm (HR, 2.67; 95% CI, 1.40-6.20), bowel dilation (HR, 2.19; 95% CI, 1.02-4.68), and abscess size greater than 6 cm (HR, 2.47; 95% CI, 1.17-5.21) were all independent risk factors for future surgery in an adjusted multivariable analysis.

A potential exception lies in the case of smaller abscesses, which

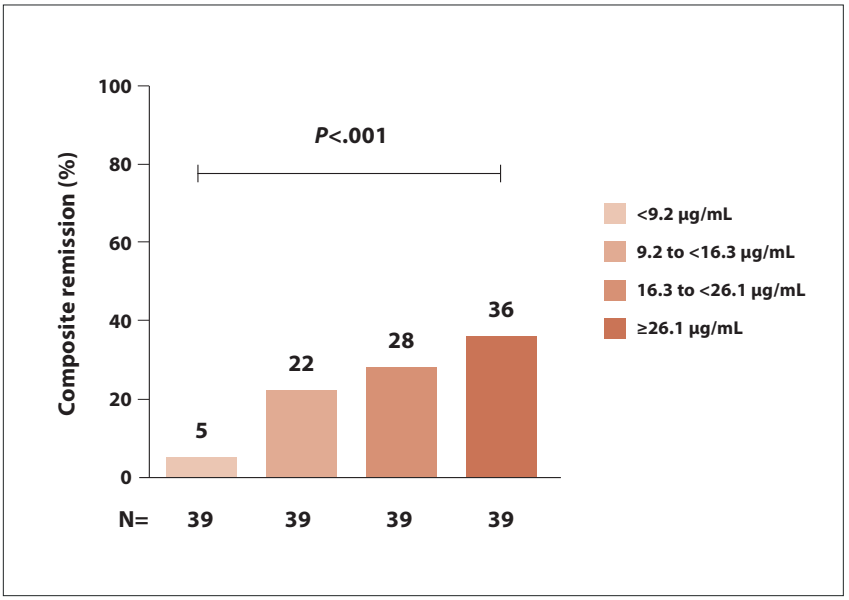

Figure 2. Rates of week 14 therapeutic outcomes by week 6 infliximab concentration quartiles regarding composite remission in a post hoc analysis of the ACCENT-II trial.[3] Adapted from Regueiro M. Management of complicated Crohn's disease. Presented at: 2024 Advances in Inflammatory Bowel Disease Conference; December 9-11, 2024; Orlando, Florida.[1]

may respond to biologic therapy. In a prospective study from the Groupe d'Etude Thérapeutique des Affection Inflammatoires Digestives conducted in biologic-naive patients with CD and resolved intra-abdominal abscess, 117 patients received adalimumab and were followed for 2 years.[15] At week 24, 74% of patients had achieved treatment success (no need for corticosteroids after week 12, intestinal resection, abscess recurrence, or clinical relapse). Of the 30 patients who experienced failure with adalimumab, 15 proceeded to surgery. At week 104, 72.9% of patients showed no abscess recurrence or surgery. Patients with abscess drainage were significantly more likely to have experienced adalimumab failure at week 24 (OR, 4.18; 95% CI, 1.06-16.5; *P*=.043) with factors that increased this risk, including disease duration (HR, 1.32; 95% CI, 1.09-1.59; *P*=.008), abscess drainage (HR, 5.59; 95% CI, 2.21-14.15; *P*=.001), and inflammatory changes in mesenteric fat (HR, 0.4; 95% CI, 0.17-0.94; *P*=.046).

Stricturing CD

A global consensus on the definition of small bowel stricture includes a combination of luminal narrowing, wall thickening, and prestenotic dilation.[16] Although corticosteroids may temporarily control luminal narrowing and improve symptoms, they are not considered an effective long-term solution.[17]

The prospective observational CREOLE study assessed the efficacy of adalimumab in patients (n=97) with CD and symptomatic small bowel stricture.[18] At week 24, 64% of the adalimumab-treated patients had achieved success, defined as adalimumab continuation without prohibited treatment (corticosteroids after 8 weeks or other anti-TNFα agents), endoscopic dilation, or bowel resection. After a median follow-up of 3.8 years, 45.7% of patients who were in success at week 24 continued in prolonged success at 4 years.

> Fistulizing and stricturing CD often require a combined medical and surgical approach to prevent these complications from significantly impacting quality of life. It is important to recognize early when medical or endoscopic treatment alone is not going to turn things around, and to involve our surgical colleagues in the discussion and decision-making process.
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> — Corey A. Siegel, MD, MS

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Progression of Disease When Mesalamine Fails

Dr Maia Kayal, from the Icahn School of Medicine at Mount Sinai, reviewed the progressive nature of ulcerative colitis (UC) and treatment options for patients who experience disease progression on mesalamine therapy.[1]

UC as Progressive Disease

The mainstay of therapy for patients with mild or moderate UC consists of 5-ASA, which have been established as superior to placebo as maintenance therapy. For patients with proctitis, 5-ASA are generally administered as rectal-based therapy (eg, enemas or suppositories), whereas patients with left-sided colitis or extensive pancolitis are typically treated with a combination of oral and rectal 5-ASA formulations. The majority (88%-97%) of patients with mild or moderate UC receive 5-ASA within 1 year of diagnosis.[2] However, there are limitations to this treatment, as approximately 37% of these patients will experience disease relapse within 6 to 12 months.[3]

It is important to promptly identify patients with UC who experience a disease flare on 5-ASA therapy, as UC progression is associated with significant risks, including proximal disease extension, neoplasia, bowel damage, and reduced rectal compliance.[4] Specifically, disease extension is a significant risk factor for colectomy.[5] Up to 50% of patients with UC will have proximal disease extension, with this risk increasing over time.[6] Several risk factors for proximal disease extension have been identified, including a younger age at diagnosis (HR, 0.979; 95% CI, 0.959-0.999) and presence of sclerosing cholangitis (HR, 12.83; 95% CI, 1.36-121.10). Recognizing when patients relapse, particularly in the context of proximal disease extension, is imperative because of associated adverse outcomes such as hospitalization and colectomy.[7]

Thus, the goal should be not only to recognize patients with moderate-to-severe UC requiring treatment beyond 5-ASA, but also to understand that patients with mild or moderate UC also meet the same criteria after they have relapsed on 5-ASA and should be treated as such.

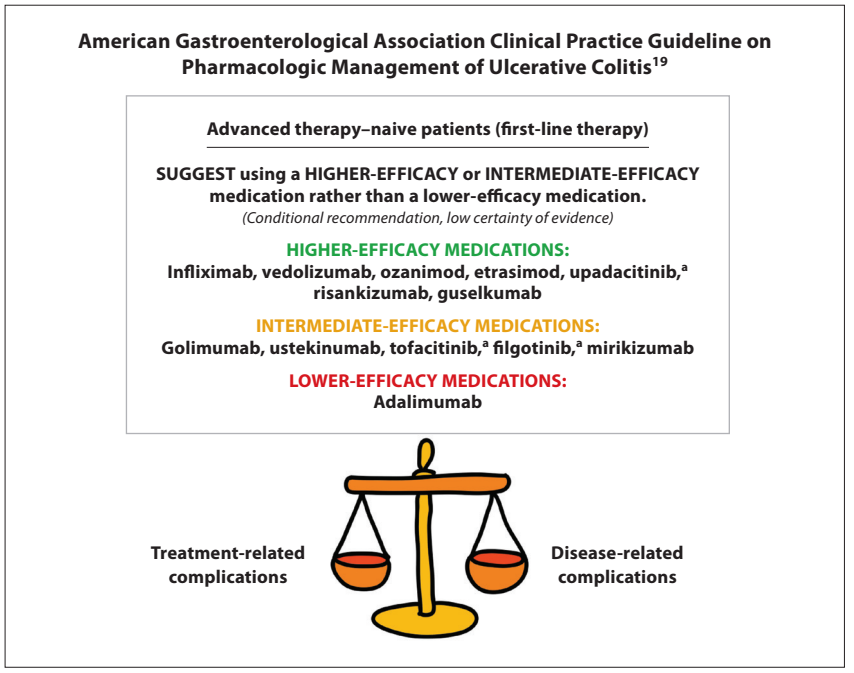

Figure 3. Considerations for choosing the first therapy. [a]The US Food and Drug Administration label recommends the use of Janus kinase inhibitors only in patients with prior failure or intolerance to tumor necrosis factor antagonists. Filgotinib is not available for use in the United States. Adapted from Kayal M. Progression of disease when mesalamine fails. Presented at: 2024 Advances in Inflammatory Bowel Disease Conference; December 9-11, 2024; Orlando, Florida.[1]

Nonbiologic Therapy Options Post–5-ASA

A multitude of therapies are now available to treat patients who experience relapse of their UC while receiving 5-ASA therapy. Newer therapies have been investigated as an option for patients who are flaring on 5-ASA but are hesitant to progress to a biologic or small molecule agent.

The nutraceutical CurQD, a combination of curcumin and Qing-Dai, was found to have greater efficacy than placebo for inducing response and remission among a small cohort of patients with active UC.[8] CurQD also appears to reduce bowel urgency in patients, an important outcome for those experiencing disease flare.[9]

The sphingosine-1 phosphate (S1P) receptor modulator etrasimod was found to be effective as induction and maintenance therapy in patients with moderately to severely active UC in the ELEVATE UC 52 and ELEVATE UC 12 phase 3 trials.[10] A post hoc analysis of week 12 and 52 data from these trials, with a focus on patients previously exposed to or receiving 5-ASA prior to enrollment, demonstrated that etrasimod was significantly beneficial in this group.[11] Patients treated with etrasimod vs placebo were significantly more likely to achieve clinical remission at week 12 (34.8% vs 6.5%; $P<.001$) and week 52 (42.0% vs 2.6%; $P<.001$), and also significantly more likely to experience endoscopic improvement at week 12

(45.2% vs 12.9%; *P*<.001) and week 52 (49.4% vs 10.5%; *P*<.001). In a separate post hoc analysis of a subset of patients with isolated proctitis, etrasimod showed significant increases compared with placebo in rates of clinical remission (week 12: 42.9% vs 13.6%, *P*<.001; week 52: 44.4% vs 11.1%, *P*<.001) and endoscopic improvement (week 12: 52.4% vs 22.7%, *P*=.001; week 52: 51.9% vs 33.3%, *P*=.125). This is a particularly important consideration, as these patients tend to be undertreated and therefore at risk for proximal disease extension.[12,13]

The novel S1P receptor antagonist amiselimod was compared with placebo in a randomized, double-blind, phase 2 trial for the induction of remission in patients with mild-to-moderate active UC.[14] The primary endpoint, which was change from baseline to week 12 in modified Mayo score (the sum of endoscopy subscore, rectal bleeding subscore, and stool frequency subscore), was significantly improved with both doses of amiselimod (decrease of 2.3 points for both the 0.2 mg/day and 0.4 mg/day groups) vs placebo (decrease of 1.6 points; *P*<.01 for both comparisons). The week 12 secondary endpoint of clinical remission was significantly improved with amiselimod (33.6% and 31.1% for the 0.2 mg/day and 0.4 mg/day groups, respectively, vs 17.8% for the placebo group; *P*=.01 and *P*=.03, respectively). Similarly, significant improvements in endoscopic remission were also observed (42.1% and 43.4% for the 0.2 mg/day and 0.4 mg/day amiselimod groups, respectively, vs 23.4% for the placebo group; *P*<.01 for both comparisons).

Biologic and Small Molecule Therapy Options Post–5-ASA

The VARSITY study was a clinical practice–changing head-to-head phase 3b trial of vedolizumab (n=383) vs adalimumab (n=386) in patients with moderate-to-severe UC.[15] At week 52, significantly greater rates of clinical remission were observed in the vedolizumab group compared with the adalimumab group (31.3% vs 22.5%; 8.8% difference; 95% CI, 2.5-15.0; *P*=.006). Vedolizumab was also superior to adalimumab for achieving endoscopic improvement (39.7% vs 27.7%; 11.9% difference; 95% CI, 5.3-18.5; *P*<.001). The rates of corticosteroid-free clinical remission were 12.6% in the vedolizumab group and 21.8% in the adalimumab group (-9.3% difference; 95% CI, -18.9 to 0.4). This landmark study established vedolizumab as a first-line treatment for patients who have moderate-to-severe UC.

The retrospective, real-world EVOLVE study compared the efficacy of an anti-TNFα agent when given either prior to (first line) or after (second line) vedolizumab therapy in biologic-naive patients with UC (n=604) or CD (n=491).[16] Two important conclusions arose from these data. First, vedolizumab and anti-TNFα agents were found to be equally effective as first-line therapies for controlling disease symptoms in biologic-naive patients with UC; vedolizumab was shown to have a more favorable safety profile. Second, there was no decrease in efficacy noted with the use of an anti-TNFα agent in the second line, providing a robust second-line option for patients.

A recent network meta-analysis of 36 studies compared the relative efficacy of a subset of biologics and small molecules in 14,270 patients with moderate-to-severe UC.[17] This analysis found that upadacitinib appeared slightly superior to other therapies in achieving clinical remission, endoscopic improvement and remission, and histologic remission. However, novel biologics such as risankizumab and guselkumab also ranked high in achieving these outcomes.

It is well established that patients with active moderate-to-severe UC have their highest rates of response and remission with their first-line therapy, and show progressively lower rates after failure of 1 or more other advanced therapies.[18] Thus, there is an increasing understanding that therapeutic decisions should position agents in order to give these patients the best possible chance to achieve clinical and endoscopic remission. To this end, the American Gastroenterological Association (AGA) recently published a living clinical practice guideline to provide clinicians with recommendations for the pharmacologic management of moderate-to-severe UC (Figure 3).[19] In these guidelines, the AGA suggests using a higher- or intermediate-efficacy medication, as opposed to a lower-efficacy medication, for the first-line treatment of advanced therapy–naive patients. In these guidelines, higher-efficacy medications include infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, and guselkumab. Intermediate-efficacy medications include golimumab, ustekinumab, tofacitinib, filgotinib

> When mesalamine fails for the treatment of UC, there are now multiple drug classes that are effective for first-line advanced therapy. Taking disease severity, treatment efficacy, risk of adverse events, and patient preference into account, we should tailor our treatment decisions, as our best shot for controlling UC is the next drug we select after mesalamine.
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> — Corey A. Siegel, MD, MS

(not available in the United States), and mirikizumab, whereas lower-efficacy medications include adalimumab. When discussing these options with patients, the conversation should balance disease-related complications with the risk of treatment-related complications.

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When the First Advanced Therapy Fails

Dr Maria T. Abreu, from the University of Miami Miller School of Medicine, discussed the clinical data supporting the use of several agents in the second-line setting of moderate-to-severe UC.[1]

The AGA living clinical practice guideline for the management of moderate-to-severe UC patients also includes suggestions for treatment options in patients with prior exposure to 1 or more advanced therapies (particularly anti-TNFα agents).[2] These guidelines suggest using a higher- or intermediate-efficacy medication, rather than a lower-efficacy medication; these categories differ from those in the first-line setting. For patients with prior exposure, higher-efficacy medications include tofacitinib, upadacitinib, and ustekinumab. Intermediate-efficacy medications include filgotinib (not available in the United States), mirikizumab, risankizumab, and guselkumab. Lower-efficacy medications include adalimumab, vedolizumab, ozanimod, and etrasimod.

IL-12/23 and IL-23 Inhibitors

Unlike ustekinumab, which targets the p40 subunit and thus inhibits both IL-12 and IL-23 signaling, subsequent members of this class were developed to specifically target the p19 subunit and thus inhibit only IL-23 signaling.[3,4] These members include mirikizumab, risankizumab, and guselkumab. An important commonality across the clinical studies of these agents is lower response rates when used in patients with prior inadequate responses to advanced therapies such as biologic agents or Janus kinase (JAK) inhibitors.

The UNIFI study established the efficacy of ustekinumab in patients with UC.[5] In this study, the percentage of patients achieving the efficacy outcomes was uniformly higher among patients who were biologic-naive compared with patients considered to have a prior biologic failure. For example, the rates of clinical remission with ustekinumab vs placebo were 18.4% vs 9.9%, respectively, in the biologic-naive group, and were 12.7% vs 1.2%, respectively, in the biologic-failure group.

The LUCENT-1 and LUCENT-2 trials evaluated mirikizumab as induction and maintenance therapy for UC.[6] Among the 1162 total patients, 36.3%, 18.8%, and 3.4% had prior treatment failure with an anti-TNFα agent, vedolizumab, and tofacitinib, respectively. In the induction portion of the studies, the rate of clinical remission in the overall population was 24.2% with mirikizumab and 13.3% with placebo. However, the rates dramatically differed when

isolated by prior treatment exposures. For example, for patients with prior failure to any biologic therapy or tofacitinib, the clinical remission rates with mirikizumab vs placebo were 15.2% vs 8.5%, lower than the 30.6% vs 16.5% rates observed in patients without prior failure to any biologic therapy or tofacitinib. The magnitude of difference was lower in the maintenance phase. For patients with prior failure to any biologic therapy or tofacitinib, the clinical remission rates with mirikizumab vs placebo were 46.1% vs 15.6%, slightly lower than the 51.9% vs 30.4% rates observed in patients without prior failure to any biologic therapy or tofacitinib.

Risankizumab, which was evaluated for treatment of UC patients in the INSPIRE (induction) and COMMAND (maintenance) phase 3 studies, showed similar trends.[7] The rate of clinical remission with induction therapy in the overall population was 20.3% with risankizumab and 6.2% with placebo. Again, when this was stratified by prior inadequate response to advanced therapy, the rates were lower (11.4% with risankizumab vs 4.3% with placebo) compared with patients with no prior inadequate response to advanced therapy (29.7% with risankizumab vs 8.4% with placebo). This observation was maintained regardless of whether the advanced therapy was an anti-TNFα agent (12.3% with risankizumab vs 3.7% with placebo), vedolizumab (9.3% with risankizumab vs 5.6% with placebo), or a JAK inhibitor (10.7% with risankizumab vs 0% with placebo). A similar trend was noted in the maintenance phase, where the rates of clinical remission were lower in patients with a prior inadequate response to advanced therapy (36.6% and 29.5% with risankizumab 180 mg and risankizumab 360 mg, respectively, vs 23.2% with placebo) compared with patients without a prior inadequate response to advanced therapy (50.9% and 61.7% with risankizumab 180 mg and risankizumab 360 mg, respectively, vs 31.1% with placebo).

Guselkumab was investigated in QUASAR, which consisted of phase 3, double-blind, randomized, placebo-controlled induction and maintenance studies.[8,9] Approximately one-half (49.1%) of the primary analysis population of the induction study had a prior inadequate response to an advanced therapy; 47.4% had an inadequate response to 2 or more advanced therapies. The majority of these were classified as primary or secondary nonresponse or intolerance to anti-TNFα agents (87.5%), followed by vedolizumab (54.1%) and tofacitinib (18.0%). After induction treatment with guselkumab, the overall rate of clinical remission was 23% compared with 8% in placebo-treated patients (15% difference; 95% CI, 10-20; *P*<.0001).[10] When these results were analyzed according to prior advanced therapy response, the rate was higher in patients who were naive to biologics and tofacitinib (32% with guselkumab vs 12% with placebo; *P*<.001) compared with patients who had a prior inadequate response to advanced therapy (12% with guselkumab vs 4% with placebo; *P*=.005). Rates of clinical remission at maintenance week 44 in the overall population were also significantly higher with guselkumab 200 mg given subcutaneously every 4 weeks (50%) and guselkumab 100 mg every 8 weeks (45%) than with placebo (19%; *P*<.0001 for both comparisons). Again, these rates were lower in patients with a prior inadequate response to an advanced therapy

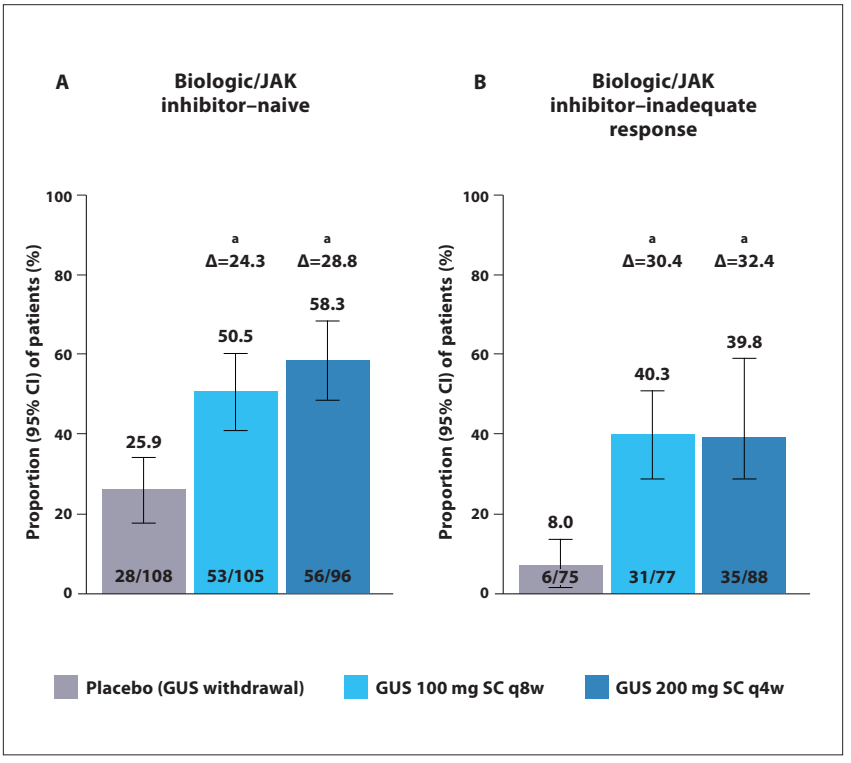

Figure 4. Clinical remission with GUS at week 52 stratified by previous advanced therapy (week 40 of maintenance study): **(A)** biologic/JAK inhibitor–naive or **(B)** biologic/JAK inhibitor–inadequate response.[11] Clinical remission = a Mayo stool frequency subscore of 0 or 1 and not increased from baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0 or 1 with no friability. Δ = treatment difference compared with placebo. [a]Nominal *P*<.001. GUS, guselkumab; JAK, Janus kinase; q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous. Adapted from Abreu MT. When the first advanced therapy fails. Presented at: 2024 Advances in Inflammatory Bowel Disease Conference; December 9-11, 2024; Orlando, Florida.[1]

> The choice of second-line advanced therapy for UC is highly dependent on why the first-line treatment failed. If anti-TNF therapy was first line and never effective (primary failure), the next treatment should be either a JAK inhibitor or an IL-12/23 or IL-23 medication.
>
> — Corey A. Siegel, MD, MS

(39.8% and 40.3% vs 8.0% with placebo; *P*<.001 for both comparisons) compared with patients without a prior inadequate response to an advanced therapy (58.3% and 50.5% vs 25.9% with placebo; *P*<.001 for both comparisons) (Figure 4).[11]

Data from the proof-of-concept VEGA study suggested that combination therapy with guselkumab and golimumab might be more effective than either therapy alone; future studies may elucidate the effectiveness of this combination in patients with prior inadequate responses to advanced therapy.[12]

JAK Inhibitors

JAK inhibitors can have broad immunologic effects in UC.[13] The efficacy of the first JAK inhibitor approved in UC, tofacitinib, was established in the OCTAVE Induction 1 and OCTAVE Induction 2 pivotal trials.[14]

Upadacitinib was evaluated as induction and maintenance therapy in three phase 3, multicenter, double-blind, randomized trials in patients with moderately to severely active UC.[15] In the U-ACHIEVE and U-ACCOMPLISH induction studies, the rates of clinical remission in the overall population treated with upadacitinib were 26% and 33%, respectively, compared with placebo (5% and 4%, respectively; *P*<.001 for both comparisons). The percentage differences in clinical remission between the upadacitinib and placebo groups were decreased in patients with vs without a prior inadequate response to an anti-TNFα agent (21.7% vs 47.6%, respectively) and in patients with vs without a prior inadequate response to vedolizumab (18.5% vs 28.7%, respectively). Similar effects were noted with maintenance therapy, although the magnitude of the difference was smaller.

One of the benefits of the broad immunologic effects of JAK inhibitors are favorable outcomes particularly in patients with concomitant autoimmune conditions, such as psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and atopic dermatitis.[16] Upadacitinib is also preferred in patients who desire an oral medication or who have a positive varicella zoster virus titer. Patients in whom upadacitinib is not preferred include those aged over 75 years and those who are active smokers, are pregnant or breastfeeding, or with active infection (especially herpes zoster), cardiovascular disease, or a history of or increased risk of thromboembolic disease.

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