Etiology and Management of Lack or Loss of Response to Anti–Tumor Necrosis Factor Therapy in Patients With Inflammatory Bowel Disease

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Abstract: The management of patients with moderate to severe inflammatory bowel disease was transformed with the arrival of anti–tumor necrosis factor (TNF) therapy. Nevertheless, a considerable number of patients do not respond to anti-TNF induction therapy (primary nonresponse) or lose response to treatment over time after initially experiencing clinical improvement (secondary loss of response). Studies suggest that these outcomes are often due to inadequate drug concentrations. Therapeutic drug monitoring (TDM) is a practical tool that can be used to better define the etiologies of and help manage primary nonresponse or secondary loss of response. Proactive TDM, or drug titration to a target trough concentration, can improve the efficacy of anti-TNF treatment and lead to favorable clinical outcomes. However, in patients with adequate anti-TNF drug concentrations and active disease, alternate pathways of inflammation (not driven by TNFα agents) are at play, and therapies with another mechanism of action should be employed.

Keywords
Primary nonresponse, secondary loss of response, therapeutic drug monitoring, antidrug antibody

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, progressive immune-mediated disease of the gastrointestinal tract. Inflammation is a result of a dysregulated immune response that leads to a cascade of inflammatory cells and cytokines that have become the hallmark targets for therapies. The introduction of the first biologic agent directed against the cytokine anti–tumor necrosis factor (TNF) α 2 decades ago[1] and agents since have revolutionized the treatment of IBD. Despite newer therapies, anti-TNF agents remain an important part of the therapeutic armamentarium for first-line treatment of moderate to severe IBD.[2,3] However, anti-TNF agents are not an effective therapy for a subset of patients with IBD who experience primary nonresponse (PNR). PNR to anti-TNF agents can be described as a lack of improvement in clinical signs or symptoms after the induction phase, leading to discontinuation of the medication. The incidence of PNR has been reported to occur in 10%

to 40% of patients depending on disease type and trial design.[4] In patients who initially respond to anti-TNF therapy, secondary loss of response (SLR) may prompt intensification or discontinuation of treatment in up to 50% of patients after 12 months on therapy.[5] SLR can be defined as worsening symptoms attributable to active IBD during maintenance therapy in a patient who previously had disease control after induction treatment. It is important to note that patients may also develop a serious adverse reaction to anti-TNF therapy that may include infection, dermatologic issues (eg, refractory psoriasis-like rash), and infusion- or injection-site reactions necessitating drug cessation.

Both PNR and SLR to anti-TNF agents can mainly be explained by pharmacokinetic issues related to undetectable or subtherapeutic drug concentrations with or without antidrug antibodies (ADAs). Therapeutic drug monitoring (TDM), defined as the evaluation of drug concentration and ADAs, can be performed to assess the etiology and management of PNR or SLR. Reactive TDM is commonly practiced when patients are not responding to or are flaring while on treatment to better rationalize management and determine if there will be a benefit from dose escalation vs an alternative treatment strategy. Proactive TDM is the practice of drug titration to a target trough concentration with the goal of optimizing circulating drug concentrations. Proactive TDM is emerging as an important tool to better optimize dosing with anti-TNF therapy during induction and maintenance, improve outcomes, and avoid drug discontinuation. When patients are found to have adequate drug trough concentrations but do not respond to treatment, changing to a therapy with an alternate mechanism of action is warranted.

Primary Nonresponse

Anti-TNF agents approved for the treatment of moderate to severe IBD include infliximab (indicated for CD and UC), adalimumab (indicated for CD and UC), golimumab (Simponi, Janssen; indicated for UC), and certolizumab pegol (Cimzia, UCB; indicated for CD). All agents have been shown to induce and maintain clinical remission, achieve mucosal healing, and improve quality of life. However, 10% to 40% of patients do not respond to treatment with anti-TNF therapy.[4] Rates of PNR to anti-TNF therapy may vary based on definition and the design of the study (Table 1).[6-16] Furthermore, some patients may exhibit only a partial response to initial therapy but fail to achieve remission (primary nonremission). The etiologies of PNR to anti-TNF agents are not clearly defined; however, mechanisms appear to be similar to those involved in SLR, including pharmacokinetic and pharmacodynamic issues.

Pharmacokinetic Failure

Pharmacokinetic issues are related to undetectable or subtherapeutic drug concentrations due to either rapid nonimmune clearance or immunogenicity and the development of ADAs. The ability of the monoclonal antibody to completely saturate the target antigen can affect both the clearance and half-life of the agent. At high doses, the monoclonal antibody is able to progressively saturate the target antigen, leading to an increased half-life and decreased clearance, while at low doses, the monoclonal antibody does not saturate the antigen, resulting in a shortened half-life and more rapid clearance.[17] This concept appears to parallel what is observed in patients with a higher inflammatory burden marked by elevated C-reactive protein and TNF levels with insufficient circulating anti-TNF drug concentrations. Studies for certolizumab pegol,[18] adalimumab,[19] and infliximab[20,21] have all shown that higher C-reactive protein levels (higher inflammatory burden) correlate with lower drug concentrations and worse outcomes. Another possible explanation for low anti-TNF drug concentrations in patients with severe disease is the loss of drug through an ulcerated gastrointestinal tract. In a small prospective study of 30 biologic-naive patients with moderate to severe UC treated with infliximab, 66% of stool samples at 2 weeks contained measurable concentrations of infliximab, and patients who were nonresponders had higher measurable fecal concentrations of infliximab compared to patients with clinical response (5.01 μg/mL vs 0.54 μg/mL, respectively; P=.0047).[22] Low circulating drug concentrations may also be the result of immune-related clearance via the development of ADAs. These antibodies bind to the circulating drug, neutralize its effect, and ultimately lead to increased clearance. ADAs can develop early during the induction phase and significantly impact treatment success. A study involving 125 patients with IBD demonstrated that 90% of patients treated with infliximab who develop antibodies to infliximab (ATI) do so within the first 12 months of therapy, and ATI can be detected by as early as 2 weeks (interquartile range, 0.5-5.5 months).[23] The presence of ATI of any value was significantly predictive of undetectable drug concentrations; however, this correlation with undetectable drug concentrations was more robust for more than 8 mcg/mL-eq of ATI.[23] Similarly, a prospective study of 19 patients with moderate to severe UC who were treated with induction infliximab therapy showed that the development of ATI occurred by as early as 18 days (median, 28 days; interquartile range, 18-42 days).[24] The 7 patients who developed ATI had higher C-reactive protein levels and lower serum infliximab concentrations, which were associated with PNR to treatment.[24]

Table 1. Reported Rates of PNR to Anti-TNF Agents in Patients With Inflammatory Bowel Disease

Anti-TNF Agent	Disease	Study Design	PNR, %	Definition of Response
Infliximab	CD	RCT[7]	42	≥70-point decrease in CDAI score from baseline and ≥25% reduction in the total score assessed at week 2 after a single infusion
	UC	RCT[8]	31	Decrease in Mayo score by ≥3 points and ≥30% from baseline, with an accompanying decrease in the rectal bleeding subscore by ≥1 point or an absolute rectal bleeding subscore of 0 or 1 assessed at week 8 after 3 doses
	CD	Cohort[9]	11	Symptom-free (complete response) or distinct clinical improvement with obvious decrease of disease activity (partial response) assessed within 10 weeks
	UC	Cohort[10]	18	No clinical improvement based on Truelove and Witts scale by ≥1 category compared with disease severity at the start of infliximab therapy assessed after induction
Adalimumab	CD	RCT[11]	42	≥70-point decrease in CDAI score from baseline assessed at week 4
	UC	RCT[12]	50	Decrease in Mayo score by ≥3 points and ≥30% from baseline, with an accompanying decrease in the rectal bleeding subscore by ≥1 point or an absolute rectal bleeding subscore of 0 or 1 assessed at week 8
	CD	Cohort[13]	18	Cessation of diarrhea and abdominal cramping and, in cases of patients with fistulae, cessation of fistula drainage and complete closure of all draining fistulae (complete response). Reduction in the amount of diarrhea and abdominal cramping and, in cases of patients with fistulae, a decrease in the drainage, size, or number of fistulae (partial response)
	UC	Cohort[14]	29	Decrease in Mayo score by ≥3 points and ≥30% from baseline, with an accompanying decrease in the rectal bleeding subscore by ≥1 point or an absolute rectal bleeding subscore of 0 or 1 assessed at week 12
Certolizumab pegol	CD	RCT[15]	63	≥100-point decrease in CDAI score with a baseline CRP level of ≥10 mg/L assessed at week 6
Golimumab	UC	RCT[16]	45	Decrease in Mayo score by ≥3 points and ≥30% from baseline (observed in the preceding induction study), with either a decrease in the rectal bleeding subscore by ≥1 point or a rectal bleeding subscore of 0 or 1

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; PNR, primary nonresponse; RCT, randomized, controlled trial; TNF, tumor necrosis factor; UC, ulcerative colitis.

During induction, subtherapeutic concentrations of anti-TNF agents due to nonimmune clearance appear to be one of the greatest risk factors for PNR. Patients with CD who received induction dosing with adalimumab at 160 mg followed by 80 mg vs those who received 80 mg followed by 40 mg had higher adalimumab serum concentrations at week 4 (11.6 vs 3.6 μg/mL, respectively), a higher rate of C-reactive protein normalization, and a lower incidence of PNR (odds ratio, 0.02; P<.001).[25] A small prospective study of 32 patients with moderate to severe CD showed that higher drug concentrations of infliximab (n=15) or adalimumab (n=17) correlated with response during induction.[26] After induction (week 14), the median trough concentration of anti-TNF agents was significantly higher in responders (infliximab, 5.6 μg/mL; adalimumab, 9.07 μg/mL) vs nonresponders (infliximab, 0.032 μg/mL; adalimumab, 2.62 μg/mL; P<.01). Furthermore, the positive predictive value of elevated trough concentrations (infliximab, >3 μg/mL; adalimumab, >4.5 μg/mL) for predicting adequate response and remission after induction was greater than 90%.[26] A small study of patients with moderate to severe UC found that primary nonresponders had a lower serum drug concentration at week 6 compared to responders (2.9 μg/mL vs 8.1 μg/mL, respectively; P=.03).[24] Most recently, a prospective, observational study on personalized anti-TNF therapy evaluated factors associated with treatment failure in 1610 CD patients either on infliximab or adalimumab.[27] The only factor that independently correlated with PNR was low drug concentration at week 14. Infliximab trough

Table 2. Risk Factors for PNR to Anti-TNF Therapy

Etiology	Risk for PNR to Anti-TNF Therapy
Drug-related factors	Low drug concentrations (pharmacokinetics): nonimmune clearance, immunogenicity (development of antidrug antibodies) Adequate drug concentrations (pharmacodynamics): mechanistic failure
Patient-related factors	Smoking, obesity
Disease-related factors	Longstanding disease (>2 years), isolated small bowel disease, upper gastrointestinal involvement, severe intestinal inflammation, hypoalbuminemia

PNR, primary nonresponse; TNF, tumor necrosis factor.

concentrations of at least 7 mg/L for infliximab and at least 12 mg/L for adalimumab were associated with clinical remission at week 14.

Pharmacodynamic Failure

Pharmacodynamic issues may also explain PNR to anti-TNF agents. In patients with ongoing inflammation despite adequate drug concentrations, the disease may be driven by a non-TNF–related inflammatory pathway. PNR due to pharmacodynamics in infliximab and adalimumab has been supported by evidence demonstrating altered transcriptional factors of inflammation. Leal and colleagues conducted an observational study on whole-genome transcriptional analysis using intestinal biopsy specimens from patients with CD receiving (n=12) or not receiving (n=10) anti-TNF therapy.[28] In order to exclude pharmacokinetics as a reason for PNR, patients with low drug concentrations of infliximab or adalimumab or detectable ADAs were excluded. Patients who responded to anti-TNF treatment had significant modulation in genes that included *IL1B*, *S100A8*, and *CXCL1*, while patients who did not respond had altered gene concentration expressions of *IL1B* and *IL17A*, suggesting these as potential alternative mediators driving refractory inflammation.[28]

Risk Factors for Primary Nonresponse

Several patient and disease characteristics have been identified as risk factors for PNR (Table 2). Smoking has been shown to negatively influence the disease course for CD and lead to poor outcomes. Active smokers treated with infliximab have been shown to have lower rates of response and a shorter duration of treatment.[29,30] Patients with a high body mass index also appear to have a lower response to anti-TNF agents. In a 2011 study assessing adalimumab dosing regimens for moderate to severe UC, patients who were given an induction dose of 160 mg followed by 80 mg and who weighed 82 kg or greater were found to have significantly lower clinical remission rates at week 8 compared to patients who weighed less than 82 kg (9.6% vs 24.0%, respectively).[19] Similar results have been demonstrated for obese patients treated with infliximab and found to have an increased clearance of drug,[31] as well as an earlier time to loss of response.[32] Low serum albumin levels are associated with diminished response to infliximab.[33] Duration of disease has been postulated to be an important factor dictating response to treatment, as it is felt that patients with shorter disease duration have less irreversible bowel damage and thus a higher response. In CD, post-hoc analyses from large clinical trials demonstrated that a disease duration of less than 2 years had a higher rate of response to either certolizumab pegol or adalimumab than longer-standing disease.[11,34] Location of disease also seems to be an important factor of response to treatment with anti-TNF agents in CD. Patients with isolated colonic CD appear to have a better response to infliximab,[35] whereas isolated small bowel or upper gastrointestinal involvement may confer an increased risk of PNR.[36]

Secondary Loss of Response

SLR clinically presents when a patient who was in remission on treatment develops symptoms that are proven to be attributable to active IBD. A meta-analysis of 39 adalimumab studies[37] and a systemic review of 16 infliximab studies[38] found that the annual risk for SLR was 20.3% and 13.0% per patient year, respectively. In order to diagnose SLR, practitioners must first objectively document increased disease activity attributable to IBD with biomarkers (eg, fecal calprotectin, C-reactive protein), endoscopy, and/or imaging. Other disorders that can mimic symptoms of active IBD, such as infections (eg, *Clostridium difficile*), fibrostenotic strictures, irritable bowel syndrome, bile-salt diarrhea, and small intestinal bacterial overgrowth, should be ruled out. A retrospective study of 150 patients with IBD found that 62% of patients who were reporting clinical symptoms with therapeutic infliximab concentrations had no evidence of active inflammation by endoscopic or radiographic assessment at that time.[39] Thus, any change in IBD treatment would have not been indicated. Once active IBD is confirmed, assessment of drug concentrations and antibody levels is appropriate for explaining and managing SLR. Reactive TDM is currently the recommended standard of care for optimizing anti-TNF therapy in IBD patients

with SLR.[40] Reactive TDM has been shown to be more cost-effective and to better direct care than empiric treatment optimization.[41]

SLR is most often due to inadequate drug concentrations with or without ADAs. Most patients with SLR (approximately 70%) have subtherapeutic drug trough concentrations, and roughly half of this patient population has no detectable ADAs, while approximately 30% of patients go on to develop SLR due to mechanistic failure.[42] Numerous studies have shown that lower drug concentrations and ADAs are associated with worse clinical outcomes, including SLR.[43-45] A prospective, observational study by Kennedy and colleagues demonstrated that treatment-naive patients with CD who were treated with either infliximab or adalimumab and had suboptimal drug concentrations at week 14 (<7 mg/L for infliximab and <12 mg/L for adalimumab) were at a high risk for immunogenicity and the development of ADAs, which subsequently led to lower drug concentrations and worse outcomes at week 54.[27]

Reactive TDM can be used to help determine the next best step for patients with SLR. If SLR is due to low or undetectable drug concentrations with no ADAs, the dose of the drug should be increased. High ADA and undetectable drug concentrations cannot be overcome by increasing the dose of the drug, and a switch to another anti-TNF agent or to a medication with a different mechanism should be considered. It is important to note that patients who develop ADAs to an anti-TNF agent are more likely to develop ADAs to a second anti-TNF agent.[46] In such a case, the addition of an immunomodulator or proactive TDM should be considered. However, not all ADAs are neutralizing, and some may be transient in nature and have no clinical significance. In a small cohort study of 125 IBD patients treated with infliximab, 26% of patients developed transient ATI that were no longer detectable within 2 consecutive infusions and were not associated with any need for change in therapy.[23] In patients with persistent low-titer ADAs (eg, ATI <10 U/mL for the homogeneous mobility-shift assay and <200 ng/mL for the second-generation enzyme-linked immunosorbent assays), these antibodies may be nonneutralizing and have no lasting impact, or further optimization of the original anti-TNF agent can overcome the ADAs.[43,47,48] A recent TDM guideline[49] recommends that in patients with SLR, infliximab or adalimumab generally should not be abandoned unless drug concentrations are more than 10 μg/mL. The Building Research in IBD Globally alliance developed a biologic therapy optimizer and published recommendations that could help clinicians with the appropriate utilization of TDM in various IBD clinical scenarios.[50] The most efficient mode of dose optimization, whether shortening the interval or increasing the dose, is not clear. Shortening the interval may result in an overall higher maintained drug concentration,[31] whereas some evidence suggests that increasing the dose may allow for higher peak concentrations of the drug to be achieved that may be more mechanistically important than prolonged nonpeaking concentrations.[51]

Proactive Therapeutic Drug Monitoring

Clinically, it makes more sense to optimize therapy before immunogenicity and/or loss of response develop rather than wait for these outcomes to occur. Proactive TDM is emerging as an important tool for optimizing biologic therapies, particularly the anti-TNF therapies. The concept of proactive TDM is to preemptively measure drug trough concentrations and dose to a target therapeutic concentration when patients are in clinical response or remission. The goal is to avoid subtherapeutic drug concentrations and the development of ADAs and, thus, improve short- and long-term outcomes. Low drug concentrations are typically the culprit in clinical loss of response regardless of ADA status, and lower or undetectable drug concentrations are associated with treatment failure and drug discontinuation.[52] Ensuring adequate drug concentrations seems to be of utmost importance in both the induction phase to prevent PNR as well as the maintenance phase to avoid SLR. A prospective study on anti-TNF therapy for biologic-naive patients with CD investigated pharmacokinetic factors that predicted PNR at week 14 and primary nonremission at week 54. The study demonstrated that adequate drug concentrations at week 14 (>7 mg/L for infliximab and >12 mg/L for adalimumab) were associated with clinical remission and a decreased chance for the development of ADAs and predicted better long-term outcomes.[27]

Numerous studies have shown an exposure–response relationship, suggesting a positive correlation between elevated serum anti-TNF concentrations and favorable therapeutic outcomes.[53-58] It remains unclear whether higher drug concentrations are needed to achieve mucosal healing or if the mucosal healing itself is associated with higher drug concentrations secondary to decreased disease activity, drug clearance, and/or fecal loss.[48] Furthermore, a large multicenter, retrospective study evaluating outcomes among patients with IBD who had received proactive vs reactive TDM found that proactive TDM led to less treatment failure and ATI and fewer IBD-related surgeries, hospitalizations, and serious infusion reactions.[59] An observational study of 126 patients with IBD with a median follow-up of 3.4 years showed that patients who were dose-optimized proactively to a therapeutic window of 5 to 10 μg/mL had markedly improved persistence on infliximab when compared with the standard-of-care

Table 3. Proactive TDM Drug Concentration Targets for Anti-TNF Agents After Induction and During Maintenance That Are Associated With Improved Outcomes

Anti-TNF Agent (Disease[s])	Postinduction Drug Trough Concentration Target[a]	Maintenance Drug Trough Concentration Target[a]
Infliximab (CD/UC)	Week 14 ≥3-7 μg/mL	≥3-7 μg/mL
Adalimumab (CD/UC)	Week 4 ≥5-10 μg/mL	≥5-10 μg/mL
Certolizumab pegol (CD)	Week 6 ≥32 μg/mL	≥15 μg/mL
Golimumab (UC)	Week 6 ≥2.5-7.5 μg/mL	≥1.0-3.2 μg/mL

CD, Crohn's disease; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor; UC, ulcerative colitis.

[a]The upper limit of the range refers to drug concentration thresholds associated with more stringent therapeutic outcomes, such as mucosal healing.

control group that underwent reactive TDM or empiric dose escalation.[60] Proactive TDM was also found to be beneficial in patients who previously underwent reactive TDM when compared to patients who had reactive TDM alone.[61] A landmark prospective, randomized, controlled trial by Vande Casteele and colleagues looked at the potential benefits of proactive TDM.[62] Patients included in the study were all optimized to an infliximab trough concentration of 3 to 7 μg/mL and then randomized to either infliximab dosing based on clinical symptoms, C-reactive protein, or continued proactive TDM dosing based on trough concentrations.[62] The primary endpoint of clinical remission at 1 year was not significantly different between the groups; however, the proactive TDM group had less undetectable drug concentrations, disease relapse, and need for IBD-related surgery or hospitalization compared with the clinically based dosing group. Furthermore, 1-time dose optimization in patients with low drug concentrations led to improved remission rates and C-reactive protein. Recently, Assa and colleagues investigated outcomes in biologic-naive children with CD who responded to adalimumab and were then randomized to either proactive or reactive treatment strategies.[63] The primary endpoint, sustained corticosteroid-free clinical remission, was significantly higher in the proactive TDM group compared to the reactive TDM group (82% vs 48%; P=.002). Secondary outcomes were also higher in the proactive TDM group (C-reactive protein, ≤0.5 mg/dL; Pediatric Crohn's Disease Activity Index, <10; and fecal calprotectin, ≤150 μg/g).

Less data are available on the role of proactive TDM during the induction phase even though this is likely where its use is most important, as the inflammatory burden is highest and thus drug clearance is greater, predisposing patients to low drug concentrations and the development of immunogenicity (Table 3). In both UC and CD, higher concentrations of anti-TNF drugs during and early after induction phase are associated with both short- and long-term therapeutic outcomes.[55,64-67] A retrospective study of 285 patients with refractory UC treated with infliximab showed that postinduction (week 14) median infliximab serum concentrations were higher in patients with C-reactive protein normalization (6.27 vs 2.02 μg/mL; P<.001), clinical response (5.96 vs 2.20 μg/mL; P<.001), and short-term mucosal healing (5.96 vs 1.74 μg/L; P<.001) compared to patients without these outcomes.[68] Higher induction infliximab concentrations at week 2 (>21.3 μg/mL) and at week 6 (>22.0 μg/mL) in patients with UC have also been associated with short-term clinical remission and response.[69,70] Similarly, in an observational study in patients with CD who previously failed to respond to infliximab and were treated with adalimumab, patients who then discontinued adalimumab had lower concentrations at week 2 (6.5 vs 10.4 μg/mL; P=.02) and week 4 (2.5 vs 5.9 μg/mL; P=.012) compared to patients who continued through maintenance therapy.[25] The current barriers to TDM in clinical practice include time lag from serum sampling to test results, appropriate interpretation of the results, clear therapeutic thresholds, insurance coverage, and the potential out-of-pocket cost to the patient.

Utility of Novel Therapies in Anti–Tumor Necrosis Factor–Refractory Patients

Medications that have recently been approved by the US Food and Drug Administration for IBD include ustekinumab (Stelara, Janssen), an inhibitor of interleukin

(IL) 12/23 indicated for both CD and UC[71]; vedolizumab (Entyvio, Takeda), an anti-α4β7 integrin indicated for both CD and UC; and tofacitinib (Xeljanz, Pfizer), an inhibitor of Janus kinase (JAK) and signal transducer and activator of transcription proteins indicated for UC. These newer therapeutic agents provide options for patients who have not achieved adequate response with anti-TNF agents despite adequate drug concentrations, and can also be used as potential first-line treatments. However, these drugs do not appear to work as well in patients who have already failed anti-TNF therapy. Management remains empiric, as currently there are no clinical recommendations and/or guidelines on how to manage IBD patients with PNR to anti-TNF therapy as well as which agent to move on to when patients have a mechanistic SLR. Some evidence has shown that PNR to anti-TNF therapy is associated with an inferior response to second-line non-TNF biologic agents compared with patients who discontinued therapy due to SLR or intolerance.[72] Recent work has focused on attempts to strategize and position these biologic agents and novel small molecules with the highest chance of efficacy for patients without prior treatment exposure. In a network meta-analysis for biologic-naive patients with moderate to severe CD, infliximab and adalimumab were ranked highest for induction and maintenance of remission.[73] Similarly, in a network meta-analysis for biologic-naive patients with UC, infliximab and vedolizumab ranked highest for induction of clinical remission.[74] Tofacitinib ranked highest for induction of clinical remission in patients with UC and prior anti-TNF exposure, although vedolizumab came in higher for safety. Limitations have recently been applied to tofacitinib use in patients with UC due to an increased risk for pulmonary emboli and death with twice-daily 10-mg dosing demonstrated in a postmarketing study in patients with rheumatoid arthritis.[75] Tofacitinib is now recommended for moderate to severe UC patients who have failed or are intolerant of anti-TNF therapy.

Recent clinical trials have included patients who previously failed anti-TNF therapies in addition to anti-TNF–naive patients. Patients previously exposed to anti-TNF therapy generally do not respond as well to the newer agents as do biologic-naive patients. In the GEMINI 1 trial of vedolizumab, over 40% of patients with UC were prior TNF failures.[76] Response rates at week 6 for vedolizumab vs placebo were 47% vs 25% (P<.001). However, a post-hoc analysis revealed that the rates of response at week 6 were 53% for patients naive to anti-TNF therapy and 39% for patients with prior anti-TNF failure.[77] The VICTORY Consortium looked at real-world experience of vedolizumab for UC and demonstrated on multivariable analysis that prior exposure to anti-TNF therapy was associated with a reduced probability of achieving both clinical and endoscopic remission.[78] In the GEMINI 2 study of vedolizumab in patients with CD, almost half of the cohort consisted of patients who had previously failed anti-TNF therapy. Week 6 clinical remission for vedolizumab vs placebo was 14.5% vs 6.8% (P=.02).[79] However, CD patients who had failed anti-TNF therapy had a rate of remission at week 6 of 15% compared to 12% of patients who were treated with placebo (P=.433).[80] The UNITI-1 trial,[81] which evaluated patients with CD and included a large number of patients with prior anti-TNF failure, had a week 6 response of 34.3% and 33.7% for patients treated with 130 mg or 6 mg/kg of ustekinumab, respectively, vs 21.5% for the placebo group. In UNITI-2, in which the majority of patients were naive to treatment, response to treatment was 52.7% and 55.0% for ustekinumab dosing of 130 mg or 6 mg/kg, respectively, vs 23.0% for placebo.[81]

For patients who fail multiple agents and classes, there are several late-stage studies underway looking at agents targeting alternate pathways of inflammation. These mechanisms include several selective adhesion molecule inhibitors, IL-23 inhibitors, JAK inhibitors, and sphingomyelinase modulators. Etrolizumab, a novel integrin inhibitor agent that is being tested for UC, specifically targets the β7 unit. This drug also may be able to predict which patients with UC would benefit the most by identifying certain messenger RNAs in the colon that predict response.[82] Risankizumab targets specifically the p19 subunit of IL-23 and showed a higher rate of clinical remission vs placebo at week 12 (31% vs 15%; P=.049) for patients with CD.[83] Brazikumab has the same p19 target and has been shown to have a higher rate of clinical response in patients with CD at week 8 than placebo (49.2% vs 26.7%; P=.010).[84] The small molecule agents upadacitinib and filgotinib, both JAK1 inhibitors, have shown promising results for patients with moderate to severely active CD.[85] Ozanimod is a small molecule being investigated in moderate to severe UC that modulates sphingosine-1-phosphate receptor and sphingosine-1-phosphate receptor 5 and reduces circulating lymphocytes and migration to the gastrointestinal tract.[86] It has been shown to have a higher rate of clinical remission at week 8 compared to placebo (16% vs 6%; P=.048).[86] With the growing number of available agents for IBD, it will be important moving forward for comparative effectiveness research to define optimal treatment strategies. The recent VARSITY trial evaluated the efficacy of vedolizumab intravenous to adalimumab subcutaneous in patients with UC head to head. Vedolizumab was found to be superior to adalimumab based on the primary endpoint, clinical remission at week 52 (31.3% vs 22.5%; P=.0061).[87]

Summary

Although the treatment options for IBD have greatly expanded, there remains a limited number of biologic agents approved for the treatment of IBD. Practitioners are charged with the task of positioning these agents correctly early on in moderate to severe disease to induce and maintain remission and to hopefully prevent further mucosal damage. Anti-TNF therapies remain at the forefront of treatment of both UC and CD. Nevertheless, up to 30% of patients treated with anti-TNF agents will show no clinical improvement (PNR), and up to 50% of patients who do respond will require a change in dose or cessation of medication (SLR). It is imperative to objectively confirm active IBD and rule out other etiologies for loss of response that may mimic a flare of IBD when considering both PNR and SLR. Higher drug concentrations of anti-TNF agents have been shown to lead to higher rates of favorable outcomes, while low drug concentrations and ADAs are associated with both PNR and SLR. Reactive TDM can rationalize reasons for PNR and SLR and facilitate therapeutic decision-making. Current data demonstrate that patients who fail anti-TNF therapies do not respond as well to subsequent agents, and, therefore, optimization of biologic therapies is of utmost importance. Proactive TDM and optimization of drug concentrations are evolving as important tools to improve outcomes in IBD.

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References

1. Kornbluth A. Infliximab approved for use in Crohn's disease: a report on the FDA GI Advisory Committee conference. *Inflamm Bowel Dis*. 1998;4(4):328-329.
2. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
3. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: management of Crohn's disease in adults. *Am J Gastroenterol*. 2018;113(4):481-517.
4. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev*. 2014;13(1):24-30.
5. Papamichael K, Cheifetz AS. Therapeutic drug monitoring in inflammatory bowel disease: for every patient and every drug [published online April 9, 2019]? *Curr Opin Gastroenterol*. doi:10.1097/MOG.0000000000000536.
6. Papamichael K, Gils A, Rutgeerts P, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. *Inflamm Bowel Dis*. 2015;21(1):182-197.
7. Hanauer SB, Feagan BG, Lichtenstein GR, et al; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-1549.
8. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353(23):2462-2476.
9. Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut*. 2009;58(4):492-500.
10. Russo EA, Harris AW, Campbell S, et al. Experience of maintenance infliximab therapy for refractory ulcerative colitis from six centres in England. *Aliment Pharmacol Ther*. 2009;29(3):308-314.
11. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65.
12. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142(2):257-265.e1-e3.
13. Swoger JM, Loftus EV Jr, Tremaine WJ, et al. Adalimumab for Crohn's disease in clinical practice at Mayo clinic: the first 118 patients. *Inflamm Bowel Dis*. 2010;16(11):1912-1921.
14. García-Bosch O, Gisbert JP, Cañas-Ventura A, et al. Observational study on the efficacy of adalimumab for the treatment of ulcerative colitis and predictors of outcome. *J Crohns Colitis*. 2013;7(9):717-722.
15. Sandborn WJ, Feagan BG, Stoinov S, et al; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*. 2007;357(3):228-238.
16. Sandborn WJ, Feagan BG, Marano C, et al; PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146(1):85-95.
17. Tabrizi MA, Tseng CM, Roskos LK. Elimination mechanisms of therapeutic monoclonal antibodies. *Drug Discov Today*. 2006;11(1-2):81-88.
18. Sandborn WJ, Schreiber S, Feagan BG, et al. Certolizumab pegol for active Crohn's disease: a placebo-controlled, randomized trial. *Clin Gastroenterol Hepatol*. 2011;9(8):670-678.e3.
19. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut*. 2011;60(6):780-787.
20. Hibi T, Sakuraba A, Watanabe M, et al. C-reactive protein is an indicator of serum infliximab level in predicting loss of response in patients with Crohn's disease. *J Gastroenterol*. 2014;49(2):254-262.
21. Magro F, Rodrigues-Pinto E, Santos-Antunes J, et al. High C-reactive protein in Crohn's disease patients predicts nonresponse to infliximab treatment. *J Crohns Colitis*. 2014;8(2):129-136.
22. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. *Gastroenterology*. 2015;149(2):350-355.e2.
23. Ungar B, Chowers Y, Yavzori M, et al; ABIRISK consortium. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. *Gut*. 2014;63(8):1258-1264.
24. Brandse JF, Mathot RA, van der Kleij D, et al. Pharmacokinetic features and presence of antidrug antibodies associate with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2016;14(2):251-258.e1-e2.
25. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology*. 2009;137(5):1628-1640.
26. Echarri A, Ferreiro R, Fraga-Iriso R, et al. Drug trough levels and primary nonresponse to antiTNF therapy in moderate-severe Crohn disease. Results of the Optimiza study. *Gastroenterology*. 2014;146(5):S-247.
27. Kennedy NA, Heap GA, Green HD, et al; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol*. 2019;4(5):341-353.
28. Leal RF, Planell N, Kajekar R, et al. Identification of inflammatory mediators in patients with Crohn's disease unresponsive to anti-TNFα therapy. *Gut*. 2015;64(2):233-242.
29. Parsi MA, Achkar JP, Richardson S, et al. Predictors of response to infliximab in patients with Crohn's disease. *Gastroenterology*. 2002;123(3):707-713.
30. Arnott ID, McNeill G, Satsangi J. An analysis of factors influencing short-term and sustained response to infliximab treatment for Crohn's disease. *Aliment Pharmacol Ther*. 2003;17(12):1451-1457.
31. Dotan I, Ron Y, Yanai H, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic

study. *Inflamm Bowel Dis*. 2014;20(12):2247-2259.
32. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2013;19(10):2118-2124.
33. Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. *Int J Clin Pharmacol Ther*. 2010;48(5):297-308.
34. Schreiber S, Colombel JF, Bloomfield R, et al; PRECiSE 2 Study Investigators. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. *Am J Gastroenterol*. 2010;105(7):1574-1582.
35. Vermeire S, Louis E, Carbonez A, et al; Belgian Group of Infliximab Expanded Access Program in Crohn's Disease. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in Crohn's disease. *Am J Gastroenterol*. 2002;97(9):2357-2363.
36. Flamant M, Roblin X. Inflammatory bowel disease: towards a personalized medicine [published online January 10, 2018]. *Therap Adv Gastroenterol*. doi:10.1177/1756283X17745029.
37. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *Am J Gastroenterol*. 2011;106(4):674-684.
38. Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. *Am J Gastroenterol*. 2009;104(3):760-767.
39. Afif W, Loftus EV Jr, Faubion WA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2010;105(5):1133-1139.
40. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology*. 2017;153(3):827-834.
41. Velayos FS, Kahn JG, Sandborn WJ, Feagan BG. A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. *Clin Gastroenterol Hepatol*. 2013;11(6):654-666.
42. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Technical Review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. *Gastroenterology*. 2017;153(3):835-857.e6.
43. Yanai H, Lichtenstein L, Assa A, et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clin Gastroenterol Hepatol*. 2015;13(3):522-530.e2.
44. Baert F, Kondragunta V, Lockton S, et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial. *Gut*. 2016;65(7):1126-1131.
45. Papamichael K, Vajravelu RK, Osterman MT, Cheifetz AS. Long-term outcome of infliximab optimization for overcoming immunogenicity in patients with inflammatory bowel disease. *Dig Dis Sci*. 2018;63(3):761-767.
46. Frederiksen MT, Ainsworth MA, Brynskov J, Thomsen OO, Bendtzen K, Steenholdt C. Antibodies against infliximab are associated with de novo development of antibodies to adalimumab and therapeutic failure in infliximab-to-adalimumab switchers with IBD. *Inflamm Bowel Dis*. 2014;20(10):1714-1721.
47. Roblin X, Rinaudo M, Del Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. *Am J Gastroenterol*. 2014;109(8):1250-1256.
48. Papamichael K, Vogelzang EH, Lambert J, Wolbink G, Cheifetz AS. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory diseases. *Expert Rev Clin Immunol*. 2019;15(8):837-848.
49. Papamichael K, Cheifetz AS, Melmed GY, et al. Appropriate therapeutic drug monitoring of biologic agents for patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2019;17(9):1655-1668.e3.
50. Building Research in IBD Globally. Biologic therapy optimizer. http://www.bridgeibd.com/optimizer. Accessed November 19, 2019.
51. Katz L, Gisbert JP, Manoogian B, et al. Doubling the infliximab dose versus halving the infusion intervals in Crohn's disease patients with loss of response. *Inflamm Bowel Dis*. 2012;18(11):2026-2033.
52. Papamichael K, Cheifetz AS. Use of anti-TNF drug levels to optimise patient management. *Frontline Gastroenterol*. 2016;7(4):289-300.
53. Morita Y, Bamba S, Takahashi K, et al. Prediction of clinical and endoscopic responses to anti-tumor necrosis factor-α antibodies in ulcerative colitis. *Scand J Gastroenterol*. 2016;51(8):934-941.
54. Verstockt B, Moors G, Bian S, et al. Influence of early adalimumab serum levels on immunogenicity and long-term outcome of anti-TNF naive Crohn's disease patients: the usefulness of rapid testing. *Aliment Pharmacol Ther*. 2018;48(7):731-739.
55. Papamichael K, Baert F, Tops S, et al. Post-induction adalimumab concentration is associated with short-term mucosal healing in patients with ulcerative colitis. *J Crohns Colitis*. 2017;11(1):53-59.
56. Colombel JF, Sandborn WJ, Allez M, et al. Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12(3):423-431.e1.
57. Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT. Association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic, and histologic remission in Crohn's disease. *Inflamm Bowel Dis*. 2018;24(10):2266-2271.
58. Yarur AJ, Kubiliun MJ, Czul F, et al. Concentrations of 6-thioguanine nucleotide correlate with trough levels of infliximab in patients with inflammatory bowel disease on combination therapy. *Clin Gastroenterol Hepatol*. 2015;13(6):1118-1124.e3.
59. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved long-term outcomes of patients with inflammatory bowel disease receiving proactive compared with reactive monitoring of serum concentrations of infliximab. *Clin Gastroenterol Hepatol*. 2017;15(10):1580-1588.e3.
60. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, Moss AC, Sandborn WJ, Cheifetz AS. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. *Inflamm Bowel Dis*. 2014;20(11):1996-2003.
61. Papamichael K, Vajravelu RK, Vaughn BP, Osterman MT, Cheifetz AS. Proactive infliximab monitoring following reactive testing is associated with better clinical outcomes than reactive testing alone in patients with inflammatory bowel disease. *J Crohns Colitis*. 2018;12(7):804-810.
62. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology*. 2015;148(7):1320-1329.e3.
63. Assa A, Matar M, Turner D, et al. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring. *Gastroenterology*. 2019;157(4):985-996.e2.
64. Ungar B, Engel T, Yablecovitch D, et al. Prospective observational evaluation of time-dependency of adalimumab immunogenicity and drug concentrations: the POETIC study. *Am J Gastroenterol*. 2018;113(6):890-898.
65. Adedokun OJ, Xu Z, Marano CW, et al. Pharmacokinetics and exposure-response relationship of golimumab in patients with moderately-to-severely active ulcerative colitis: results from phase 2/3 PURSUIT induction and maintenance studies. *J Crohns Colitis*. 2017;11(1):35-46.
66. Vande Casteele N, Feagan BG, Vermeire S, et al. Exposure-response relationship of certolizumab pegol induction and maintenance therapy in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2018;47(2):229-237.
67. Vande Casteele N, Jeyarajah J, Jairath V, Feagan BG, Sandborn WJ. Infliximab exposure-response relationship and thresholds associated with endoscopic healing in patients with ulcerative colitis. *Clin Gastroenterol Hepatol*. 2019;17(9):1814-1821.e1.
68. Arias MT, Vande Casteele N, Vermeire S, et al. A panel to predict long-term outcome of infliximab therapy for patients with ulcerative colitis. *Clin Gastroenterol Hepatol*. 2015;13(3):531-538.
69. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology*. 2014;147(6):1296-1307.e5.
70. Kobayashi T, Suzuki Y, Motoya S, et al. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis—results from a multicenter prospective randomized controlled trial and its post hoc analysis. *J Gastroenterol*. 2016;51(3):241-251.
71. Sands BE, Sandborn WJ, Panaccione R, et al; UNIFI Study Group. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2019;381(13):1201-1214.
72. Singh S, George J, Boland BS, Vande Casteele N, Sandborn WJ. Primary non-response to tumor necrosis factor antagonists is associated with inferior response to second-line biologics in patients with inflammatory bowel diseases: a systematic review and meta-analysis. *J Crohns Colitis*. 2018;12(6):635-643.
73. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. *Aliment Pharmacol Ther*. 2018;48(4):394-409.

74. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. *Aliment Pharmacol Ther*. 2018;47(2):162-175.
75. US Food and Drug Administration. FDA approves boxed warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR). http://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and. Published July 26, 2019. Updated August 28, 2019. Accessed November 19, 2019.
76. Feagan BG, Rutgeerts P, Sands BE, et al; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699-710.
77. Feagan BG, Rubin DT, Danese S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol*. 2017;15(2):229-239.e5.
78. Narula N, Peerani F, Meserve J, et al. Vedolizumab for ulcerative colitis: treatment outcomes from the VICTORY consortium. *Am J Gastroenterol*. 2018;113(9):1345.
79. Sandborn WJ, Feagan BG, Rutgeerts P, et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711-721.
80. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology.* 2014;147(3):618-627.e3.
81. Feagan BG, Sandborn WJ, Gasink C, et al; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375(20):1946-1960.
82. Tew GW, Hackney JA, Gibbons D, et al. Association between response to etrolizumab and expression of integrin alphaE and granzyme A in colon biopsies of patients with ulcerative colitis. *Gastroenterology.* 2016;150(2):477-487.e9.
83. Feagan BG, Sandborn WJ, D'Haens G, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet*. 2017;389(10080):1699-1709.
84. Sands BE, Chen J, Feagan BG, et al. Efficacy and safety of MEDI2070, an antibody against interleukin 23, in patients with moderate to severe Crohn's disease: a phase 2a study. *Gastroenterology.* 2017;153(1):77-86.e6.
85. Katsanos KH, Papamichael K, Feuerstein JD, Christodoulou DK, Cheifetz AS. Biological therapies in inflammatory bowel disease: beyond anti-TNF therapies. *Clin Immunol*. 2019;206:9-14.
86. Sandborn WJ, Feagan BG, Wolf DC, et al; TOUCHSTONE Study Group. Ozanimod induction and maintenance treatment for ulcerative colitis. *N Engl J Med*. 2016;374(18):1754-1762.
87. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al; VARSITY Study Group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019;381(13):1215-1226.