A SPECIAL MEETING REVIEW EDITION

Highlights From the 2019 Advances in Inflammatory Bowel Diseases Conference

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Special Reporting on:

- A Practical Approach to Anti-Interleukins in IBD 2020
- Update: ACG Guidelines for the Treatment of Crohn's Disease
- Management of Ulcerative Colitis in Adults: ACG Clinical Guidelines
- The Road Ahead: Potential Benefits and Risks of Combining Biologics and Novel Agents
- A Practical Approach to JAK inhibitors in IBD 2020
- A Practical Approach to Anti-Integrins in IBD 2020
- A Practical Approach to Anti-TNFs in IBD 2020

PLUS Meeting Abstract Summaries

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A Practical Approach to Anti-Interleukins in IBD 2020

Dr Bruce E. Sands discussed the use of anti-interleukins.[1] Ustekinumab is the only anti-interleukin agent approved for the treatment of patients with IBD. Through recognition of the shared p40 protein subunit, ustekinumab can disrupt proinflammatory cytokines interleukin (IL) 12 and 23 signalling. In patients with Crohn's disease, the pivotal induction trials establishing the safety and efficacy of ustekinumab were UNITI-1 and UNITI-2.[2] The use of ustekinumab in the maintenance setting was established by the IM-UNITI trial.[2] In the UNITI-1 and UNITI-2 trials, patients were randomly assigned to receive a single intravenous dose of ustekinumab (either 130 mg or approximately 6 mg/kg) or placebo. The UNITI-1 trial enrolled 741 patients with a primary or secondary nonresponse to anti–tumor necrosis factor (TNF) therapy, or who developed unacceptable toxicity after treatment with these agents. The UNITI-2 trial enrolled 628 patients with an inadequate response to conventional therapy or who were intolerant to it. Patients with a response in either UNITI-1 or UNITI-2 (n=397) were randomly assigned to treatment with ustekinumab (90 mg either every 8 weeks or every 12 weeks) or placebo.

In both the UNITI-1 and UNITI-2 trials, a significantly higher proportion of patients who were treated with ustekinumab compared with placebo achieved the primary endpoint of clinical response (defined as a decrease of ≥100 points in the Crohn's Disease Activity Index [CDAI] from baseline to week 6, or a CDAI score <150). In UNITI-1, the rates of response at week 6 were 34.3% in the 130 mg arm and 33.7% in the 6 mg/kg arm, vs 21.5% with placebo ($P \leq .003$ for both comparisons with placebo). In UNITI-2, the rates of response at week 6 were 51.7%, 55.5%, and 28.7%, respectively ($P \leq .001$ for both comparisons with placebo).

The primary endpoint for the IM-UNITI maintenance trial—remission at week 44 (defined as a CDAI score <150)—was also higher with ustekinumab than placebo. This rate was 53.1% with ustekinumab given every 8 weeks and 48.8% with ustekinumab given every 12 weeks, vs 35.9% with placebo ($P = .005$ for the comparison of every 8 weeks vs placebo; $P = .04$ for the comparison of every 12 weeks vs placebo). Treatment with ustekinumab was associated with significantly higher corticosteroid-free remission rates at week 44. This rate was 46.9% with the every-8-week regimen, 42.6% with the every-12-week regimen, and 29.8% with placebo ($P = .004$ for the comparison of every 8 weeks vs placebo; $P = .035$ for the comparison of every 12 weeks vs placebo). In a long-term follow-up of the UNITI studies, the rate of remission at 2 years among patients receiving ustekinumab every 8 weeks was 47%, or 88% of the remission rate observed at 1 year (53.1%; Figure 1).[3]

Among patients with ulcerative colitis, UNIFI was the pivotal induction and maintenance trial establishing the safety and efficacy of ustekinumab in these settings.[4] The trial randomly assigned 961 patients with moderate to severe ulcerative colitis to ustekinumab (130 mg or ~6 mg/kg) or placebo. Patients with a response to induction therapy were randomly assigned again to receive subcutaneous maintenance injections of ustekinumab (90 mg every 8 weeks or every 12 weeks) or placebo.

The primary endpoint of clinical remission was defined as a total score of 2 or less on the Mayo scale and no subscore exceeding 1 on any of the
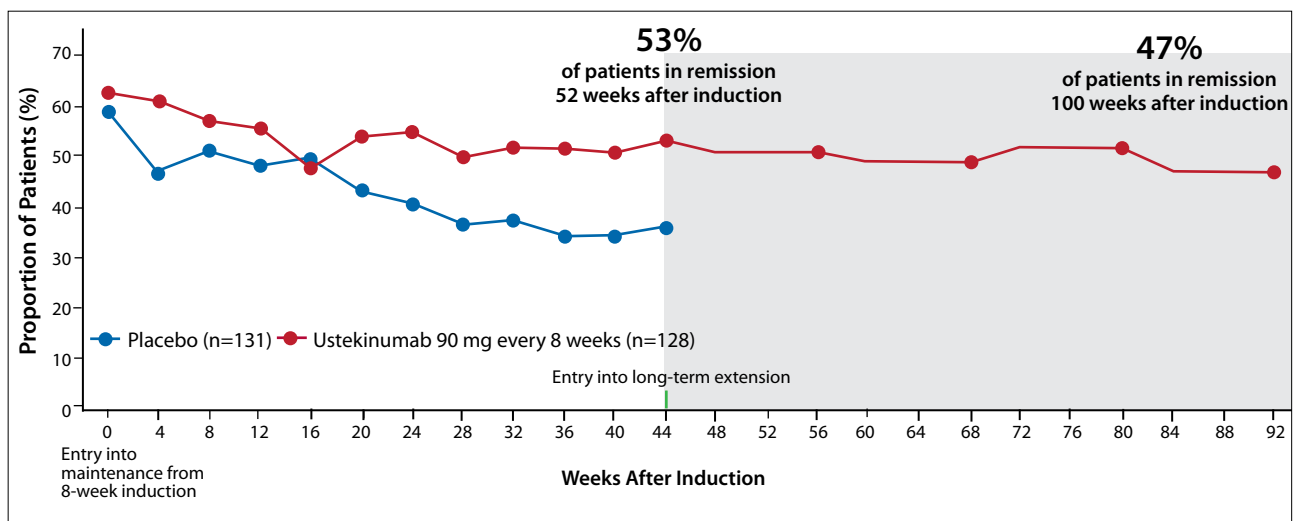

Figure 1. Remission through 2 years among patients with Crohn's disease responding to induction treatment with ustekinumab in the IM-UNITI long-term extension study. Adapted from Sands BE et al. ACG abstract 49. Presented at: American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA[3] and Sands BE. A practical approach to anti-interleukins in IBD 2020. Paper presented at: Advances in Inflammatory Bowel Diseases Conference; December 12-14, 2019; Orlando, Florida.[1]
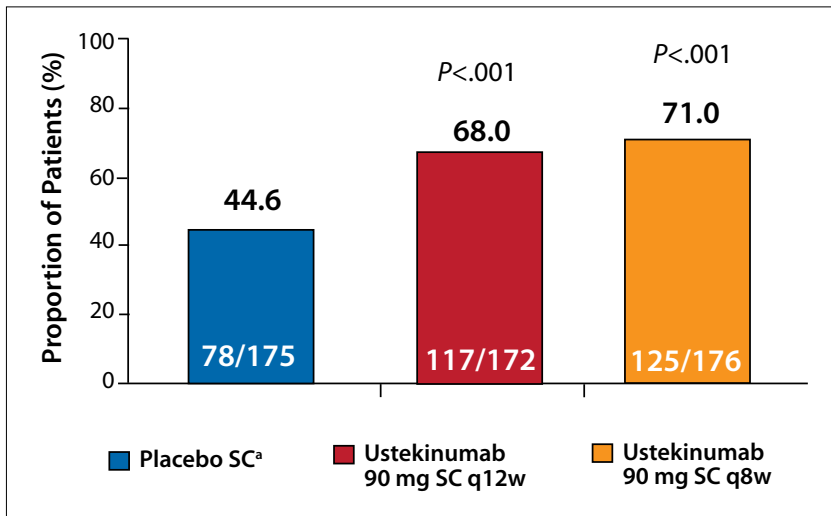
Figure 2. Clinical response through week 44 among patients with ulcerative colitis treated with ustekinumab in the UNIFI trial. [a]Patients with a clinical response to intravenous ustekinumab and were randomized to subcutaneous placebo upon entry into the maintenance study. q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous. Adapted from Sandborn WJ et al. ECCO abstract OP37. *J Crohns Colitis*. 2019;13(suppl 1)[5] and Sands BE. A practical approach to anti-interleukins in IBD 2020. Paper presented at: Advances in Inflammatory Bowel Diseases Conference; December 12-14, 2019; Orlando, Florida.[1]

Figure 3. Remission through week 44 among patients in remission at week 0 in the UNIFI maintenance trial. Adapted from Sandborn WJ et al. ECCO abstract OP37. *J Crohns Colitis*. 2019;13(suppl 1)[5] and Sands BE. A practical approach to anti-interleukins in IBD 2020. Paper presented at: Advances in Inflammatory Bowel Diseases Conference; December 12-14, 2019; Orlando, Florida.[1]
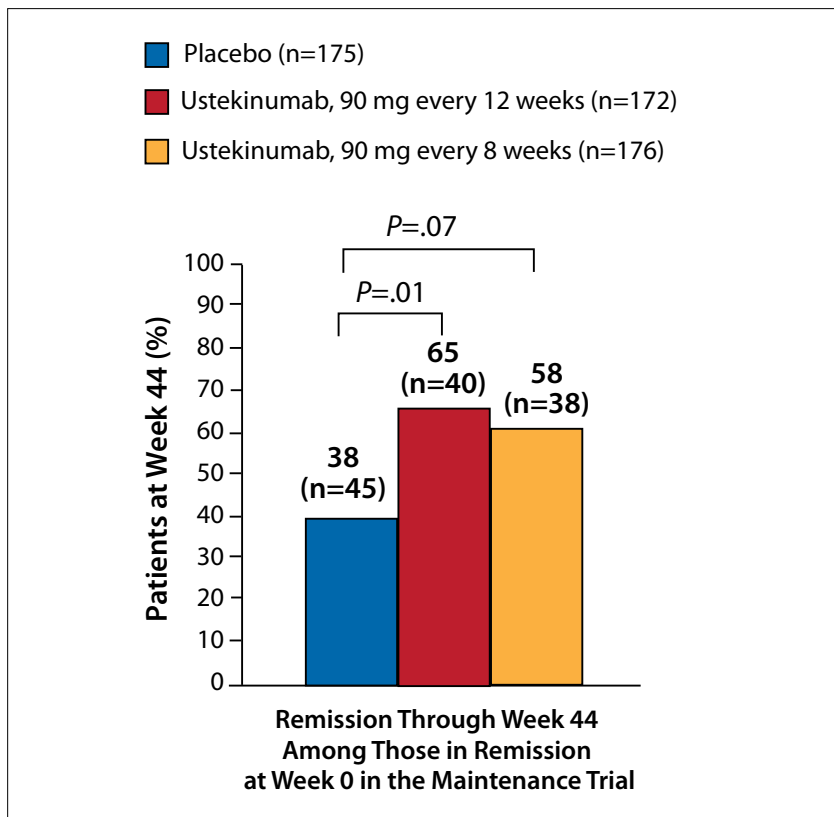
4 Mayo scale components. The rate of clinical remission at week 8 was 15.6% with ustekinumab at 130 mg, 15.5% with ustekinumab at 6 mg/kg, and 5.3% with placebo ($P<.001$ for both comparisons to placebo). Among responding patients, the rate of clinical remission at week 44 was 43.8% with ustekinumab given every 8 weeks, 38.4% with ustekinumab given every 12 weeks, and 24.0% with placebo ($P=.002$ and $P<.001$, respectively). Other outcomes through week 44 are shown in Figures 2 and 3.[5] Long-term symptomatic remission was observed in the group of patients who continued to receive ustekinumab in a long-term extension trial.[6]

In summary, ustekinumab was effective in Crohn's disease and ulcerative colitis, where it may be useful in both the first-line setting and after anti-TNF agent failure. Ustekinumab confers a very good corticosteroid sparing and maintenance effect. The onset of efficacy associated with ustekinumab was observed as early as 2 weeks, but efficacy can increase over 16 weeks and beyond. The safety of ustekinumab has been well established, with minimal immunogenicity and a minimal need for laboratory monitoring.

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Update: ACG Guidelines for the Treatment of Crohn's Disease

Dr Gary R. Lichtenstein discussed updates to guidelines from the American College of Gastroenterology (ACG) for the management of Crohn's disease in adult patients.[1,2] The guidelines were updated in 2018, with several notable changes. Traditional laboratory evaluation is a component of the diagnosis of Crohn's disease. There is a role for fecal calprotectin at diagnosis to differentiate IBD from irritable bowel syndrome (strong recommendation; moderate quality of evidence). In contrast, there is no role for serologic markers in the diagnosis of Crohn's disease. Genetic testing is also not indicated. Ileocolonoscopy is recommended to confirm the diagnosis.

Approximately 20% to 30% of patients with Crohn's disease will have an indolent disease course. Most patients require therapies that control inflammation. Hospitalization is required in up to 80% of patients with Crohn's disease, and the 10-year risk of surgery is 40% to 55% (this rate may be 30% in the era of biologic therapies).[1] Factors associated with an increased risk of progressive disease include young age at diagnosis (<30 years), extensive bowel involvement at presentation, severe perianal or rectal disease, and penetrating or stenosing phenotype at diagnosis. A higher number of poor prognostic factors corresponds to a worse prognosis (as defined by the likelihood of requiring surgery).

The former definition of Crohn's disease severity relied upon a description of symptoms alone (using the CDAI or other indices). In contrast, the updated definition of severity adds endoscopic findings, such as the presence of deep ulcerations. Moderate to severe disease is now defined as a Simple Endoscopic Score for Crohn's Disease (SES-CD) exceeding 6.

The goals of therapy for Crohn's disease were also updated, with an emphasis on symptom-based and endoscopic-based (mucosal healing) endpoints. The guidelines note a lack of correlation between symptoms and endoscopic findings, and therefore identify mucosal healing as a treatment goal. Endoscopic scores may be used to monitor response to treatment. The guidelines recommend evaluation within 1 year of resection for postoperative endoscopic recurrence to guide therapy. Quality of life is another goal, with a focus on the management of stress, anxiety, and depression.

There is now an understanding that mild Crohn's disease is relatively uncommon. For patients with mild disease, mesalamine is not indicated for either induction or remission therapy. Instead, budesonide is recommended for induction therapy.

Multiple agents are now available for patients with moderate or severe Crohn's disease. Selection of treatment should be based on the specifics of the patient's disease and comorbidities, as well as medication efficacy, speed of onset, and safety. The guidelines still include corticosteroids as a recommended therapy for induction of remission. Thiopurines or methotrexate are recommended for maintenance therapy. However, for induction and maintenance of Crohn's disease, the updated guidelines now include a focus on biologic therapies, notably anti-TNF agents (infliximab, adalimumab, and certolizumab pegol), anti-integrin agents (vedolizumab and
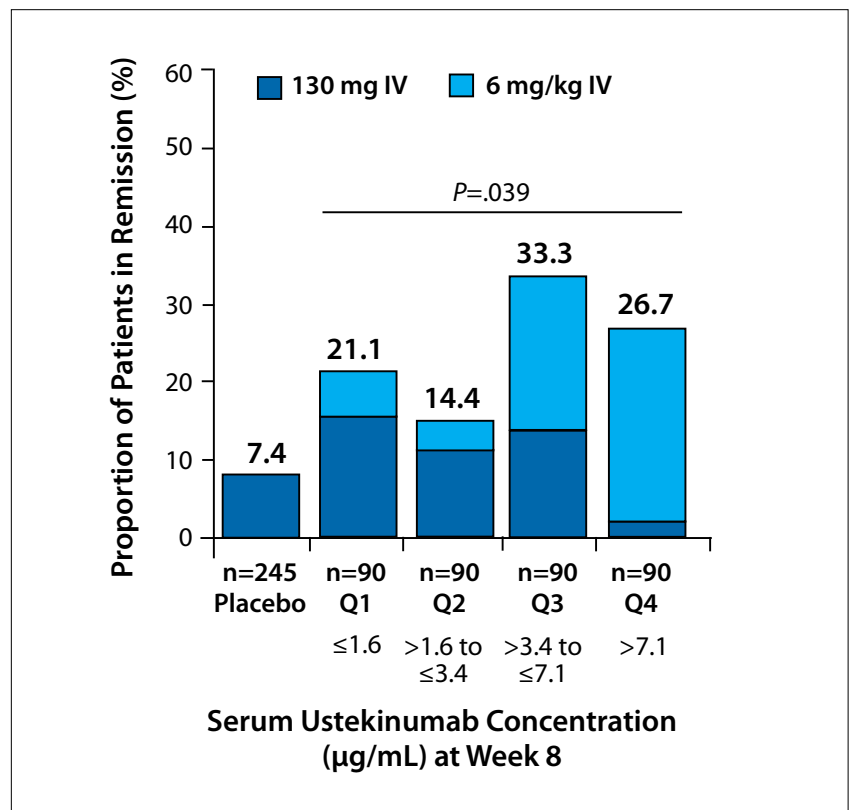

Figure 4. Clinical remission in the UNITI-1 trial of ustekinumab according to serum ustekinumab concentration. Q, quartile. Adapted from Adedokun OJ et al. *Gastroenterology.* 2018;154(6):1660-1671[3] and Lichtenstein GR. Update: ACG guidelines for the treatment of Crohn's disease. Paper presented at: Advances in Inflammatory Bowel Diseases Conference; December 12-14, 2019; Orlando, Florida.[2]

ABSTRACT SUMMARY Serum Ustekinumab and Anti-Ustekinumab Antibody: Analysis of Over 2000 Patient Results Using Lab Developed Electrochemiluminescent Immunoassays

Samples from patients treated with ustekinumab were analyzed using laboratory-developed immunoassays to measure concentrations of the drug and antidrug antibodies (Abstract P020). Among the 2097 samples, 2012 (96%) had no measurable antidrug antibodies. Among these samples, 38 (1.9%) had an undetectable ustekinumab level (<0.1 µg/mL). These samples would be considered subtherapeutic in 9.2% using a cutoff of 1 µg/mL trough ustekinumab concentration, in 24.6% using a cutoff of 2 µg/mL, and in 50.4% using a cutoff of 4 µg/mL. Antidrug antibodies were detected in 4% (85/2097 samples). Titers were categorized as low in 52%, intermediate in 47%, and high in 3.5%. The mean free ustekinumab drug concentration was 4.5 µg/mL (2.3% with undetectable levels) in low titer samples and 0.1 µg/mL (67% with undetectable levels) in high titer samples. This finding suggests that while low titer antidrug antibodies were not associated with decreased ustekinumab drug levels, high titer antidrug antibodies were associated with very low or absent free ustekinumab levels.

natalizumab), and the monoclonal antibody ustekinumab.[1] Ustekinumab is among the newer treatments for patients with IBD. Analyses of the UNITI trials identified an apparent exposure-response relationship with this treatment (Figure 4).[3,4]

With the increasing availability of biologic agents, there is now an emphasis on optimizing outcomes. The CALM study was a prospective, multicenter, open-label study in Crohn's disease.[5] Patients were randomly assigned to a treatment strategy consisting of tight disease control or clinical management. In both arms, treatment was escalated in a stepwise manner, initiating with no treatment, to adalimumab induction followed by adalimumab every other week, to adalimumab every week, and to weekly adalimumab and daily azathioprine. Escalation was based on treatment failure criteria, which differed between the treatment groups. For the tight control group, failure was based on clinical symptoms combined with biomarkers. For the clinical management group, failure was based on clinical symptoms alone. The primary endpoint of mucosal healing with absence of deep ulcers at week 48 was met by 46% of patients in the tight control group vs 30% of those in the clinical management group (*P*=.010). This study was the first to demonstrate that timely escalation with tight control of anti-TNF agent therapy on the basis of clinical symptoms combined with biomarkers resulted in better clinical and endoscopic outcomes compared with clinical management alone.

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Management of Ulcerative Colitis in Adults: ACG Clinical Guidelines

D r Ashwin N. Ananthakrishnan presented updates to guidelines for the management of ulcerative colitis from the ACG.[1] These guidelines for the management of ulcerative colitis in adult patients were updated in 2019, and include several key recommendations for patients according to disease severity.[2] Diagnosis of ulcerative colitis is made using colonoscopy. At this time, biopsies of affected and unaffected areas should be taken. Biomarkers can be useful to prioritize patients for endoscopic evaluation, as shown in a systematic review and meta-analysis of 2499 patients with IBD.[3] In this analysis, fecal calprotectin was a more sensitive measure than C-reactive protein (CRP) for both ulcerative colitis and Crohn's disease. Fecal calprotectin was more sensitive in ulcerative colitis than Crohn's disease.

The updated guidelines recommend against serologic antibody testing in patients with ulcerative colitis, whether for diagnosis or prognosis. Stool tests to rule out *Clostridium difficile* should be performed at diagnosis.[2] This recommendation is supported by findings from the Ocean State Crohn's and Colitis Area Registry cohort of newly diagnosed patients with IBD.[4] In this cohort of 227 patients with reported diarrhea, 49.8% were tested for *C difficile* infection. Among the patients who were tested, 5.1% were positive.

The severity index proposed in the ACG guidelines for ulcerative colitis categorizes disease severity as mild, moderate, or severe. The guidelines also include a definition for disease remission. Mild disease is defined by fewer than 4 stools per day, intermit-

tent blood in stools, mild or occasional urgency, normal hemoglobin levels, and an erythrocyte sedimentation rate (ESR) of less than 30 mm/hr. Moderate ulcerative colitis is defined by more than 6 stools per day, frequent urgency and blood in stools, hemoglobin levels less than 75% of normal, and an ESR exceeding 30 mm/hr. Severe disease is defined by more than 10 stools per day, with continuous urgency and blood in stools, low hemoglobin levels that require transfusion, and an ESR exceeding 30 mm/hr. This severity index is limited because it lacks endoscopic severity indices, newer inflammatory markers (eg, fecal calprotectin), and longitudinal representation of the disease course.[2]

According to the ACG guidelines, a comprehensive assessment of ulcerative colitis should also include consideration of patient-specific predictors of an aggressive course and need for colectomy. These factors include young age (<40 years) at diagnosis, extensive colitis, severe endoscopic disease (Mayo subscore of 3, Ulcerative Colitis Endoscopic Index of Severity >7), hospitalization for colitis, elevated CRP, and low serum albumin. The guidelines recommend that patients with mild disease who have poor prognostic factors should be treated with therapies for moderately to severely active disease.[2]

Initial treatment of ulcerative colitis should focus on restoration of normal bowel frequency, as well as control of symptoms such as bleeding and urgency. Although histologic healing is associated with improved outcomes, there is still uncertainty regarding its routine clinical application. Histologic healing is therefore not currently considered a treatment goal.[2]

For patients with mild ulcerative colitis, oral mesalamine is recommended for induction of remission. (Alternative options are budesonide or oral systemic corticosteroids.) For the treatment of patients with moderate ulcerative colitis, mesalamine monotherapy can be used to induce remission. However, there is no incremental benefit of con-

tinuing mesalamine in patients who have escalated to anti-TNF agents. The ACG guidelines recommend against the use of thiopurine or methotrexate for induction of remission in moderately to severely active ulcerative colitis.[2] Instead, the following biologic therapies are recommended: an anti-TNF therapy (infliximab, adalimumab, or golimumab), an anti-integrin (vedolizumab), a Janus kinase (JAK) inhibitor (tofacitinib), or an anti–IL-12/23 inhibitor (ustekinumab).[2] Comparative effectiveness of therapies for induction of remission is largely inferred from indirect comparisons in network meta-analyses or observational cohorts. The only comparative efficacy study of biologics in IBD, the VARSITY trial, demonstrated that vedolizumab was superior to adalimumab for both clinical remission and mucosal healing (Figure 5).[5] In addition to the biologic agents mentioned above, other treatments to maintain remission include thiopurines (after corticosteroid-induced remission) and mesalamine (for moderately active disease).

Patients who develop a secondary nonresponse should undergo thera-

peutic drug monitoring. Low trough levels may require optimization of the treatment dose. Adequate trough levels indicate a need to switch to an agent from a different therapeutic class. High titers of antidrug antibodies require consideration of an alternate anti-TNF agent. There is insufficient evidence to recommend proactive therapeutic drug monitoring in unselected patients with ulcerative colitis in remission.[2]

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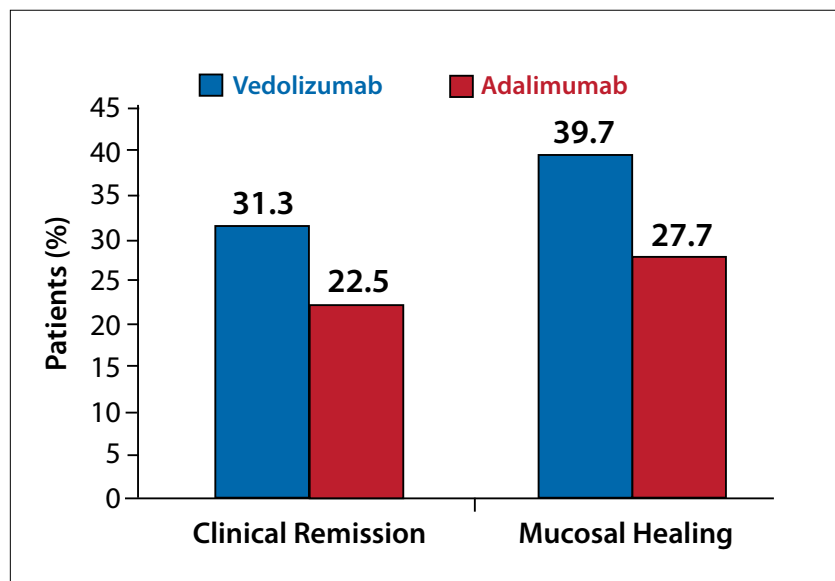
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The Road Ahead: Potential Benefits and Risks of Combining Biologics and Novel Agents

Dr Maria T. Abreu discussed biologic therapies.[1] The wide variety of approved and investigational agents targeting different components within the inflammatory immune response reflects an increasing understanding that the multifactorial pathogenesis of IBD. Targeting just one signaling pathway at a time may prove insufficient in some patients.

Currently, most patients who are treated with biologic agents for IBD receive these agents in a sequential manner, typically beginning with an anti-TNF agent. As patients lose response or become intolerant to treatment, they progress through a sequence of vedolizumab, tofacitinib, and ustekinumab. However, approximately one-third of patients never respond to induction therapy with the anti-TNF agent, and approximately half of those patients who do achieve a response subsequently lose that response within a few years.[2,3]

Unfortunately, patients who fail anti-TNF agent therapy tend to show muted responses to treatment with subsequent biologic agents, regardless of the mechanistic target.[4,5] In a retrospective study, outcomes were similar among patients treated with first-line biologic therapy with an anti-TNF agent as compared with those who received first-line therapy with vedolizumab, had an inadequate response, and then received second-line therapy with an anti-TNF agent (Figure 6).[6] In contrast, receiving vedolizumab in the first-line setting does not hamper the response to an anti-TNF agent in the second-line, as observed in a real-world population of patients with ulcerative colitis or Crohn's disease enrolled in the EVOLVE trial.[7]

Preliminary work has suggested that combination regimens are an effective strategy, although results have been inconsistent and require further investigation. The EXPLORER study (NCT02764762) is an ongoing phase 4 trial evaluating a triplet regimen consisting of vedolizumab, adalimumab, and methotrexate among patients with moderately to severely active Crohn's disease who are considered at high-risk for complications. The primary outcome of this study is endoscopic remission at week 26.

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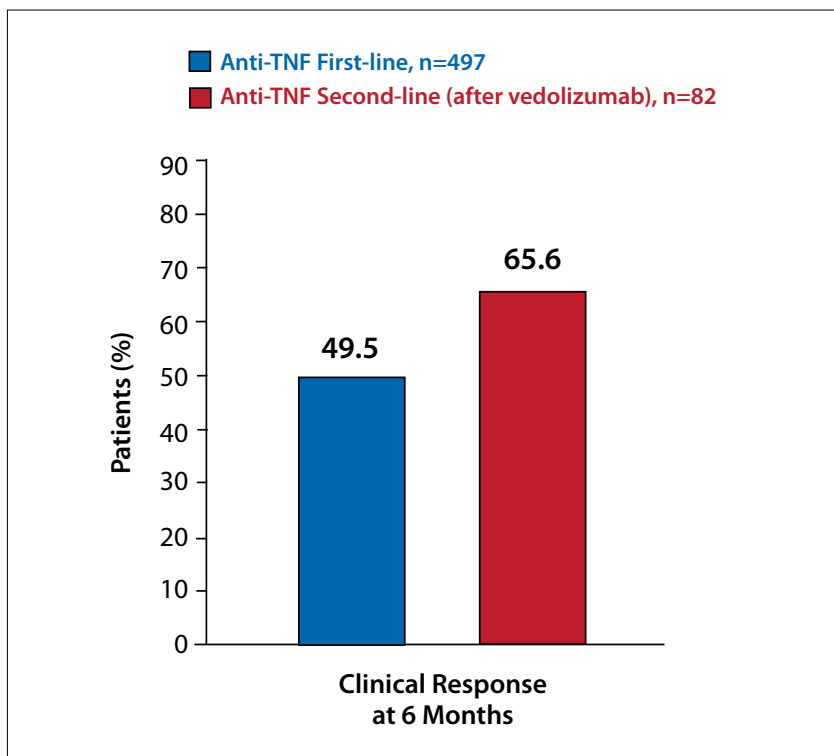
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A Practical Approach to JAK inhibitors in IBD 2020

Dr Edward V. Loftus Jr discussed JAK inhibitors.[1] Inhibition of JAK signaling pathways has proven effective in the treatment of moderate to severe IBD. JAK inhibitors provide a potent, fast-acting mechanism of action for reducing inflammation in IBD. Tofacitinib inhibits all JAKs, specifically JAK1, JAK2, and JAK3. Approval of tofacitinib was based on the OCTAVE 1 and OCTAVE 2 induction studies.[2] In the OCTAVE Sustain maintenance trial, the overall rate of infections (including infection with herpes zoster) was higher with tofacitinib vs placebo.[3] However, the rate of withdrawal due to an adverse event was lower with tofacitinib than placebo. The US Food and Drug Administration (FDA) added thromboembolism to a boxed warning for tofacitinib. Concurrently, the FDA mandated a change in the indication for the use of tofacitinib in ulcerative colitis. The 10-mg twice-daily dose of tofacitinib is approved for ulcerative colitis for initial treatment and for long-term use in limited situations.

Tofacitinib was associated with negative outcomes in two phase 2b clinical studies in moderate to severe Crohn's disease.[4] Several alternative investigational JAK inhibitors have been explored in Crohn's disease. The selective JAK1 inhibitor filgotinib was associated with significantly improved rates of remission and response compared with placebo in the phase 2 FITZROY induction study in moderate to severe Crohn's disease.[5] Another selective JAK1 inhibitor, upadacitinib, has shown efficacy in both the CELEST trial in Crohn's disease and the U-ACHIEVE trial in ulcerative colitis (Figure 7).[6-8] A novel gut-selective pan-JAK inhibitor, TD-1473, was recently shown to have activity in moderate to severe ulcerative colitis.[9] This agent was well tolerated, with a minimal risk for systemic immunosuppression.

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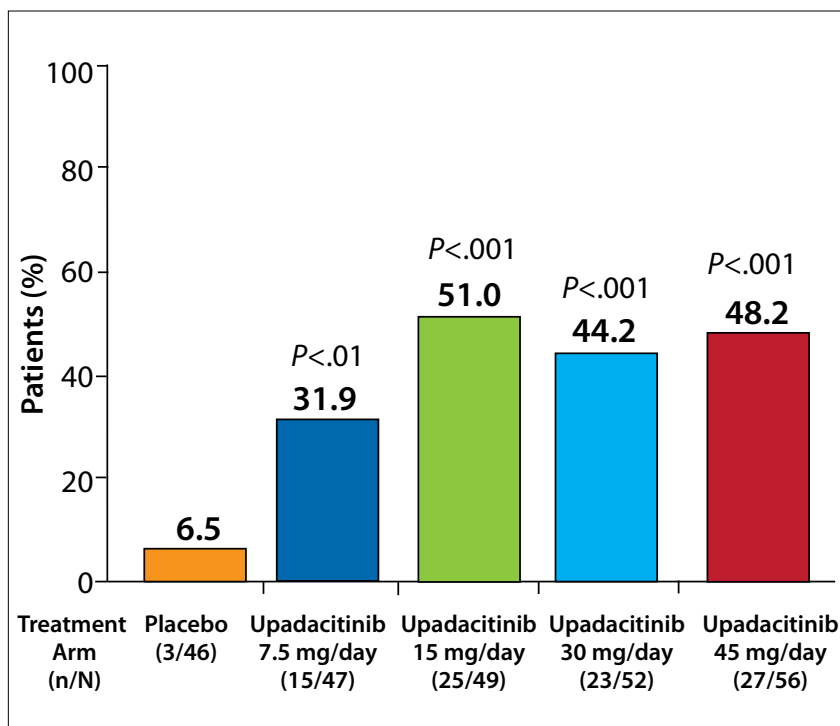
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A Practical Approach to Anti-Integrins in IBD 2020

Dr Brian G. Feagan discussed anti-integrins.[1] The anti-α4β7 integrin agent vedolizumab was proven effective and safe in ulcerative colitis and Crohn's disease in the GEMINI 1 and GEMINI 2 studies, respectively.[2,3] In the VARSITY trial, vedolizumab had a superior safety profile when compared with the anti-TNF agent adalimumab.[4] Additionally, there is evidence that vedolizumab is effective for relief of extraintestinal manifestations of IBD, including arthralgia.[5] Vedolizumab can be administered intravenously or subcutaneously. Dose intensification, in which administration is increased from every 8 weeks to every 4 weeks, may be necessary and effective in 20% to 40% of patients.[6,7] The rates of exposure-adjusted incidence of any infections, upper respiratory tract infections, and lower respiratory tract and lung infections with vedolizumab were not increased compared with placebo.[8] Although clinical safety data in pregnancy are evolving, no signals have been reported.[9] Combination therapy with vedolizumab remains unproven, but may be beneficial, particularly in high-risk patients.

The SERENE trials evaluated whether a higher dose of adalimumab would improve outcome in patients with ulcerative colitis or Crohn's disease.[10,11] The higher dose was 160 mg given on weeks 0, 1, 2, and 3. The standard dose was 160 mg given on week 0 and 80 mg on week 2. From week 4, all patients received 40 mg every other week. There were no significant differences between the dosing strategies in terms of clinical remission at week 4 or endoscopic response at week 12 (Figure 8).

The novel anti-integrin etrolizumab selectively targets the β7 subunit of the integrins α4β7 and αEβ7. The phase 2 EUCALYPTUS trial investigated etrolizumab in patients with ulcerative colitis, finding it was associated with a higher rate of clinical remission at week 10 vs placebo.[12] Additional evaluation of this investigational agent in IBD is ongoing.

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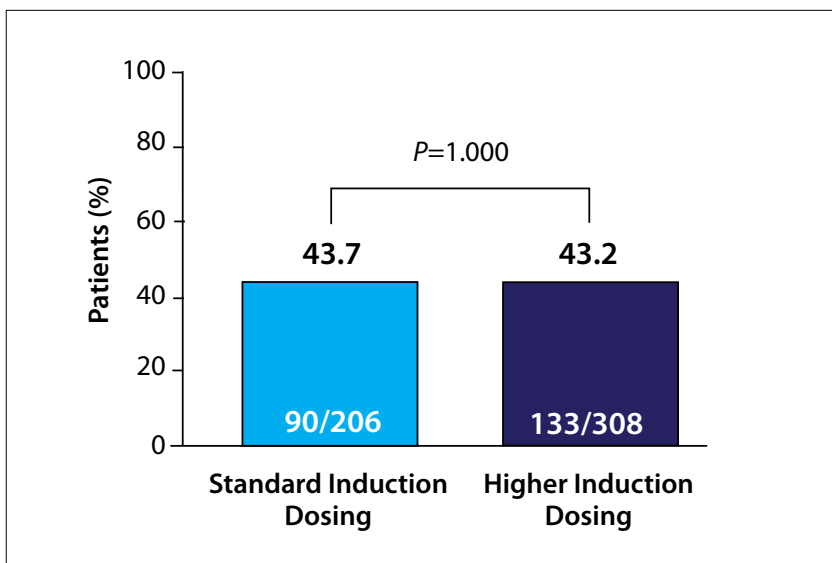
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A Practical Approach to Anti-TNFs in IBD 2020

Dr William J. Sandborn discussed anti-TNF therapy.[1] A systematic review and network meta-analysis assessed comparative efficacy and safety of first-line (biologic-naive) and second-line (previous exposure to anti-TNF agents) biologic therapy in patients with moderate to severe Crohn's disease.[2] Among biologic-naive patients, infliximab and adalimumab were associated with the highest ranking for induction of clinical remission, whereas adalimumab and ustekinumab were ranked highest among patients with prior exposure to anti-TNF agents. Among patients who achieved a response to induction therapy, adalimumab and infliximab had the highest ranking of maintenance of remission. Ustekinumab had the lowest risk of serious adverse events and infection during maintenance therapy.

Among patients with ulcerative colitis who were biologic-naive, infliximab and vedolizumab were ranked highest for induction of clinical remis-sion, as well as mucosal healing, in a similar systematic review and network meta-analysis.[3] In patients who had received previous treatment with anti-TNF therapy, tofacitinib was ranked highest for induction of clinical remission and mucosal healing (moderate quality of evidence). In patients with ulcerative colitis, vedolizumab was ranked safest in terms of serious adverse events and infection during maintenance therapy.

Anti-TNF agents, particularly infliximab, remain the preferred option for several patient groups, including hospitalized patients, patients with perianal fistulas, and patients who would benefit from prevention of postoperative recurrence of Crohn's disease. Switching to a different anti-TNF therapy in the second-line setting is not highly effective in patients with inflammatory bowel disease. This lack of efficacy may be related to the substantial immunogenicity seen with anti-TNF agents. Reactive and proactive therapeutic drug monitoring may prove useful, but data from the SERENE study suggested that dose escalation may be less effective than anticipated.[4] Anti-TNF agents are associated with a substantial risk for infection and lymphoma (Figure 9).[5] Highly effective agents without these risks are needed.

The anti-TNF agent landscape is changing with the increasing availability of biosimilar agents. These biosimilars appear to be similarly effective to the branded agents. For example, the biosimilar CT-P13 was shown to be noninferior to its originator, infliximab, in a double-blind phase 3 trial in patients with active Crohn's disease.[6]

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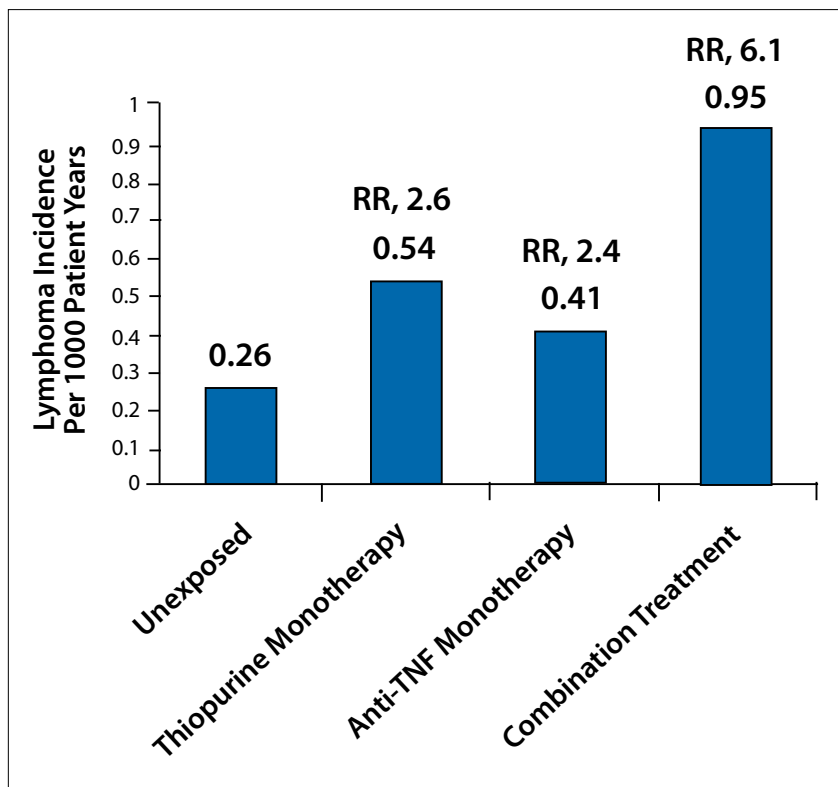
Figure 9. Risk of lymphoma among patients with inflammatory bowel disease according to treatment. RR, relative risk; TNF, tumor necrosis factor. Adapted from Lemaitre M et al. *JAMA.* 2017;318(17):1679-1686[5] and Sandborn WJ. A practical approach to anti-TNFs in IBD 2020. Paper presented at: Advances in Inflammatory Bowel Diseases Conference; December 12-14, 2019; Orlando, Florida.[1]

Highlights From the 2019 Advances in Inflammatory Bowel Diseases Conference: Commentary

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The annual Advances in Inflammatory Bowel Diseases (AIBD) conference provides an important forum that combines education sessions with presentation of new data. At the 2019 conference, experts in the field provided comprehensive reviews of current treatment options for patients with inflammatory bowel disease (IBD), such as anti-integrin therapy, anti-interleukins, Janus kinase (JAK) inhibitors, and anti–tumor necrosis factor (TNF) agents. Guideline updates were also presented. Several posters provided updates regarding the management of IBD.

Reviews of Treatment Classes

Dr Brian G. Feagan discussed anti-integrin treatment for patients with IBD.[1] Biologic therapies have changed clinical practice. Infliximab, an anti-TNF agent, was the first biologic approved by the US Food and Drug Administration (FDA) for IBD. Infliximab was approved in 1998 for the treatment of Crohn's disease.[2] The use of infliximab has evolved to optimize outcome. Initially, a single dose was given to treat luminal disease, and 3 doses were administered for fistulizing disease. It was recognized, however, that maintenance therapy is needed in both scenarios to optimize therapy. Infliximab is therefore now given as continued maintenance therapy, and not just episodic treatment.

Combination therapy with an anti-TNF agent (as was demonstrated with infliximab as the biologic agent) and azathioprine is superior to monotherapy with each agent. A 2015 study by Khanna and colleagues showed that combined immunosuppression decreased the time to hospitalization, surgery, and complications vs each therapy alone.[3] Rates of mortality, as well as disease- and drug-related complications, were numerically less with combination therapy. Data from the TREAT registry demonstrated that infliximab is associated with a risk of serious infections.[4] The key, however, is to initiate treatment with infliximab and avoid or withdraw corticosteroids. Corticosteroids have been shown to confer a significantly higher rate of mortality and morbidity. In the TREAT registry, risk factors for serious infections were highest with infliximab and corticosteroids. The hazard ratio was 4.73 (95% CI, 2.373-9.416) for the combination vs 2.12 (95% CI, 1.228-3.657) for infliximab alone.

Infliximab has been associated with hypersensitivity reactions, drug-induced lupus, and psoriasis-like lesions. In the TREAT registry, use of infliximab was not an independent risk factor for the development of lymphoma.[4] More recent data, however, suggested that monotherapy with an anti-TNF agent increased the risk of lymphoma by 2.4.[5] The concept of whether anti-TNF therapy use is associated with the development of lymphoma in IBD patients remains controversial.

Vedolizumab has been approved by the FDA for the treatment of both ulcerative colitis and Crohn's disease. Approval was based on the GEMINI studies, which showed that vedolizumab can induce clinical remission, durable clinical response, mucosal healing, durable clinical remission, and corticosteroid-free remission in these settings.[6,7]

Prior to 2019, there were no studies in patients with IBD comparing efficacy of one biologic agent to another. The VARSITY trial randomly assigned patients with active ulcerative colitis to vedolizumab or adalimumab at the labeled doses.[8] Twenty percent of the patients had received prior treatment with a TNF antagonist. This study is the only head-to-head, randomized, comparative effectiveness trial of biologic therapy in IBD. The study had a treat-through design. The primary endpoint was remission at week 52. Clinical remission at week 52 with mucosal healing was seen in 31.3% of the vedolizumab arm vs 22.5% of the adalimumab arm (P=.006). Rates of mucosal healing were similar, at 39.7% with vedolizumab vs 27.7% with adalimumab. Reports of mild, moderate, or severe adverse events were similar in both treatment groups.

It was exciting to see results from a trial that compared the efficacy of biologic therapies in IBD. There are now multiple ongoing comparative effectiveness trials. Data from these trials will help clinicians gauge which drug

is most effective for different clinical treatment scenarios (Table).

Vedolizumab is currently approved by the FDA as an intravenous formulation. Data from a phase 3 trial evaluating a subcutaneous formulation were recently submitted for approval.[9] This trial enrolled patients with moderately to severely active ulcerative colitis. Patients received open-label treatment with intravenous vedolizumab at 300 mg at weeks 0 and 2. Patients with a clinical response at week 6 were randomly assigned to maintenance treatment with subcutaneous vedolizumab at 108 mg every 2 weeks, intravenous vedolizumab at 300 mg every 8 weeks, or placebo. At week 52, the rates of clinical remission were 46.2% for subcutaneous vedolizumab, 42.6% for intravenous vedolizumab, and 14.3% for placebo.

The onset of clinical benefit is relatively rapid in patients with ulcerative colitis, but somewhat slower in Crohn's disease.[8,10] In the GEMINI 2 trial of patients with Crohn's disease, differences emerged between patients treated with vedolizumab vs placebo at 2 weeks.[10] Benefits were maintained in patients with extraintestinal manifestations. Dr Feagan noted that an analysis of the GEMINI data showed no

evidence that vedolizumab increased risk of arthralgias and arthritis; rather, there was a benefit.[11-13]

The SERENE trials evaluated whether a higher dose of adalimumab would improve benefit in patients with ulcerative colitis or Crohn's disease.[14,15] The same dosing strategies were used for both patient populations. The higher dose was 160 mg on weeks 0, 1, 2, and 3, and the standard dose was 160 mg on week 0 and 80 mg on week 2. From week 4, all patients received 40 mg every other week. Similar rates of clinical remission at week 4 and endoscopic response at week 12 were seen with the higher dose compared with the standard dose.

Several studies of vedolizumab in pregnancy were recently published.[16-18] Dr Feagan noted that there appears to be no safety signal in this setting. He also emphasized the low rate of immunogenicity in the trials of vedolizumab.

Dr Feagan reviewed data on etrolizumab, a novel humanized monoclonal antibody, from the EUCALYPTUS trial. Etrolizumab is novel, given that it is a dual mechanism inhibitor. Specifically, it selectively binds the β7 subunit of the heterodimeric integrins α4β7 and αEβ7. This agent demonstrated benefit over placebo.[19]

Dr Bruce E. Sands presented data on anti-interleukin biologic therapy.[20] Ustekinumab is a monoclonal antibody that inhibits the P40 component of the interleukin-12/23 complex, leading to inhibition of STAT3 and STAT4 downstream. Ustekinumab is approved by the FDA for the treatment of plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. The UNITI-1, UNITI-2, and the IM-UNITI maintenance trials evaluated ustekinumab among patients with Crohn's disease who were anti-TNF refractory or who required treatment after conventional therapy.[21] Ustekinumab has no black box warning for malignancy or infection.

The UNITI trials of patients with Crohn's disease evaluated intravenous ustekinumab at 2 doses: 130 mg or 6 mg/kg.[21] Ustekinumab was associated with a significantly higher rate of response vs placebo. The IM-UNITI trial evaluated subcutaneous ustekinumab at 90 mg every 12 weeks or every 8 weeks compared with placebo.[21] At week 44, rates of clinical remission were 48.8%, 53.1%, and 35.9%, respectively (*P*=.040 for the first comparison and *P*=.005 for the second). Patients treated with ustekinumab were significantly less

Table. Ongoing Comparative Effectiveness Trials of Biologic Therapies for the Treatment of Inflammatory Bowel Disease

Trial Name	Agents Studied	Disease	Anticipated Trial Completion Date	ClinicalTrials.gov Identifier
GARDENIA	Etrolizumab vs infliximab	UC	2020	NCT02136069
HIBISCUS I	Etrolizumab vs adalimumab	UC	2020	NCT02163759
VEGA	Guselkumab + golimumab vs guselkumab vs golimumab	UC	2021	NCT03662542
EXPEDITION	Brazikumab vs vedolizumab vs placebo	UC	2022	NCT03616821
SEAVUE	Ustekinumab vs adalimumab	CD	2021	NCT03464136
INTREPID	Brazikumab vs adalimumab vs placebo	CD	2022	NCT03759288
VIVID-1	Mirikizumab vs ustekinumab vs placebo	CD	2023	NCT03926130
GALAXI	Guselkumab vs ustekinumab vs placebo	CD	2026	NCT03466411

CD, Crohn's disease; UC, ulcerative colitis.

likely to require corticosteroids. The use of immunomodulators did not impact treatment outcomes. These data led to regulatory approval.

Throughout the studies, investigators measured trough serum concentrations of ustekinumab. The appropriate cutoff level for ustekinumab was less clear than the ones used for anti-TNF agents. However, patients in the highest quartile of ustekinumab drug levels had the best response, whether assessing a reduction in the Simple Endoscopic Score for Crohn's Disease or endoscopic remission. Ustekinumab is now routinely used in the induction and maintenance settings in clinical practice. In a 2017 real-world study by Ma and colleagues, ustekinumab was associated with clinical remission and corticosteroid-free objective remission at 3, 6, and 12 months, as well as at the end of follow-up.[22] This treatment is clearly beneficial. Dr Sands noted that fistula resolution ranged from 24% to 28% in an analysis of data from the UNITI-1 and UNITI-2 trials.[21] Fistula resolution, a secondary endpoint in the trials, is an important aspect of patient care.

Ustekinumab recently gained FDA approval for the treatment of ulcerative colitis.[23] The UNIFI study randomly assigned patients to treatment with ustekinumab at the standard intravenous dose of 130 mg, ustekinumab at approximately 6 mg/kg, or placebo.[24] The ulcerative colitis patient population evaluated in this study was relatively refractory. Patients could receive concomitant corticosteroids or immunomodulators. The primary endpoint of clinical remission at week 8 (defined as a Mayo score ≤2, with no individual subscore >1) was met by 15.6% of patients receiving ustekinumab at 130 mg and 15.5% of those receiving the 6 mg/kg dose, vs 5.3% of patients treated with placebo ($P<.001$ for both comparisons). Patients without prior biologic failure had a better outcome, as has been noted with most other biologics in clinical trials. Endoscopic "healing" in clinical response was clearly superior among patients treated with ustekinumab. The relatively novel endpoint of histo-endoscopic mucosal healing at week 8 was reached by 20.3% of the 130 mg arm and 18.4% of the 6 mg/kg arm, vs 8.9% of the placebo arm ($P<.001$ for both comparisons). This endpoint refers to an endoscopic Mayo score of 0 or 1, no more than 5% neutrophils in the epithelium, and no crypt destruction, erosions, ulcerations, or granulations.

The question has arisen regarding whether this endpoint should be a new standard in trials. In a population of asymptomatic patients in clinical remission who are undergoing routine surveillance colonoscopy (based on an endoscopy subscore of 0 or 1), the finding of persistent microscopic inflammation would not necessarily mandate that a practitioner switch therapy from mesalamine to a biologic agent. In this scenario, however, it might be reasonable to escalate the dose of mesalamine (or, similarly, to optimize the biologic agent [while maintaining use of the same agent]).

In the UNIFI study, patients who received ustekinumab had improvements in the partial Mayo score and fecal calprotectin through week 8.[24] Rates of clinical remission at week 44—whether defined as the primary endpoint of clinical remission or corticosteroid-free secondary remission—were 38.4% among patients receiving 90 mg of ustekinumab every 12 weeks, 43.8% among patients receiving 90 mg of ustekinumab every 8 weeks, and 24.0% among patients receiving placebo ($P=.002$ for the first comparison and $P<.001$ for the second). Rates of clinical and endoscopic response were also superior compared with placebo. All of these endpoints have direct implications for clinical practice. In a long-term extension study, patients in the intention-to-treat group with an inadequate response to therapy at week 92 could have their dose adjusted. Ustekinumab was associated with a durable response, which is important for clinical practice.

The rates of serious adverse events were low. Ustekinumab was relatively safe overall. No malignancies were reported. In the UNIFI trial of patients with ulcerative colitis, the rates of serious infections were 3.5% with 90 mg every 12 weeks and 1.7% with 90 mg every 8 weeks, vs 2.3% with placebo.

To summarize, ustekinumab has been demonstrated to have a favorable safety profile and has been shown to be effective for the treatment of

ABSTRACT SUMMARY Efficacy and Safety of Ustekinumab in Patients With Moderate to Severe Crohn's Disease: a Real World Study in Brazil

An open-label, prospective, multicenter study evaluated the real-world efficacy and safety of ustekinumab in Brazilian patients with moderate to severe Crohn's disease (Abstract P065). The study included 161 patients. At baseline, many patients were anemic (55.5%), with a mean CRP level of 21.3 mg/L (interquartile range, 0.08-125) and a mean Harvey-Bradshaw Index (HBI) of 10.1 (interquartile range, 2-19). Most patients had received previous treatment with anti-TNF therapy (85.7%). The clinical response rate to ustekinumab (defined as a decrease of ≥3 points in the HBI) was 76.9% at week 8. The rate of clinical remission (defined as an HBI score of ≤3) improved from week 8 (38.9%) through week 48 (62.5%). The proportion of patients with an elevated CRP level significantly decreased over the same period. Several factors were significantly associated with better outcomes, including Montreal system–scored inflammatory behavior (B1), no previous exposure to biologic therapy, and disease duration of 2 years or less. No new safety signals were reported.

Crohn's disease and ulcerative colitis. Ustekinumab can be initiated as a first-line biologic agent, as well as given to patients previously treated with anti-TNF therapy. The onset of effect is as early as 2 weeks, and this effect can increase over the next 4 months and beyond. Ustekinumab has a very good corticosteroid sparing and maintenance effect. Among patients with Crohn's disease, the rate of endoscopic response is approximately 25% at 8 weeks and 50% at 6 months. In a real-world analysis, the rate of endoscopic response in ulcerative colitis was approximately 50%. In post hoc analyses, less than a third of patients had fistulas. These impressive data have led to the addition of ustekinumab to the medical armamentarium for treatment of patients with Crohn's disease and ulcerative colitis.

Dr Edward V. Loftus Jr reviewed data on the JAK inhibitors.[25] Inhibition of JAK1, JAK2, JAK3, and TYK2 impacts different cytokines. Tofacitinib is approved by the FDA for the treatment of moderate to severe ulcerative colitis. This agent improves outcomes at 8 and 52 weeks, and it induces and maintains remission.[26] The FDA recently suggested that the use of tofacitinib is associated with thromboembolism. The FDA required a safety study of tofacitinib in patients with rheumatoid arthritis who are older than 50 years and have at least 1 cardiovascular risk factor. The study evaluated tofacitinib at doses of 5 mg or 10 mg twice daily. An interim analysis led to discontinuation of the 10 mg twice-daily arm, which was associated with a higher rate of thromboembolism. The same association has not been reported in patients with ulcerative colitis. However, based on these data, the FDA has suggested that practitioners avoid the 10 mg twice-daily dose in patients with ulcerative colitis, when possible.[27] Tofacitinib is not an effective treatment for Crohn's disease.[28]

Filgotinib is a selective JAK1 inhibitor administered orally. The phase 2 FITZROY study showed a clear benefit of filgotinib (200 mg) vs placebo for patients with moderately to severely active disease who had been treated with other agents.[29] Upadacitinib, similar to filgotinib, is an orally administered selective JAK1 inhibitor. A study of upadacitinib evaluated several dosing strategies: 3 mg, 6 mg, or 12 mg twice daily, or 24 mg once daily. The study enrolled patients with Crohn's disease who had an inadequate response to immunosuppressive therapy or an anti-TNF agent. Upadacitinib improved clinical and endoscopic remission, clinical response, and endoscopic response. Preliminary data on corticosteroid-free remission appear to be promising. Adverse events included 1 case of herpes zoster, which is a class effect for these agents. There were no perforations. Upadacitinib is also effective in patients with ulcerative colitis.[30,31] Large phase 3 clinical trials will provide more insight into the benefit of this drug.[32,33]

TD-1473 is a pan-JAK inhibitor with colonic release. In a phase 1b study of patients with moderately to severely active ulcerative colitis, TD-1473 improved clinical response, endoscopic healing, rectal bleeding, and endoscopy subscores in patients with active ulcerative colitis.[34] It will be important to assess which patients benefit most from each of these JAK inhibitors, and whether adverse events differ based upon patient profiles. JAK inhibitors provide a potent, fast-acting mechanism of action that reduces inflammation in patients with IBD. Selective JAK1 inhibition seems to have efficacy in moderately to severely active Crohn's disease.

Dr William J. Sandborn discussed data on anti-TNF therapy.[35] A highlight of his discussion was the recent data for a network meta-analysis evaluating inductive pharmacotherapy for moderate to severe Crohn's disease.[36] The analysis showed that infliximab and vedolizumab had somewhat higher rates of efficacy in patients who were naive to biologic therapies. Tofacitinib was associated with better outcomes in the second-line settings. However, Dr Sandborn noted that this analysis is outdated already, as it lacks studies of ustekinumab. Dr Sandborn emphasized that a network meta-analysis does not substitute for prospective randomized comparative effectiveness trials.

A 2003 report by Baert and colleagues showed that patients who develop immunogenicity to infliximab had shortened intervals of effectiveness and lessened durations of response.[37]

ABSTRACT SUMMARY Biosimilar BI 695501 Demonstrates Non-Inferior Efficacy and Comparable Safety to Adalimumab Reference Product in Patients With Active Crohn's Disease

A double-blind, multicenter, randomized, noninferior, phase 3 trial compared the biosimilar BI 695501 with its reference product, adalimumab, in 140 patients with moderate to severe Crohn's disease (Abstract P052). Patients had a disease duration of at least 4 months, mucosal ulceration, and a CDAI score between 220 and 450. Patients were either naive to anti-TNF agents, or had previously developed resistance or intolerance to infliximab. The primary endpoint of a CDAI response at week 4 (defined as a ≥70-point decrease in CDAI from baseline) was reported in 89.7% of the BI 695501 arm and 94.4% of the adalimumab arm. This difference corresponds to a risk ratio of 0.945 (90% CI, 0.870-1.028). The lower bound of the 90% CI was higher than 0.76, the exploratory noninferiority limit. Similar safety profiles were observed with the 2 agents to week 24. There were no unexpected safety signals.

Several studies have provided further insights since that time. Immunogenicity can be seen with all treatments, particularly anti-TNF agents. Dr Sandborn discussed therapeutic drug monitoring. To date, the best evidence supports a reactive, rather than proactive, approach to therapeutic drug monitoring. However, studies of the proactive strategy that showed negative results may have been limited by flaws in the trial design. This area is still under investigation.

Measurement of biologic drug levels can help provide insight into patient prognosis. In general, patients with higher drug levels have a better outcome. During treatment with anti-TNF agents, levels of serum albumin are a strong predictor of response. The SERENE trials recently compared adalimumab induction therapy at the standard dose (160 mg on week 0 and 80 mg on week 2) vs a higher dose (160 mg on weeks 0, 1, 2, and 3) for patients with Crohn's disease or ulcerative colitis.[14,15] The primary endpoints were clinical remission and endoscopic response. Rates of endoscopic improvement and fecal calprotectin less than 150 μg, as well as scores on the Inflammatory Bowel Disease Questionnaire, did not differ between the treatment arms. Clinical response, but not endoscopic remission, was better with the higher dose in patients with ulcerative colitis. The SONIC trial reviewed the efficacy of combination therapy.[38] Patients treated with infliximab plus azathioprine or infliximab monotherapy were more likely to achieve corticosteroid-free remission than patients receiving azathioprine monotherapy.

Recent data have highlighted that higher serum anti-TNF levels are associated with perianal fistula healing and fistula closure in patients with Crohn's disease.[39] This strategy has been used in clinical practice since the initial SENTINEL trial was reported 20 years ago.[40] A 2016 study showed that infliximab was not superior to placebo in preventing clinical recurrence after resection related to Crohn's disease.[41] Infliximab did reduce rates of severe endoscopic recurrence.

Dr Sandborn concluded that anti-TNF agents are an important first-line therapy for the treatment of patients with Crohn's disease. After the initial use of a TNF antagonist, subsequent use of anti-TNF therapy as second-line therapy is less effective. Anti-TNF therapy is immunogenic. Optimally, it is administered as a component of combination therapy. In the SONIC trial, anti-TNF therapy was administered with azathioprine.[38] Combination therapy was more effective than monotherapy with each agent. Reactive and proactive therapeutic drug monitoring can be used to guide treatment. The SERENE data suggested that dose escalation might be less effective than previously thought in patients who are receiving adalimumab.[14,15]

Guideline Update

Dr Ashwin N. Ananthakrishnan discussed updates to the American College of Gastroenterology guidelines for the management of ulcerative colitis.[42,43] He reviewed diagnosis, induction, maintenance, and management of acute and severe colitis, as well as cancer surveillance. Dr Ananthakrishnan noted that during diagnosis, it is important to exclude pathogens such as *Clostridium difficile*. Current data do not support the use of serologic antibody testing for diagnosis or predicting prognosis. Diagnostic assessment should include biomarkers such as C-reactive protein, fecal calprotectin, and fecal lactoferrin. These levels should be tested throughout treatment to see if they parallel disease activity. Not all patients have high levels of C-reactive protein or calprotectin. In a recent meta-analysis, the sensitivity for assessing disease activity in patients with ulcerative colitis was 49% for C-reactive protein, 82% for lactoferrin, and 88% for fecal calprotectin.[44] Measurement of these biomarkers may provide a way to track the disease course.

It is important to assess whether the patient is in remission, or has mild, moderate, or severe disease activity. Disease activity can inform prognosis. Patients have more aggressive disease and a higher risk of colectomy if they have low serum albumin, have elevated serum C-reactive protein, were hospitalized for colitis, have a Mayo subscore of 3, have an Ulcerative Colitis Endoscopic Index of Severity score of 7 or higher, or are younger than 40 years.[42,43]

ABSTRACT SUMMARY Patterns of Care Among Patients Treated With Ustekinumab for Crohn's Disease: Results From a Chart Review

Ruetsch and colleagues described findings from a retrospective chart review of 100 patients with Crohn's disease who initiated ustekinumab and completed at least 6 months of treatment (Abstract P037). Patients were drawn from 7 US gastroenterology practices. Most patients were female (65.0%). Their mean age was 42.2 ± 14.9 years. Previous treatment with biologic therapy was reported in 82.0%. These treatments included adalimumab in 49.1%, vedolizumab in 21.1%, infliximab in 17.5%, and certolizumab pegol in 12.3%. More than half of patients (54.9%) had received at least 2 biologic agents before starting ustekinumab. The most frequent reason for initiating ustekinumab among patients with prior biologic agent exposure was secondary loss of response to treatment (48%). The most frequent reason in patients who were biologic-naive was nonresponse to treatment (with a physician recommendation based on symptoms). Nearly half of the charts (44%) reported no laboratory results or testing before or after initiation of ustekinumab. Only 2 charts recorded endoscopic scores.

Treatment goals for patients with ulcerative colitis include normal bowel frequency and control of bleeding and urgency. A patient who is able to achieve mucosal healing (a Mayo score of 0 or 1) has an increased chance of sustained corticosteroid-free remission and decreased risks of hospitalizations and surgery. Histologic healing is a desirable, although not mandatory, endpoint. Measurement of calprotectin can be used as a surrogate when endoscopy is not available or feasible. Calprotectin levels can provide insight into whether the mucosa is improving. The use of mesalamine is effective in patients with active ulcerative colitis. Corticosteroids plus budesonide MMX might be considered for patients who do not respond or have a partial response.

Dr Ananthakrishnan reviewed the subsequent use of biologics in patients with ulcerative colitis. Approved therapies include the anti-TNF agents infliximab, adalimumab, and golimumab; vedolizumab; ustekinumab; and tofacitinib. Tofacitinib is approved as a pill formulation. Initial dosing is 10 mg orally twice daily for 8 weeks. If this treatment is beneficial, then attempting to lower the dose to 5 mg orally twice daily is advocated. If no benefit is observed after 8 weeks, then further observation at 10 mg orally twice daily is recommended. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent.

Data from the OCTAVE trials demonstrated that tofacitinib can induce remission in patients with active ulcerative colitis.[26] Data from the comparative effectiveness VARSITY trial showed that vedolizumab was superior to adalimumab in inducing and maintaining remission.[8]

Dr Ananthakrishnan discussed the role of therapeutic drug monitoring among patients who do not respond to treatment. When patients have low trough levels but no antibodies, the dose must be optimized. Among patients with high titers of antidrug antibodies, options include an alternate anti-TNF agent, an anti-integrin, or an interleukin 12/23 antagonist. If the patient has adequate trough levels but is not responding, then the treatment is inadequate and the case is considered a mechanistic failure.

During the initial care of these patients, the clinician should check for *C difficile*, document disease activity, exclude cytomegalovirus (by means of endoscopic mucosal biopsy), and provide deep venous thrombosis prophylaxis when appropriate. Broad-spectrum antibiotics or total parenteral nutrition can be used when needed. If the patient did not respond to oral corticosteroids, then parenteral administration can be considered. Biologics such as infliximab or cyclosporine might be considered as salvage therapy in patients who fail parenteral corticosteroids. Patients should undergo surveillance for colorectal cancer after 8 years of disease, and then subsequently every 1 to 3 years (with targeted biopsies of raised lesions). It is uncertain whether segmental, random biopsies are required. In a French study of approximately 1000 colonoscopies, the yield for random biopsies was low, identifying an additional 1.2% of patients.[45] Among patients with neoplasia, segmental random biopsies had a yield of 12.8%.

When using high-definition colonoscopy, narrow-band imaging or dye spray chromoendoscopy with methylene blue or indigo carmine is preferred. When the dysplasia is discrete or has been removed, colectomy may not be needed. In these cases, the surveillance intervals should be shortened. Colectomy should be considered in cases of unresectable or multifocal dysplasia.

Posters of Interest

Dr Kelly Y. Chun and coworkers evaluated ustekinumab levels in more than 2000 patient samples.[46] Antibodies to ustekinumab were present in 4%. There was an inverse relationship between trough ustekinumab drug levels and anti-ustekinumab antibody concentrations. The therapeutic range is not yet confirmed. The range appears to be in the single digits—1 µg/mL, 2 µg/mL, or 4 µg/mL—and therefore clinicians should try to choose an assay with adequate sensitivity. This analysis suggests that therapeutic drug monitoring for ustekinumab requires better target concentrations.

A retrospective chart review by Dr Charles Ruetsch and colleagues evaluated patterns of care among 100 patients treated with ustekinumab.[47] More than 80% of patients had documented prior use of another biologic. More than 90% of patients who begin treatment with ustekinumab receive it for at least 6 months. Most patients had no ongoing Crohn's disease–related complications. Six months before the initiation of ustekinumab, 15% of patients were using corticosteroids. This rate decreased to 6% by 6 months after initiation of ustekinumab. More than half of patients did not have laboratory results. Only 2 patients had undergone endoscopic examination during the study period. This last finding is of interest because many clinicians advocate—albeit without evidence-based data—that patients treated with biologic therapy undergo monitoring for relevant laboratory parameters at least every 3 months.

Dr Stephen B. Hanauer and colleagues evaluated whether BI 695501, a biosimilar to adalimumab, was noninferior to the reference product in patients with moderate to severe Crohn's disease.[48] Rates of clinical response and remission at week 4 were high in this control study. The biosimilar had noninferior efficacy compared with adalimumab after 4 weeks. There were no unexpected safety signals, which is comforting, although the primary aim of this study was not to assess safety.

A real-world study from Brazil evaluated the ability of ustekinumab to induce and maintain remission and to improve laboratory studies among patients with moderate to severe Crohn's disease.[49] Patients who were refractory to anti-TNF therapy

did well. Both induction and maintenance regimens were well-tolerated by patients. The safety and efficacy profiles provide further support for the use of ustekinumab in clinical practice.

Disclosure

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