

IBD Management: State of the Art in 2018



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Target Audience

This CME monograph will target gastroenterologists, primary care physicians, nurse practitioners, physician assistants, and nurses.

Learning Objectives

After completing this activity, participants should be better able to:

- Personalize treatment plans for patients based on risk of aggressive disease
- Describe strategies for managing loss of response to biologic therapies in patients with IBD
- Position and incorporate newer therapies effectively into clinical practice
- Differentiate among various oral and IV iron formulations

Accreditation Statement

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Abstract: The management of patients with inflammatory bowel disease (IBD) is evolving based on new therapies and treatment goals. Current management of IBD follows a personalized approach based on disease extent and severity, the projected natural history of disease, and the probability of response to specific treatments. An informed strategy to address loss of response to therapies is also required. Although the goals in IBD treatment have historically focused on improving symptoms and achieving clinical remission, recognition that inflammation can persist in the absence of symptoms is challenging conventional treatment objectives and paradigms. Mucosal healing is now recognized as an important goal of therapy. Patients with risk factors for an unfavorable disease course are treated more aggressively than those with fewer risk factors for progression. Several classes of biologics and targeted therapies are now available, and their selection and sequencing can be challenging. This article details the management of Crohn's disease and ulcerative colitis through the discussion of 2 case reports, with a focus on anemia, the role of therapeutic drug monitoring, and selection of therapy throughout the treatment course.

Patient Case

A. G. is a 26-year-old man diagnosed with ileocecal Crohn's disease 2 years previously. At that time, colonoscopy showed ulcerations in the cecum and terminal ileum. Pathology showed chronic active colitis and ileitis without granuloma. He was treated with 8 weeks of budesonide and improved. He began treatment with mesalamine, which he took for 6 months. He was then lost to follow-up.

He presents now with 8 weeks of progressive abdominal pain, non-bloody loose stools, and a 20-pound weight loss. He has not recently traveled or taken antibiotics. There is no family history of inflammatory bowel disease (IBD). He drinks 6 to 10 beers

on the weekend and has smoked 1 pack of cigarettes daily since age 18. He works in retail, but has missed the previous 10 days of work.

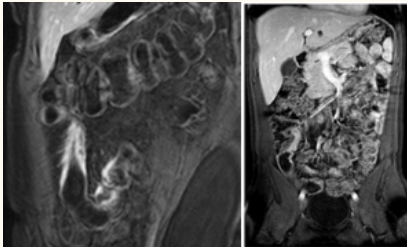
A physical examination demonstrates a blood pressure of 106/62 mm Hg, a pulse of 105 beats per minute, and a temperature of 100.6°F. His body mass index is 22 kg/m². The patient experiences mild right lower quadrant pain during the examination. The perianal examination is normal. Laboratory assessments reveal the presence of iron deficiency anemia, as well as elevated levels of C-reactive protein and fecal calprotectin (Table 1). A QuantiFERON-TB Gold test and hepatitis B serologies are ordered. The patient had received the human papillomavirus vaccine as an adoles-

cent, and he agrees to get an influenza vaccination at his local pharmacy.

Magnetic resonance enterography shows a 35-cm segment of active inflammatory changes in the terminal ileum with associated cecal inflammation. There is no proximal small bowel dilation. A colonoscopy demonstrates deep cecal and proximal ascending colon ulcerations. The terminal ileum is ulcerated and could be intubated only for several centimeters. Biopsies again show chronic active ileitis and colitis.

The patient begins treatment with oral budesonide (enteric coated) at 9 mg/day, oral ferrous sulfate at 325 mg/day, and weekly B₁₂ injections. Three weeks later, the patient returns to his doctor feeling worse. He has lost an

Table 1. Initial Case Presentation

Initial presentation		
<ul style="list-style-type: none"> • 26-year-old man with Crohn's disease diagnosed 2 years earlier and treated initially with budesonide for 2 months and mesalamine for 6 months • Currently experiencing progressive abdominal pain and nonbloody stools, with a recent weight loss of 20 pounds 		
Physical examination		
Blood pressure	106/62 mm Hg	
Pulse	105 bpm	
Temperature	100.6°F	
Body mass index	22 kg/m ²	
Perianal exam	Normal	
Laboratory assessments		
WBC	12,200/ μ L	TTG was normal
Hematocrit	29.2%	Testing for <i>Clostridium difficile</i> was negative
MCV	78 fL	Testing for enteric pathogens was negative
Platelets	673,000/ μ L	QuantiFERON-TB Gold was negative
CMP	Normal except for albumin 2.9 g/dL	TPMT was normal
Ferritin	15 ng/mL	Testing for HbsAb was positive
Vitamin B ₁₂	220 ng/mL	Testing for HbcAb was negative
Vitamin D	18 ng/mL	Testing for HAV was negative
CRP	25 mg/L (normal <5 mg/L)	
Fecal calprotectin	875 μ g/g (normal <50 μ g/g)	
Imaging		
		
<p>MRE shows a 35-cm segment of active inflammatory changes in the terminal ileum with associated cecal inflammation. There is no proximal small bowel dilation. Colonoscopy demonstrates deep cecal and proximal ascending colon ulcerations. The terminal ileum is ulcerated and could be intubated only for several centimeters. Biopsies again show chronic active ileitis and colitis.</p>		

bpm, beats per minute; CMP, complete metabolic panel; CRP, C-reactive protein; HAV, hepatitis A virus; HbcAb, hepatitis B core antibody; HbsAb, hepatitis B surface antibody; MCV, mean corpuscular volume; MRE, magnetic resonance enterography; TTG, tissue transglutaminase; TPMT, thiopurine methyltransferase; WBC, white blood cell.

additional 6 pounds, and he is getting up at night to move his bowels. The iron pills upset his stomach and made him nauseated.

How common is anemia in IBD?

Anemia is a frequent comorbidity and by far the most common extraintestinal manifestation of IBD.¹⁻³ Anemia is estimated to affect one-third of patients with IBD, but the prevalence varies considerably based on a number of factors, including patient age, disease severity and activity, geography, and setting (outpatient vs hospitalized).^{3,4} Indeed, one study found the prevalence of anemia to range from 16% to 74% in patients with IBD, with mean values of 16% in outpatients and 68% in hospitalized patients.⁵ More recently, a nationwide cohort study involving 836 newly diagnosed patients with ulcerative colitis found that 585 patients (70%) developed anemia over the course of a median of 8 years of follow-up.⁶ Subsequent analysis of these data indicated that African-American race, older age, lower albumin level, and the presence of mild anemia at the time of diagnosis predicted the future occurrence of moderate to severe anemia.⁷

Multiple factors contribute to the development of anemia in patients with IBD, but iron deficiency is the most frequent cause, reported in up to 90% of all anemic patients with IBD.^{1,7,8} Iron deficiency in IBD is caused by blood loss through ulcerations of the intestinal mucosa, reduced iron intake, and reduced iron absorption due to increased hepcidin production.^{1,8,9} Hepcidin is an acute-phase protein that plays a crucial role in controlling iron availability to tissues by binding to ferroportin and preventing iron entry into plasma.^{10,11} Hepcidin expression is upregulated during infection and inflammation, such as occurs in active IBD, leading to reduced iron absorption in the duodenum and reduced iron availability for heme formation in the bone marrow.² Accordingly, hepcidin expression has an inverse relationship with plasma iron concentrations.¹¹ Given this

Table 2. IV Iron Preparations Available in the United States^{a 19-22}

	Iron Dextran	Iron Sucrose	Ferumoxytol	Ferric Carboxymaltose
Brand name	INFeD [®]	Venofer [®]	Feraheme [®]	Injectafer [®]
Elemental iron	50 mg/mL	20 mg/mL	30 mg/mL	50 mg/mL
Indications IDA in patients intolerant to or with an unsatisfactory response to oral iron	✓		✓	✓
IDA in CKD		✓	✓	✓
Test dose required	Yes	No	No	No
Administration	Slow IV or IM injection	Slow IV injection or IV infusion ≥15 min	IV infusion over ≥15 min	Slow IV injection (100 mg/min) or IV infusion ≥15 min
Black box warning	Anaphylaxis	None	Hypersensitivity/anaphylaxis	None
Observation	1 hour after test dose	≥30 min during and after administration	≥30 min during and after administration	≥30 min during and after administration

^aSodium ferric gluconate (not listed) is approved for use only in adults and children >6 years of age with CKD on hemodialysis who are receiving epoetin.²³

CKD, chronic kidney disease; IDA, iron-deficiency anemia; IM, intramuscular; IV, intravenous; min, minutes.

relationship, it is not surprising that serum hepcidin correlates positively with disease activity and negatively with ferroportin in patients with IBD.¹²

Is management of anemia a priority in patients with IBD?

Anemia is a source of significant morbidity for patients, leading to fatigue and impaired quality of life, as well as negative effects on work capacity, physical functioning, and emotional well-being.^{11,13} Further, the presence of anemia is an independent predictor of poor outcomes (hospitalization and surgeries) and health care resource utilization (visits and telephone calls to the gastroenterology office) in patients with IBD.¹⁴ Given the enormous impact of anemia on patient quality of life as well as clinical outcomes, recent consensus and expert recommendations highlight the need to screen and treat anemia in IBD, and management of anemia has become an independent treatment target and quality metric in IBD.^{8,13,15}

According to the recent Anemia Care Pathway developed by the Crohn's and Colitis Foundation, iron

supplementation should be administered in all cases of anemia and inadequate iron stores.^{1,8} Despite a common perception that anemia is a secondary problem in IBD patients, treatment of anemia should not be delayed during active disease and should be provided concurrently with IBD therapy.^{8,13} Experts recommend that the timing and optimization of anti-inflammatory therapy and iron therapy in IBD go hand in hand.¹³

Is this patient's anemia being treated adequately?

This patient is receiving daily ferrous sulfate, an appropriate therapy for those with quiescent IBD.⁸ However, parenteral iron is recommended for patients such as this with active disease, as oral iron may not be absorbed sufficiently in the setting of active inflammation, likely due to a hepcidin-mediated mechanism.^{4,8,16,17} Comparative studies have generally found that parenteral iron is faster, more effective, and better tolerated than oral iron supplementation, and it also improves quality of life to a greater extent.^{16,18} Further, given that more than 90% of ingested iron remains unabsorbed, oral iron supple-

mentation can cause a number of gastrointestinal adverse effects, such as nausea, flatulence, diarrhea, and even gastric erosion.¹ Accordingly, as in this patient, tolerance of oral iron may be a particular concern in the setting of active IBD.

How do parenteral iron formulations differ from each other?

The 5 intravenous (IV) iron preparations available in the United States differ considerably with respect to their formulations, dosing, pharmacokinetic properties, and indications (Table 2).¹⁹⁻²³ Although iron dextran preparations have demonstrated efficacy in patients with IBD,²⁴⁻²⁶ they are associated with a substantial rate of immunoglobulin E-mediated anaphylactic reactions, in some studies approaching 6%, despite successful test infusions. Ferumoxytol, an iron polyglucose sorbitol carboxymethyl ether complex approved in 2009 for use in patients with chronic kidney disease, was recently approved for treating iron-deficiency anemia in adults with an unsatisfactory response or intolerance to oral iron.²¹ This agent can be infused intravenously over at least 15 minutes at doses of

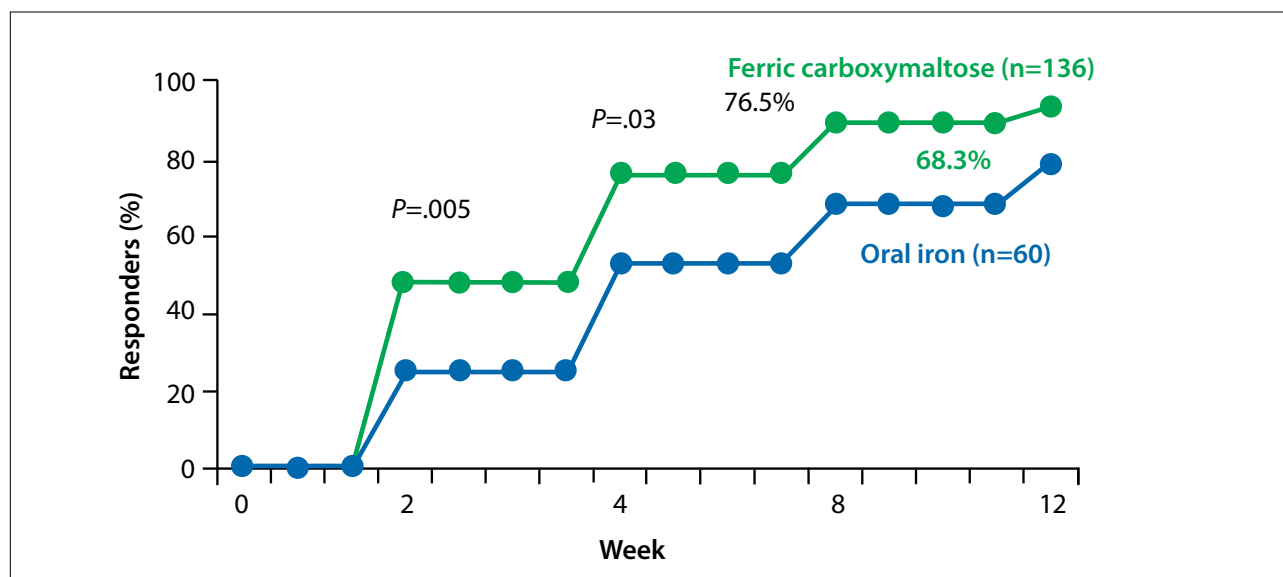


Figure 1. Response to oral vs intravenous iron replacement in patients with iron-deficiency anemia and irritable bowel syndrome. Response was defined as an increase in hemoglobin >2.0 g/dL. Adapted from Kulnigg S et al. *Am J Gastroenterol.* 2008;103(5):1182-1192.¹⁸

510 mg with no test dose, and therefore a full treatment course (1.02 g) can be administered in 2 office visits separated by 3 to 5 days. In an analysis of 231 patients with iron-deficiency anemia and gastrointestinal disorders, treatment with ferumoxytol (510 mg \times 2) was effective and generally well-tolerated, achieving a mean increase in hemoglobin of 2.8 g/dL at week 5 after administration (vs a reduction of 0.1 g/dL with placebo; $P < .001$).²⁷

Additionally, patients treated with ferumoxytol experienced significant improvement in most patient-reported outcomes, including Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scores and various domains of the Short Form (36) Health Survey. More recently, in a large phase 3 trial, 93 patients with IBD responded to ferumoxytol and ferric carboxymaltose with a significant increase in hemoglobin, and the safety profile was comparable with that seen in the overall study population.²⁸

Ferric carboxymaltose, the first high-dose non-dextran IV iron available,²⁹ is unique in that it allows administration of 750 mg of iron over 7.5 minutes or as an infusion over at least 15 minutes. This allows for a total cumulative dose of 1500 mg (ie, 2

doses of 750 mg separated by at least 7 days), making it suitable for intensive iron repletion. This formulation has been found to be safe and effective specifically in patients with IBD.^{30,31} In one study involving 200 patients with iron-deficiency anemia and IBD, patients treated with ferric carboxymaltose achieved a response (defined as a hemoglobin increase of >2.0 g/dL) significantly faster than those receiving oral ferrous sulfate (Figure 1).¹⁸ Further, adverse events led to discontinuation of therapy in fewer patients treated with ferric carboxymaltose than ferrous sulfate (1.5% vs 7.9%, respectively).

What are the goals in treating Crohn's disease in 2018?

Although the goals in IBD treatment have historically focused on improving symptoms and achieving clinical remission, recognition that inflammation can persist in the absence of symptoms is challenging conventional treatment goals and paradigms.^{15,32} Not only do clinical symptoms correlate poorly with underlying inflammation, but treating to symptom resolution alone is not sufficient to prevent disease progression to complications of fistulas, strictures, and abscesses.³³ Accordingly,

treatment goals are evolving beyond symptom resolution alone to include sustained control of inflammation, with mucosal healing now recognized as an important goal of therapy.^{15,34,35} Studies have demonstrated that achieving mucosal healing improves outcomes in Crohn's disease, including corticosteroid-free remission, reduced risk of major abdominal surgery, and improved quality of life.³⁵⁻³⁸ Thus, current guidelines recommend that objective evaluation by endoscopic or cross-sectional imaging be conducted to substantiate the subjective improvement of symptoms.¹⁵

In light of these observations, a "treat-to-target" approach has been increasingly adopted in an effort to incorporate both clinical and inflammatory parameters to define remission.¹⁵ In particular, the concept of deep remission—the improvement of clinical symptoms partnered with objective measures indicating control of underlying inflammation—has become increasingly important.^{15,32} This strategy was recently investigated in the CALM study (Efficacy and Safety of Two Treatment Algorithms in Adults With Moderate to Severe Crohn's Disease), a phase 3, multicenter, randomized, open-label

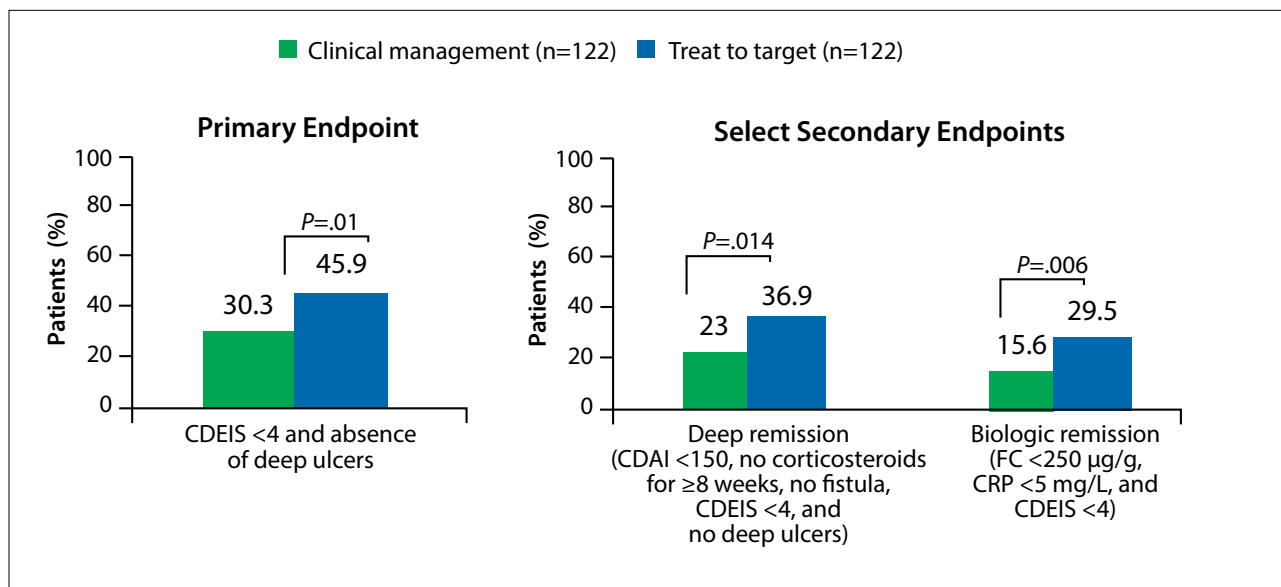


Figure 2. Endoscopic and clinical outcomes in the CALM study. CALM, Efficacy and Safety of Two Treatment Algorithms in Adults With Moderate to Severe Crohn's Disease. CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index Severity; CRP, C-reactive protein; FC, fecal calprotectin. Adapted from Colombel JF et al. *Lancet*. 2018;390(10114):2779-2789.³⁹

active-controlled trial that enrolled 244 patients with active, moderate to severe Crohn's disease who were naive to immunomodulators and biologic therapies.³⁹ After induction therapy with corticosteroids, patients received adalimumab, which was escalated in a stepwise fashion based on either symptomatic criteria (clinical management group) or symptoms combined with objective markers of inflammation (tight control group). Patients with persistent symptoms and/or objective markers of inflammation after adalimumab dose escalation received azathioprine in addition to adalimumab. At week 48, significantly more patients in the tight control group achieved the primary endpoint of mucosal healing with absence of deep ulcers compared with those in the clinical management group (46% vs 30%; $P=.010$; Figure 2). In addition, the tight control group experienced higher rates of clinical remission, corticosteroid-free remission, and normalization of C-reactive protein and fecal calprotectin compared with conventional management alone. Despite these encouraging findings, further data are needed to evaluate the effects of a treat-to-target

Table 3. Risk Stratification in Crohn's Disease

Low Risk	High Risk
<ul style="list-style-type: none"> • >30 years at diagnosis • Limited anatomic involvement • No perianal and/or severe rectal disease • Superficial ulcers • No prior surgical resection • No stricturing and/or penetrating behavior 	<ul style="list-style-type: none"> • <30 years at diagnosis • Extensive anatomic involvement • Perianal and/or severe rectal disease • Deep ulcers • Prior surgical resection • Stricturing and/or penetrating behavior

Adapted from Sandborn WJ. *Gastroenterology*. 2014;147(3):702-705.³³

strategy on long-term outcomes such as bowel damage, surgeries, hospital admissions, and disability.

What is the approach to managing this patient's Crohn's disease?

Current management of IBD embraces a personalized approach based not only on disease extent and severity, but also on the projected natural history of disease, the probability of response to specific treatments, and an informed strategy to address loss of response to current therapies.^{35,40,41} With this approach, patients with risk factors for an unfavorable disease course are treated more aggressively after diagnosis than those with fewer risk factors for progression, who are managed with

a conventional "step-up" approach.^{35,40} To that end, the American Gastroenterological Association (AGA) Clinical Pathway for Crohn's Disease recognizes a number of clinical factors that can help clinicians predict the risk of a disabling disease course (Table 3).

The strategy of targeting high-risk patients for early intervention is based on the concept that, as in other immune-mediated diseases, there is likely a window of opportunity for treatment of Crohn's disease that may reduce bowel damage, hospitalizations, surgeries, and disability (Figure 3).⁴² This approach is supported by the results of several post-hoc analyses of large randomized, controlled trials, indicating better outcomes among

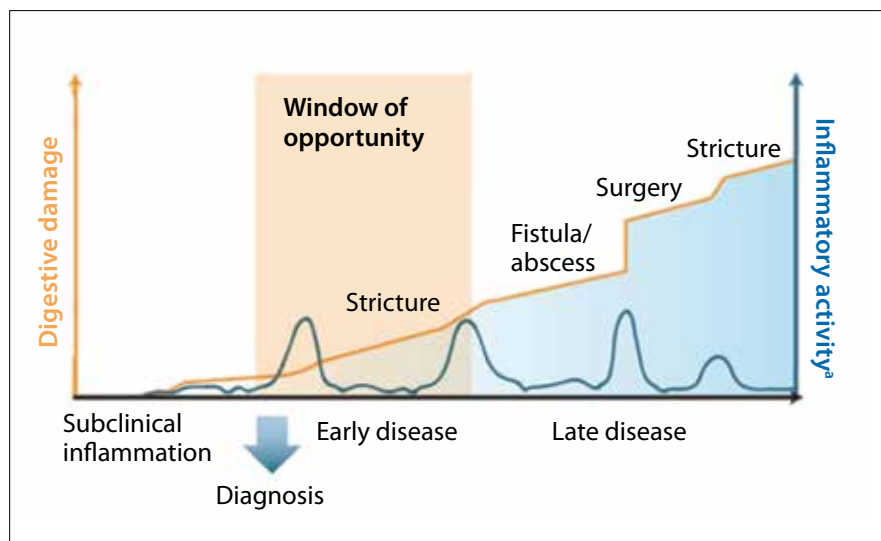


Figure 3. Progression of cumulative digestive damage and inflammatory activity (measured by symptoms, endoscopy, and biomarkers) in patients with Crohn's disease. *Assessed by the Crohn's Disease Activity Index, the Crohn's Disease Endoscopic Index Severity, and C-reactive protein. Adapted from Colombel J-F et al. *Gastroenterology*. 2017;152(2): 351-361.⁴²

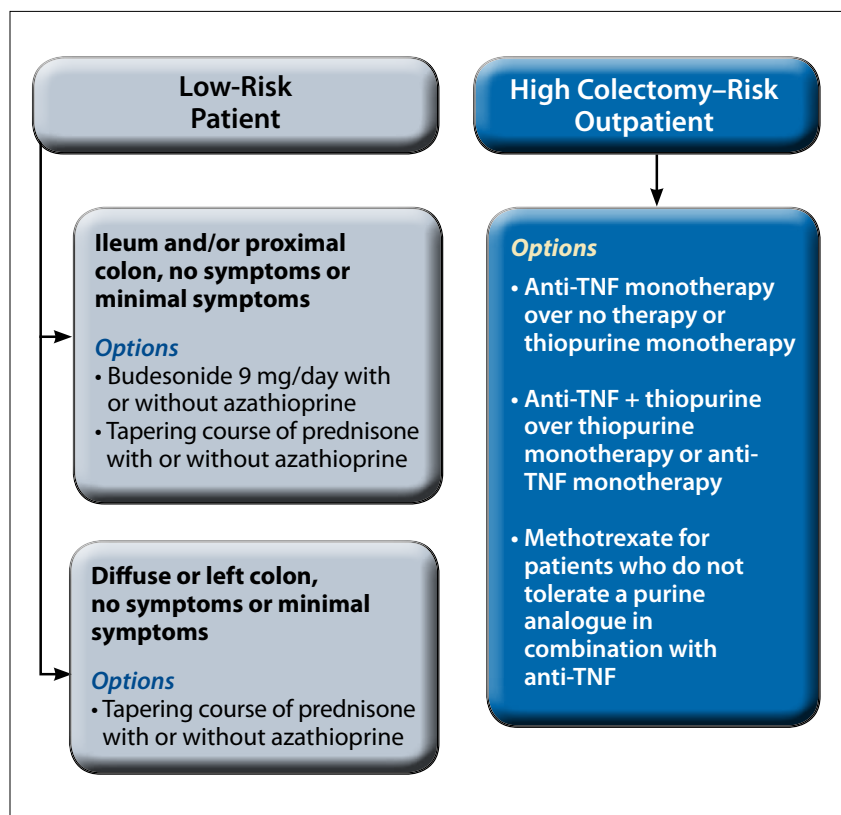


Figure 4. The American Gastroenterological Association clinical pathway for induction and maintenance in Crohn's disease. TNF, tumor necrosis factor. Adapted from Sandborn WJ. *Gastroenterology*. 2014;147(3):702-705.³³

patients who were treated earlier in their disease course relative to those treated at a later stage.^{43,44} Indeed, current evidence suggests that response and remission rates are higher if anti-

tumor necrosis factor (TNF) therapies are given within 2 years of disease onset.¹⁵ Additionally, several trials have evaluated the impact of early intervention in Crohn's disease. Results

from the Step-Up vs Top-Down study showed that patients who received early treatment with combination infliximab and azathioprine were more likely to achieve clinical remission, corticosteroid-free remission, and mucosal healing compared with those treated with a conventional sequential approach.⁴⁵ Similarly, the landmark SONIC trial (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) demonstrated improved outcomes in Crohn's disease patients treated with the combination of infliximab and azathioprine compared with either agent as monotherapy.⁴⁶ More recently, the REACT 1 trial (Randomized Evaluation of an Algorithm for Crohn's Treatment) found that the early use of adalimumab combined with azathioprine or methotrexate did not achieve higher clinical remission rates than conventional step-up therapy; however, early combination therapy was associated with significantly reduced rates of surgery and serious complications.⁴⁷ Given these findings, further data are needed to better characterize the effects of early intervention on bowel damage and disability in Crohn's disease.

Given this patient's young age at diagnosis, presence of deep ulcerations, and failure to respond to budesonide, he is at moderate to high risk of developing a disabling disease

course. Accordingly, initiation of treatment with an anti-TNF therapy, with or without thiopurines, should be considered (Figure 4). The anti-TNF agents act rapidly, often achieving benefit within several weeks of initiation, an effect attributed to their ability to directly neutralize circulating TNF- α .¹⁵ In addition to efficacy in inducing and maintaining clinical remission in Crohn's disease, anti-TNF therapies have been shown to reduce the risks of hospitalization and surgery, particularly when introduced earlier in the treatment course.^{15,47-49} Other options for this patient include vedolizumab and ustekinumab.

According to current American College of Gastroenterology guidelines on Crohn's disease management, combination therapy with an anti-TNF agent and an immunomodulator is preferred over either agent as monotherapy.¹⁵ This recommendation is based on a number of studies demonstrating superior outcomes with the combination of infliximab and an immunomodulator treatment relative to either agent alone in patients who are naive to these therapies.^{45,46}

Case Continuation

The patient is started on combination adalimumab and methotrexate, plus folic acid, after he agrees to stop drinking alcohol and his loose stools resolve. With IV iron, his energy level increases, and he feels better. The C-reactive protein normalizes, as does the fecal calprotectin, after 4 months of therapy. On the days he receives methotrexate, he experiences nausea. The nausea persists despite a decrease in the weekly subcutaneous dose of methotrexate from 25 mg to 15 mg, and after a switch to the oral formulation. The patient refuses to continue methotrexate and declines azathioprine. He is referred for smoking cessation and is able to stop smoking.

After 16 months of therapy, he develops recurrent abdominal pain and loose stools. The fecal calprotectin level had increased 3 months earlier,

but he declined any further investigations because he felt well. A polymerase chain reaction test for *Clostridium difficile* is negative, and fecal calprotectin is elevated at 860 $\mu\text{g/g}$ (normal, <50 $\mu\text{g/g}$). Adalimumab dosing is increased to 40 mg subcutaneously weekly, but symptoms continue. After the dose escalation, the trough adalimumab level is 14.2 $\mu\text{g/mL}$, without antidrug antibodies.

What, if any, is the role of therapeutic drug monitoring in this patient?

An important first step in evaluating loss of response to biologic therapy is to ensure that the symptoms are caused by active IBD.⁵⁰ It is necessary to rule out common infections in IBD, including *C difficile* and cytomegalovirus, as well as disease complications.⁵⁰⁻⁵² Once evidence of active inflammation is confirmed and other sources of symptoms have been excluded, measurement of serum drug concentrations and antidrug antibodies (ie, therapeutic drug monitoring) can help differentiate reasons for loss of response and guide treatment decisions.⁵⁰⁻⁵³

The use of therapeutic drug monitoring with biologic therapies in IBD is based on data demonstrating a correlation between high serum anti-TNF concentrations and favorable outcomes, including clinical, biomarker, and endoscopic remissions.⁵³⁻⁵⁹ Conversely, the presence of antidrug antibodies has been linked to lower serum drug concentrations, reduced clinical responses, and infusion reactions.⁶⁰⁻⁶⁴ Other factors that can affect serum levels of anti-TNF biologics include disease severity, concomitant immunomodulatory use, and body mass index.^{65,66}

Anti-TNF failure and/or loss of response in patients with active IBD can be caused broadly by either pharmacokinetic or mechanistic failures.⁶⁵ A pharmacokinetic failure is defined as no response to therapy in the setting of subtherapeutic drug concentrations and the absence of antidrug antibodies. This type of failure typically results from rapid drug clearance in patients with a high inflammatory burden.

Patients with a pharmacokinetic failure benefit more from dose escalation (ie, shortening the interval and/or increasing the dose) than switching to another anti-TNF agent (Figure 5). The formation of neutralizing antidrug antibodies can also lead to pharmacokinetic failures observed in patients with subtherapeutic drug concentrations and high titers of antidrug antibodies.⁶⁵ Strategies recommended for such immune-mediated pharmacokinetic failures include increasing the dose of the anti-TNF agent (if antidrug antibody concentrations are low), adding an immunomodulator, or, in the case of high adalimumab concentrations, switching to another anti-TNF agent or another class of biologic.⁵⁹

In a patient such as this, who is not responding to an anti-TNF agent despite optimal drug trough concentrations, the failure is likely related to the disease process being driven by non-TNF inflammatory mediators.⁶⁵ In cases such as this, current evidence suggests that changing to a biologic with a different mechanism is likely more beneficial than switching to another drug in the same class.^{59,65}

What are the treatment options at this point?

Given that the patient did not respond to anti-TNF therapy in the face of adequate serum concentrations, appropriate options for therapy include both ustekinumab and vedolizumab. Ustekinumab, an anti-p40 antibody that inhibits interleukin (IL) 12 and 23, was approved for the management of moderate to severe Crohn's disease in 2016.⁶⁷ This agent has demonstrated efficacy regardless of whether the patient has received treatment with an anti-TNF agent,⁶⁸ with an effect on symptoms that appears to be of similar magnitude as that achieved with anti-TNF therapies.⁴⁸ Data from phase 3 trials in Crohn's disease, in conjunction with an extensive database in psoriasis, indicate that ustekinumab has an excellent safety profile, with a low rate of immunogenicity and serious infections, and no increased risk of

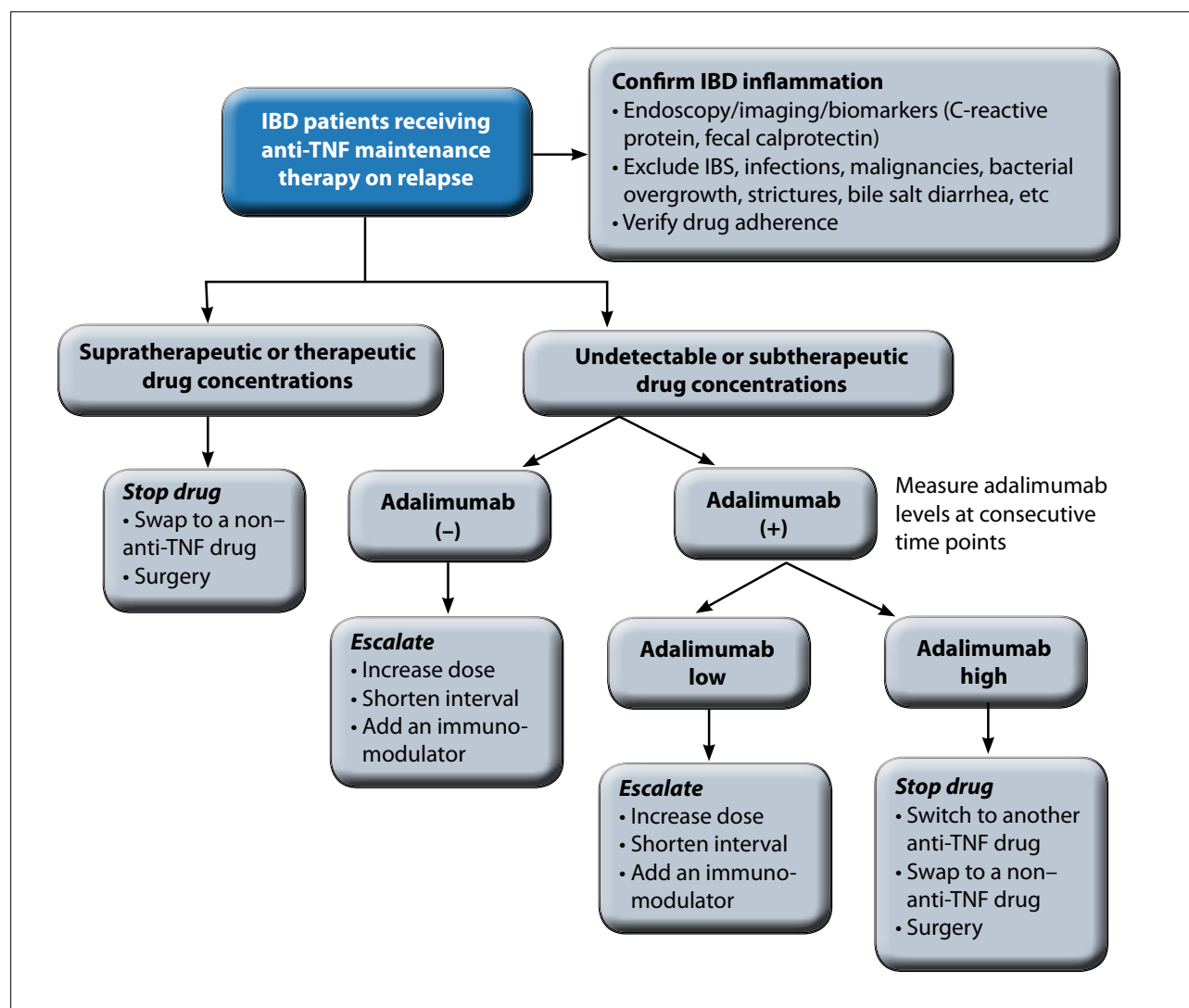


Figure 5. Reactive therapeutic drug monitoring algorithm of patients with irritable bowel syndrome receiving anti-TNF therapies. IBD, irritable bowel disease; IBS, irritable bowel syndrome; TNF, tumor necrosis factor. Adapted from Papamichael K, Cheifetz AS. *Frontline Gastroenterol.* 2016;7(4):289-300.⁵⁹

malignancies.^{15,48,69} However, further data are needed to better characterize the effect of ustekinumab on mucosal healing and to evaluate its impact on surgeries and hospitalization.⁴⁸

In contrast to the systemic action of the anti-TNF agents in neutralizing TNF- α , vedolizumab is a gut-selective agent that acts by binding $\alpha_4\beta_7$ integrin, a receptor found on the surface of gut-homing leukocytes.^{70,71} Blocking these receptors results in decreased migration of leukocytes across blood vessels at the inflammatory site and a decreased inflammatory response.⁷⁰ Because vedolizumab selectively blocks

gut lymphocyte trafficking without interfering with trafficking to the central nervous system,⁷² it is not expected to reduce immunosurveillance in the brain or increase the risk of progressive multifocal leukoencephalopathy, a serious and usually fatal brain infection.^{48,72}

Vedolizumab is effective in achieving clinical response, remission, and mucosal healing in Crohn's disease, although its onset of action may be slower than that observed with anti-TNF therapies.^{15,73,74} Current evidence indicates that patients who have received anti-TNF therapies require longer treatment with vedolizumab, with efficacy

rates at 10 weeks comparable to those observed in anti-TNF-naïve patients at 6 weeks.^{15,74} In addition to efficacy in this setting, data from 2830 patients indicate that vedolizumab has a favorable safety profile, with low incidence rates of serious infections, infusion-related reactions, and malignancies over an extended treatment period.⁷⁵

Although there are no head-to-head trials comparing second-line therapies in moderate to severe Crohn's disease, a recent network meta-analysis evaluated data from 6 randomized, controlled studies involving 1606 patients with Crohn's disease previously treated

Table 4. Initial Case Presentation

Initial presentation		
<ul style="list-style-type: none"> • 37-year-old woman with left-sided ulcerative colitis diagnosed 2 years earlier • Reports symptom improvement, but not complete resolution, after 2 weeks of initial treatment with prednisone 40 mg/day orally and mesalamine 3.6 g/day orally 		
Physical examination		
Body mass index	19.9 kg/m ²	
Laboratory assessments		Imaging
WBC	6,400/ μ L	Colonoscopy at diagnosis showed moderate endoscopically active colitis from the rectum to the splenic flexure. The proximal colon and terminal ileum were normal. Biopsies from the left colon and rectum demonstrated severely active chronic colitis without granulomas.
Hemoglobin	13.0 mg/dL	
Platelets	334,000/ μ L	
CRP	1.1 mg/L	
ESR	2 mm/h	
QuantiFERON-TB Gold	Negative	
Hepatitis B serologies	Negative	
TPMT	22.3 U/mL	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TPMT, thiopurine methyltransferase; WBC, white blood cell.

Table 5. Risk Stratification in Ulcerative Colitis

Low Colectomy Risk	High Colectomy Risk
<ul style="list-style-type: none"> • Limited anatomic extent • Mild endoscopic disease 	<ul style="list-style-type: none"> • Extensive colitis • Deep ulcers • Age <40 years at diagnosis • High CRP and ESR • Corticosteroid-requiring disease • History of hospitalization • <i>Clostridium difficile</i> infection • CMV infection

CMV, cytomegalovirus; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. Adapted from Dassopoulos T et al. *Gastroenterology*. 2015;149(1):238-245.⁷⁷

with anti-TNF therapy.⁷⁶ Ustekinumab and adalimumab were found to be superior to placebo in inducing clinical remission in this setting, with respective odds ratios (ORs) of 2.58 (95% CI, 1.50-4.44) and 3.57 (95% CI, 1.66-7.65). A small effect of vedolizumab was observed, with an associated OR of 1.53 (95% CI, 0.77-3.06). However, given the differences among the patients in the trials, no agent was clearly superior to the others.

Case Conclusion

A decision is made to switch to ustekinumab. The patient receives 390

mg intravenously followed by 90 mg subcutaneously every 8 weeks. Within 12 weeks, he is in clinical remission, and his fecal calprotectin normalizes at 16 weeks. He remains well 12 months after initiation of ustekinumab.

Patient Case

J. D. is a 37-year-old white woman diagnosed with pancolonic ulcerative colitis in 2016. In the 10 years before this diagnosis, she experienced intermittent abdominal pain and non-bloody diarrhea. The symptoms were particularly severe initially, requiring hospitalization. She underwent

computed tomography and an upper endoscopy, which showed nothing remarkable.

In early 2016, her symptoms changed, with increasing stool frequency and urgency, nocturnal awakenings to defecate, and rectal bleeding. She had an associated 15-pound weight loss. She underwent a colonoscopy later that year, which showed moderately active colitis from the rectum to the splenic flexure. The proximal colon and terminal ileum were normal. Biopsies from the left colon and rectum demonstrated severely active chronic colitis without granulomas. After the colonoscopy, the patient began treatment with prednisone at 40 mg/day orally and mesalamine at 3.6 g/day orally.

She presents 2 weeks later, reporting dramatic improvement in her symptoms. She now has 3 to 4 semiformal stools daily with decreased urgency and no nocturnal awakenings. The bleeding has significantly decreased, but is still present.

The patient's medical history is notable for infection with human papillomavirus and abnormal Pap smears. In addition to the above medications, she is taking a nonprescription probiotic daily. Her only medication allergy is to tramadol, which causes hypertension and confusion. She has a maternal cousin with Crohn's disease. She is a lifetime never-smoker, and she does not drink alcohol or take illicit drugs. She is separated and has 1 child. She is a veterinarian.

The physical examination is notable for a height of 64 inches and a weight of 116 pounds (body mass index, 19.9 kg/m²), but is otherwise unremarkable. Relevant laboratory assessments are summarized in Table 4.

Are any changes in treatment needed at this point?

The management of ulcerative colitis is based on an assessment of disease activity as well as the disease risk, which is defined in the AGA Ulcerative Colitis Care Pathway as the risk of colectomy (Table 5).⁷⁷ This patient's

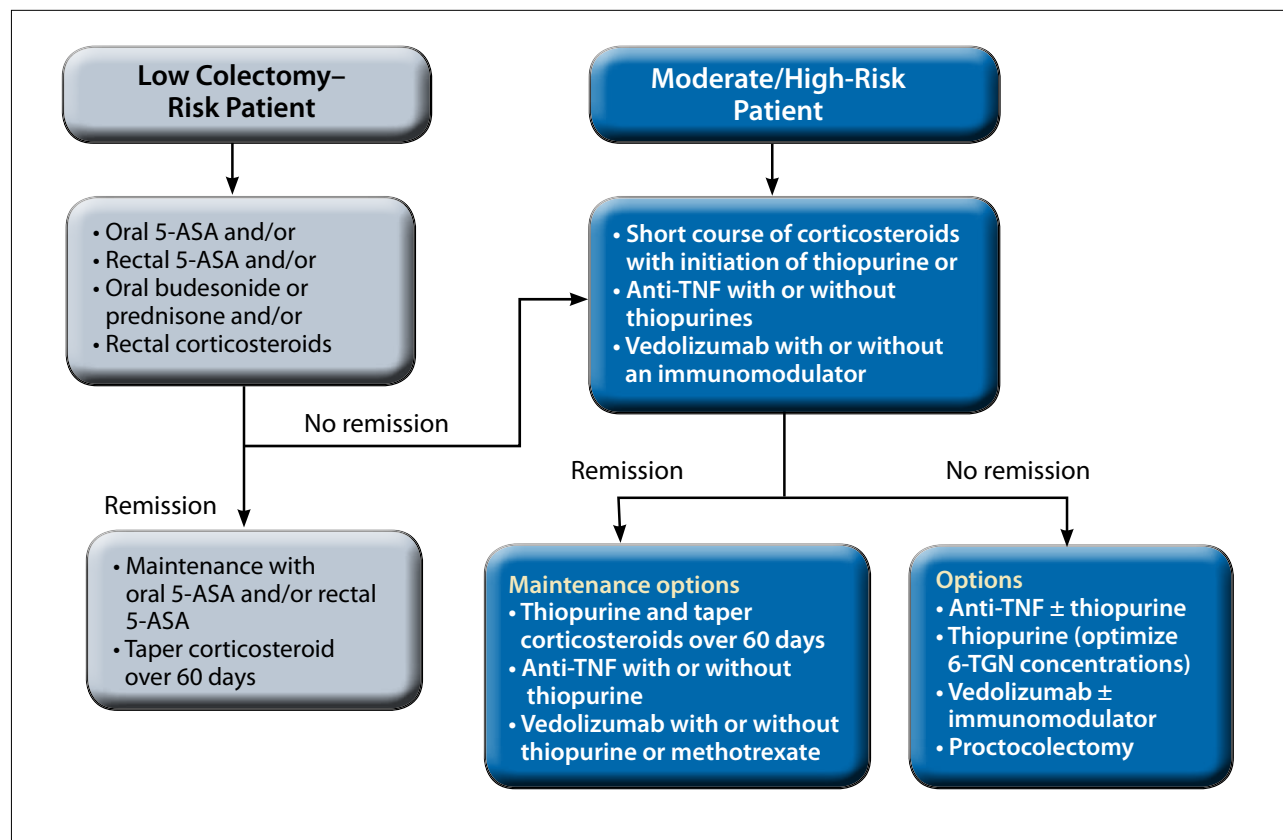


Figure 6. The American Gastroenterological Association Care Pathway for ulcerative colitis: induction and maintenance therapy. 5-ASA, 5-aminosalicylate; 6-TGN, 6-thioguanine nucleotide; TNF, tumor necrosis factor. Adapted from Dassopoulos T et al. *Gastroenterology*. 2015;149(1):238-245.⁷⁷

risk factors for colectomy include her young age at diagnosis and her initial requirement for hospitalization and corticosteroids. Although her current therapy of mesalamine at 3.6 g/day is reasonable, evidence indicating a dose-response relationship of the 5-aminosalicylate (5-ASA) agents in moderate disease suggests that titrating that dose to 4.8 g/day might improve outcomes.⁷⁸ Further, in a patient such as this with distal disease, the addition of a rectal 5-ASA formulation may provide greater symptom relief than oral therapy alone.⁷⁹

What are the targets of treatment in this case?

Consistent with Crohn's disease, the treatment goals in ulcerative colitis are evolving beyond clinical targets to include endoscopic parameters. Unlike Crohn's disease, however, the symptoms of ulcerative colitis correlate quite well

with endoscopic disease activity, and the significance of mild endoscopic activity in ulcerative colitis patients remains uncertain.⁷⁷ Nevertheless, achieving symptom resolution alone is insufficient to alter the course of the disease, and objective evidence of underlying inflammation is important when making clinical decisions.¹³ To that end, recent expert consensus from the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Steering Committee recommends a composite target of clinical remission (defined as resolution of rectal bleeding and diarrhea/ altered bowel habits) and endoscopic remission (defined as resolution of friability and ulceration based on flexible sigmoidoscopy or colonoscopy).⁸⁰

Is there a role for fecal calprotectin?

Fecal calprotectin has been shown in a number of studies to be a sensitive

marker of mucosal healing in ulcerative colitis, correlating with various endoscopic indices, including the Rachmilewitz index, the modified Baron index, the Partial Mayo Score, and the Simple Clinical Colitis Activity Index.⁸¹⁻⁸⁴ In a large cross-sectional study in 228 patients with ulcerative colitis, a cut-off value of fecal calprotectin of 57 µg/g detected patients with endoscopically active disease with 91% sensitivity and 90% specificity.⁸⁵ Based on this evidence, current expert opinion suggests that although fecal calprotectin is not a treatment target, it can be used as an adjunctive measure to facilitate enhanced monitoring of patients.^{80,86} With this in mind, obtaining a fecal calprotectin level in this patient 8 to 12 weeks after starting therapy would be a reasonable alternative to repeating a sigmoidoscopy or colonoscopy. An abnormal fecal calprotectin value

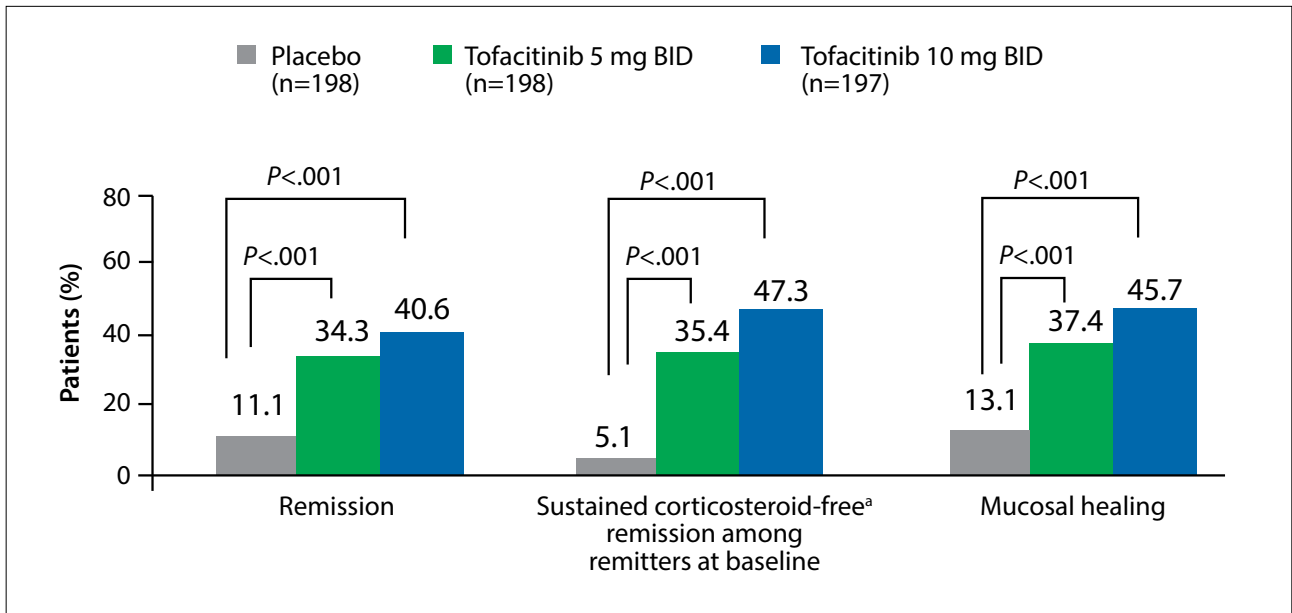


Figure 7. Primary and key secondary endpoints in the OCTAVE Sustain study. Sustained endpoints are defined as achieving response/remission at both week 24 and week 52. ^aCorticosteroid-free is defined as not requiring corticosteroids for ≥ 4 weeks prior to each visit. BID, twice daily; OCTAVE, Oral Clinical Trials for Tofacitinib in Ulcerative Colitis. Adapted from Sandborn WJ et al. *N Engl J Med.* 2017;376(18):1723-1736.⁹⁰

should prompt further endoscopic evaluation to document the presence or absence of active disease, regardless of the patient's symptoms.⁸⁰

Case Continuation

The patient's dose of prednisone is tapered by 5 mg per week until it reaches 10 mg per day. It is then tapered by 5 mg every other week until it is discontinued. The mesalamine is increased to 4.8 g/day. A colonoscopy is planned 6 months later to confirm mucosal healing. The prednisone is successfully tapered off. However, within a month, the patient develops cramping abdominal pain, gas, and abdominal bloating, as well as increased stool frequency without rectal bleeding and passage of mucus in the stool. Testing for *C difficile* is negative. A colonoscopy reveals a diffuse area of moderately altered vascular pattern, erythema, granularity, friability (contact bleeding), and eroded mucosa from the rectum to the splenic flexure. Scattered erosions are present in the transverse colon; the ascending colon and terminal ileum are normal. Biopsies

demonstrate marked chronic active colitis with ulceration and cryptitis. There are no cytomegalovirus inclusions.

What are the treatment options at this point?

Patients who do not respond to optimized treatment with 5-ASAs and/or corticosteroids are considered at high risk for colectomy and should be treated with more aggressive therapies (Figure 6). According to the AGA Care Pathway, options for this patient at this point include initiating a thiopurine with a short course of corticosteroids or beginning a biologic agent—either an anti-TNF agent or vedolizumab—with or without an immunomodulator.⁷⁷

Another treatment option for this patient is tofacitinib, an oral Janus kinase (JAK) inhibitor approved in 2018 for the treatment of moderate to severe ulcerative colitis.⁸⁷ The efficacy of tofacitinib in ulcerative colitis is based on its ability to inhibit members of the JAK family, proteins that facilitate signal transduction of several cytokines that are needed for lymphocyte

activation and proliferation as part of the immune response.^{88,89} Inhibiting JAK leads to downstream modulation of multiple inflammatory cytokines that are implicated in the pathogenesis of IBD.^{88,90} The efficacy and safety of tofacitinib in moderate to severe ulcerative colitis has been demonstrated in a dose-finding phase 2 trial⁹¹ and in a large phase 3 clinical program known as OCTAVE (Oral Clinical Trials for Tofacitinib in Ulcerative Colitis).⁹⁰ In the OCTAVE Induction 1 and 2 trials, tofacitinib at 10 mg twice daily was superior to placebo in achieving remission (18.5% vs 8.2%; $P=.007$), clinical response (59.9% vs 32.8%; $P<.001$), and mucosal healing (31.3% vs 15.6%; $P<.001$) at 8 weeks. The onset of action was rapid, with significant improvement in the partial Mayo score observed at 2 weeks.⁹⁰ In the OCTAVE Sustain maintenance trial, more than one-third of patients receiving tofacitinib maintained clinical remission and mucosal healing at 52 weeks, significantly more than placebo-treated patients ($P<.001$ for each comparison; Figure 7). Among patients treated with tofacitinib, the

most frequently reported adverse events (excluding worsening ulcerative colitis) were nasopharyngitis, arthralgia, and headache. However, tofacitinib was also associated with higher rates of overall infection and herpes zoster infection than placebo, as well as with increased levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol.

What guides the selection of thiopurine monotherapy, an anti-TNF biologic with or without an immune suppressant, anti-integrins, and tofacitinib in biologic-naïve patients?

The thiopurines azathioprine and 6-mercaptopurine have significant corticosteroid-sparing effects in ulcerative colitis, and they are considered first-line maintenance therapies in patients who experience a flare when corticosteroids are withdrawn.⁹²⁻⁹⁴ However, because these agents have a relatively slow onset of effect, patients with active disease despite corticosteroid therapy also require appropriate induction therapy.^{92,95} Currently, the strongest indication for the use of thiopurines in ulcerative colitis is in combination with anti-TNF agents, as this combination has been demonstrated to improve efficacy over either agent alone, and also minimizes immunogenicity of the anti-TNF agent.⁹⁶ In the UC SUCCESS trial (Comparison of the Efficacy and Safety of Infliximab, as Monotherapy or in Combination With Azathioprine, Versus Azathioprine Monotherapy in Moderate to Severe Active Ulcerative Colitis [Part 1] Comparison of Maintenance Versus Intermittent Infliximab Treatment in Maintaining Remission: A Follow-Up of Efficacy and Safety [Part 2]), 39.7% of 239 patients receiving combination infliximab and azathioprine achieved corticosteroid-free remission at week 16 compared with 22.1% of those receiving infliximab alone ($P=.017$) and 23.7% of those receiving azathioprine alone ($P=.032$).⁹⁷ Further, fewer patients receiving combination therapy developed antidrug antibodies compared with those receiving

infliximab monotherapy (3% vs 19%, respectively).

The anti-TNF agents are effective as both induction and maintenance therapy in ulcerative colitis, and they achieve rapid symptom improvement.^{48,98-102} In addition, these agents have been found to achieve mucosal healing,⁹⁹ improve quality of life,¹⁰³ and reduce hospitalizations and surgeries in patients with ulcerative colitis.¹⁰⁴ The most important safety concern with these agents is the risk of serious infection, which may be reduced by screening for hepatitis B and tuberculosis and ensuring appropriate immunization before initiating treatment.⁴⁸ Another key concern with these agents is loss of response, which is often a consequence of immunogenicity and is estimated to occur in more than 30% of patients within the first year of therapy.^{60,105,106} Given the recognized efficacy of immunomodulators in suppressing antibody formation,^{46,53,55,107,108} combination therapy with an immunomodulator is currently a preferred strategy.⁴⁸

Approved in 2014 for moderately to severely active ulcerative colitis,¹⁰⁹ vedolizumab has emerged as a first-line agent for induction of remission in patients with moderately active ulcerative colitis who did not respond to conventional therapy.⁴⁸ As discussed previously, the gut selectivity of vedolizumab leads to a favorable safety profile, with low rates of serious infections and infusion-related reactions observed to date.⁷⁵ Further, the low rate of immunogenicity with vedolizumab could reduce the need for combination therapy with an immunomodulator.⁷¹ Given its efficacy and safety profile, it is anticipated that vedolizumab will increasingly be used as maintenance therapy in ulcerative colitis.⁴⁸

With the availability of several classes of biologics and targeted therapies with variable efficacy and safety profiles, positioning different agents as first-line therapies in the treatment course of biologic-naïve patients can be challenging.⁷⁶ This decision is further complicated by the lack of

comparative head-to-head trials. In the absence of such evidence, a recent network meta-analysis of 14 randomized, controlled trials involving 4212 biologic-naïve and -exposed patients with moderate to severe ulcerative colitis was conducted to evaluate the comparative efficacy and safety of various therapies.¹¹⁰ Analysis of data from 2720 biologic-naïve patients in 12 trials indicated that although all agents were more effective than placebo at inducing remission, the effect sizes were largest for infliximab (OR, 4.22) and vedolizumab (OR, 4.26). Similarly, the ORs for inducing mucosal healing were highest for infliximab (OR, 3.32) and vedolizumab (OR, 2.91).¹¹⁰

Beyond efficacy, however, a number of other factors influence treatment choice, including clinician experience, safety and tolerability profile, patient profile, patient preference, and insurance reimbursement.⁷⁶ Although current evidence indicates that all biologics used in ulcerative colitis are considerably safe, vedolizumab appears to have a particularly favorable safety profile owing to its gut-selective action.^{71,75,110} Indeed, in the previously described network meta-analysis, vedolizumab was ranked safest—with the lowest rate of serious adverse events and infections among therapies—followed by infliximab.¹¹⁰ Despite this finding, the authors cautioned that the lack of direct comparisons and low rates of serious infections and other serious events, such as malignancy, limit the conclusions that can be drawn.

Because the introduction of vedolizumab into the market is recent, the positioning of this agent in the treatment paradigm for ulcerative colitis is unclear at this time. This agent achieves remission rapidly in patients with moderate to severe disease, while offering the important advantages of oral administration and lack of immunogenicity.⁹⁰ Although the safety profile of vedolizumab is acceptable in the short-term, the risk of serious infections, particularly reactivation of herpes zoster, may be problematic

for some patients and precludes the use of this agent in combination with immunomodulators.⁴⁸ Further, proper patient selection is important when using tofacitinib, given its potential for dose-dependent increases in serum LDL and HDL cholesterol and liver enzymes. More data and clinical experience are needed to better characterize if tofacitinib is best positioned as an alternative to the thiopurines, ahead of biologic drugs, or whether it should be reserved for patients with ulcerative colitis who did not respond to biologic therapies.⁴⁸

Case Continuation

Prednisone is restarted at 40 mg/day orally, along with vedolizumab infusions of 300 mg at weeks 0, 2, and 6. Mesalamine is continued at 4.8 g/day orally. The patient experiences significant improvement in symptoms, although she continues to have moderate, intermittent cramping abdominal pain and fecal urgency. The dose of prednisone is successfully tapered and discontinued. The patient continues to receive vedolizumab maintenance therapy at 300 mg administered intravenously every 8 weeks.

Is there a role for proactive drug monitoring in this case?

Most current research has explored the utility of therapeutic drug monitoring in the reactive setting to assess loss of disease control with anti-TNF therapies.⁶⁵ Emerging data, however, suggest that proactive monitoring of serum infliximab concentrations may be associated with better clinical outcomes and less need for IBD-related surgery or hospitalization compared with reactive monitoring.¹¹¹ In a retrospective multicenter study, 264 patients (167 with Crohn's disease) receiving infliximab maintenance therapy received proactive or reactive drug monitoring based on first infliximab concentration and antibodies to infliximab.¹¹¹ Proactive monitoring was used in patients without any

IBD-related symptoms to prospectively titrate infliximab to a target therapeutic window of 5 µg/mL to 10 µg/mL, whereas reactive monitoring was used to guide treatment decisions in patients with symptoms suggestive of loss of response or drug intolerance due to acute or delayed infusion reactions. Multiple Cox regression analysis independently correlated proactive drug monitoring with a reduced risk for treatment failure compared with reactive monitoring (hazard ratio, 0.16; 95% CI, 0.09-0.27; $P < .001$). A lower cumulative probability of treatment failure was observed with proactive therapeutic drug monitoring in patients with both ulcerative colitis and Crohn's disease. Additionally, when compared with reactive monitoring, proactive monitoring was independently associated with a reduced risk of IBD-related surgery, IBD-related hospitalization, lower antibodies to infliximab, and serious infusion reactions. These results, however, have not been demonstrated consistently. In the TAXIT study (Trough Concentration Adapted Infliximab Treatment), after initial infliximab dose optimization based on drug levels, the proportions of patients achieving remission at 1 year were comparable between those who received routine proactive therapeutic drug monitoring and those who received no therapeutic drug monitoring.¹¹² Given these inconsistencies, the AGA guidelines on therapeutic drug monitoring consider current evidence insufficient to inform the use of routine proactive monitoring in patients who are being treated with anti-TNF agents.⁶⁵

Despite the large body of evidence supporting the exposure response with anti-TNF drug concentrations,⁶⁵ the role of therapeutic drug monitoring with vedolizumab is less clear. Emerging data from post-hoc analyses of phase 3 studies and observational series suggest that clinical outcomes do vary between vedolizumab concentrations at the extremes of the measurable range.¹¹³ However, prospective data

are needed to better characterize the exposure-response relationship of vedolizumab in both the reactive and proactive settings.

Case Continuation

The patient undergoes a colonoscopy 4 months later and is found to have a mildly altered vascular pattern in the rectum. The more proximal colon and ileum are normal. Biopsies show mild, chronic active colitis in the left colon and rectum. The vedolizumab is continued, but the mesalamine is stopped. Three months later, the patient reports increased stool frequency without rectal bleeding, mild abdominal cramping, and severe fecal urgency. Her level of fecal calprotectin is 68 µg/g. The mesalamine is restarted, with improvement in symptoms.

However, over the ensuing months, the frequency of bowel movements increases to 8 per day, with intermittent bleeding and tenesmus. Results from routine laboratory tests are unremarkable, including a polymerase chain reaction test that was negative for *C difficile*. However, the fecal calprotectin is increased, at 284 µg/g. A colonoscopy demonstrates severely ulcerated mucosa in the rectosigmoid colon and a moderately altered vascular pattern, erythematous, and eroded mucosa in the ascending colon. The descending and transverse portions of the colon are spared. The terminal ileum is normal. Biopsies show markedly active chronic colitis with extensive cryptitis and crypt abscesses.

What guides the selection of therapy in biologic-exposed patients?

As is the case in biologic-naïve patients, positioning agents as second-line therapies in biologic-exposed patients is challenging in the absence of direct head-to-head comparative trials. Network meta-analysis of 4 randomized, controlled trials involving 967 patients with moderate to severe ulcerative colitis with prior anti-TNF exposure supported the efficacy of tofacitinib in

inducing clinical remission over vedolizumab and adalimumab, with respective ORs for induction of remission of 11.88 (95% CI, 2.32-60.89), 3.30 (95% CI, 0.68-16.11), and 1.36 (95% CI, 0.49-3.80).¹¹⁰ Similar results were found for mucosal healing. Recognizing the limitations of this analysis, the authors concluded that tofacitinib would likely be most effective in patients who fail infliximab, although vedolizumab may be a reasonable alternative. As with first-line therapies, important factors driving treatment choice in this setting include the safety and tolerability profile, the patient profile, patient preference, and insurance reimbursement.⁷⁶

Case Conclusion

The vedolizumab level at trough is 21.6 µg/mL. The patient is counseled on the available treatment options. She prefers an oral medication and selects tofacitinib. However, her insurance will not authorize tofacitinib unless adalimumab is tried first without success. Treatment begins with subcutaneous adalimumab administered at 160 mg at week 0, 80 mg at week 2, 40 mg at week 4, and 40 mg every other week thereafter.

In follow-up at 12 weeks, the patient has complete resolution of symptoms. Fecal calprotectin is undetectable (<16 µg/g). A repeat sigmoidoscopy 6 months after induction therapy shows quiescent colitis. Biopsies show no evidence of histologic activity.

Summary

The management of IBD in 2018 embraces a personalized approach based not only on disease extent and severity, but also on an individual patient's projected natural history of disease, probability of response to specific therapies, and shared decision-making when selecting treatment.^{35,40,41} With this approach, patients with risk factors for an unfavorable disease course are treated more aggressively after diagnosis than those with fewer risk factors

for progression, who are managed with a conventional "step-up" approach.^{35,40} Further, traditional treatment goals have been challenged by increasing evidence that inflammation can persist in the absence of symptoms, as well as by the failure of conventional treatment approaches to prevent disease progression.³³ Accordingly, treatment goals have evolved beyond symptom control alone to include sustained control of inflammation, with mucosal healing now recognized as an important goal of therapy.^{15,34,35} With measures of inflammation (eg, fecal markers, serum markers, endoscopic assessment) now allowing for tighter control of the inflammatory process, a treat-to-target approach has been increasingly adopted in an effort to incorporate both clinical and inflammatory parameters to define remission.¹⁵

Although the management of IBD was dominated for many years by anti-TNF therapies,⁴⁸ new treatment options have expanded the therapeutic landscape over the past decade. In addition to 2 new classes of biologics (anti-integrins and the IL-12/23 antagonist ustekinumab), tofacitinib recently became the first JAK inhibitor to be approved for use in ulcerative colitis.^{48,87} With the availability of these new therapies, positioning different agents as first- and second-line therapies in the treatment course can be challenging, particularly in the absence of comparative head-to-head trials.^{76,110} Beyond efficacy, key factors that influence treatment choice among available therapies include the safety and tolerability profile, the patient profile, and patient preference.⁷⁶

In addition to treating intestinal inflammation, clinicians caring for patients with IBD must also recognize extraintestinal complications and then manage them effectively. Anemia is a particularly frequent comorbidity and by far the most common extraintestinal manifestation of IBD.¹⁻³ Indeed, anemia occurs in approximately 30% of patients and is associated with high rates of IBD-related complications, resource utilization, and impaired

quality of life.^{2,8,14} Although oral iron may be useful in patients with quiescent disease, IV iron is recommended in active disease because it is more effective, better tolerated, and improves quality of life to a greater extent than oral iron supplementation.^{16,18}

Disclosures

Dr Cross engages in consulting and advisory boards with AbbVie, Janssen, Pfizer, and UCB, and has a research grant from AbbVie. Dr Farraye attends advisory boards with Ferring, Janssen, Merck, Pfizer, and Takeda. He is a consultant for Braintree Labs, a stockholder of Innovation Pharmaceuticals, and a member of a DSMB for Lilly and Theravance.

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