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INFORM UC: An Update on Contemporary Management of UC

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Goal Statement

The primary goal of this CME monograph is to encourage the application of the latest advances in evidence-based medicine to improve the quality of care and improve outcomes for patients affected by UC.

Target Audience

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

Educational Objectives

Upon completion of this educational activity, participants should be able to:

- Discuss key data regarding the latest diagnostic and treatment strategies for UC presented at DDW 2020
- Incorporate the latest advances in UC management into clinical practice
- Summarize implications of the current coronavirus pandemic on the management of patients with UC

Accreditation Statement and Credit Designation

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Introduction

In July 2020, a group of clinical experts in the field of inflammatory bowel disease (IBD) convened virtually to discuss current issues and advances in the management of ulcerative colitis (UC). The faculty began by reviewing abstracts from Digestive Disease Week (DDW) 2020 with particular relevance to the understanding and management of UC. Key advances in the contemporary management of UC were then reviewed, followed by an update on coronavirus disease 2019 (COVID-19) and its implications for patients with IBD. This supplement, which summarizes discussions from the meeting, is intended to provide clinicians with the latest information regarding current treatment options and paradigms for UC.

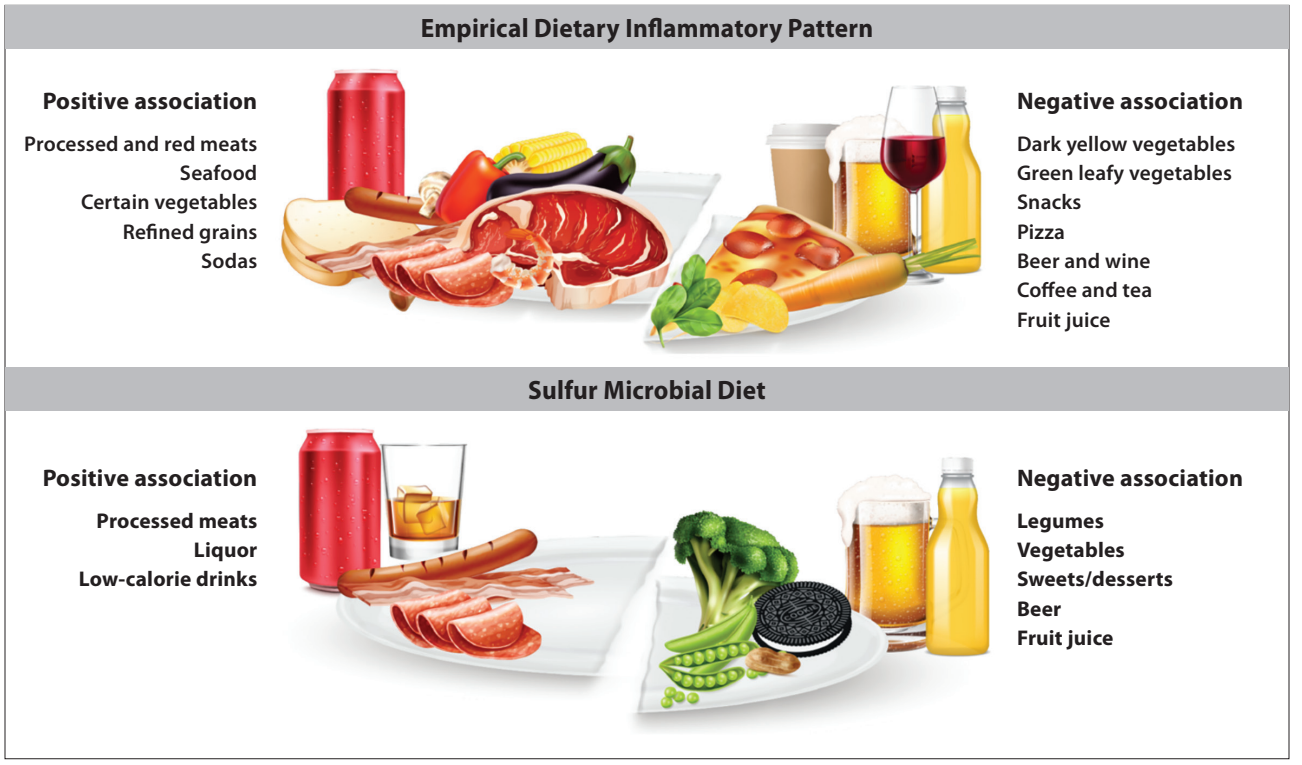

Figure 1. Dietary patterns associated with increased risk of Crohn's disease. Adapted from Lo et al[1] and Nguyen et al.[2]

UC Highlights From DDW 2020

Pathogenesis, Natural History, and Epidemiology for Clinicians

Dietary Patterns and Risk of IBD The effects of various dietary patterns on the risk of developing IBD were assessed in 2 studies using data from participants from the Nurses' Health Studies and Health Professionals Follow-Up Study.[1,2] Dietary information was obtained from validated questionnaires administered every 4 years, and self-reported diagnoses of IBD were confirmed through review of medical records. Lo and colleagues used this information to calculate an empirical dietary inflammatory pattern (EDIP) score, based on a weighted sum of 18 food groups (Figure 1).[1] In this analysis, participants with the most inflammatory diet (ie, highest quartile of cumulative average EDIP score) had a 45% increase in risk of Crohn's disease (CD) (hazard ratio, 1.45; 95% CI, 1.06-1.99) compared with those in the lowest quartile. In addition, dietary information was used to calculate a score for each participant's adherence to the sulfur microbial diet, an intake pattern associated with increased sulfur-metabolizing bacteria and characterized by intake high in processed meats and low in mixed vegetables and legumes (Figure 1).[2] As with the inflammatory diet, participants in the top quartile of sulfur microbial diet scores had an increased risk of CD compared with participants in the lowest quartiles, with a pooled multivariate relative risk of 1.49 (95% CI, 1.07-2.08; *P* trend=.01). Neither the inflammatory diet nor the sulfur microbial diet was significantly associated with the risk of developing subsequent UC.[1,2] While the cohort of nurses in these studies only reflects women and is somewhat older, and less heterogeneous than the US population of IBD patients, these data suggest the possibility of proinflammatory food groups contributing to sulfur-metabolizing bacteria and the risk of CD.

Table 1. Risk of Adverse Outcomes in Patients With Any 1 of 3 Markers of Low Social Status During the Study Period

	HR (95% CI)
Hospitalizations	1.54 (1.45-1.64)
ICU admission	1.90 (1.62-2.23)
Mortality	1.49 (1.33-1.69)
High-dose corticosteroid	1.20[a] (1.11-1.29)

[a]Relative risk. HR, hazard ratio; ICU, intensive care unit. Adapted from Bernstein et al.[3]

Social Determinants of Health in IBD Consistent with increasing evidence of health disparities in IBD, analysis of data from patients with IBD in Manitoba, Canada demonstrated a significant association between markers of low social status and poor outcomes in IBD.[3] In this study, 2905 (31.2%) of 9298 Manitoba residents with IBD were found to have at least 1 indicator of low social status (income assistance, children with endangered health or emotional well-being, and/or composite score reflecting household income and education rates). Having any of these 3 markers of low social status was linked to higher risk of hospitalization, intensive care unit (ICU) admission, high-dose corticosteroid use, and a higher rate of mortality (Table 1). These findings are consistent with other studies suggesting that socioeconomic factors contribute to poor outcomes in IBD, including hospitalizations and high corticosteroid use.[4-6]

Microbial Dysbiosis in Pregnant Women and Their Infants An analysis of data from the MECONIUM (Exploring Mechanisms of Disease Transmission in Utero Through the Microbiome) study highlighted potential effects of the altered microbiome on IBD activity in pregnant women and on their offspring during the first few years of life.[7] Fecal calprotectin levels of 341 pregnant women (90 with IBD, 251 controls) were measured at each trimester of pregnancy and in their babies (n=290) throughout the first 3 years of life. Fecal calprotectin levels were significantly higher among mothers with IBD (*P*<.001 at every trimester) than control mothers and declined during pregnancy. Higher fecal calprotectin in the babies was associated with maternal IBD (particularly with active disease), lower microbiome diversity, and the abundance of certain microbial genera (*Blautia* and *Streptococcus*). These data from the MECONIUM study suggest not only that alterations in the microbiome may affect IBD activity during pregnancy, but also that infants born of mothers with IBD, especially active IBD, demonstrate signs of intestinal inflammation in the neonatal period.

Genetic Associations and EIMs in IBD Genotype data from 3 large databases were analyzed in an effort to better understand the pathogenesis of extraintestinal manifestations (EIMs) in IBD.[8] Mega case-control regression analyses were conducted to compare cases with at least 1 joint, skin, eye, or

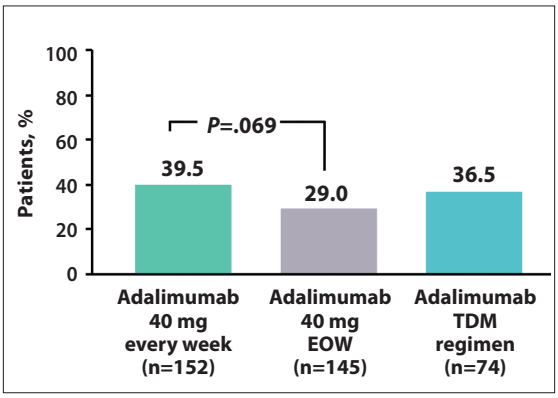

Figure 2. Clinical remission among week 8 responders at week 52 (primary endpoint) in the SERENE-UC study. EOW, every other week; SERENE-UC, Study to Evaluate the Safety and Efficacy of Two Drug Regimens in Subjects With Moderate to Severe Ulcerative Colitis; TDM, therapeutic drug monitoring. Adapted from Colombel et al.[9]

liver EIM (n=884) and those without EIMs (n=11,029). Several EIM associations were identified at established IBD susceptibility loci as well as novel loci. Further, logistic regression of classical human leukocyte antigen (HLA) alleles demonstrated significant associations of ankylosing spondylitis at the known alleles HLA-B27 and HLA-C*02. Psoriasis was associated with the known HLA-C*06 allele as well as 2 novel HLA alleles. These findings highlight the power of pooling genetic data to identify genetic pathways linked to EIMs in IBD, although better phenotyping of the patients with respect to EIMs will be needed.

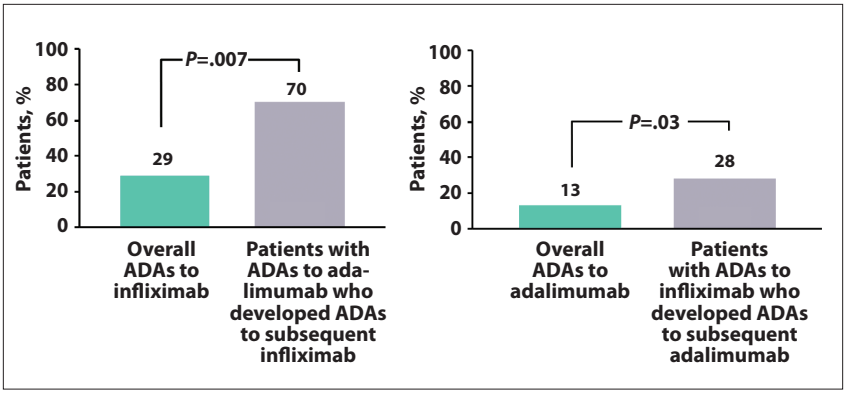

Figure 3. Rates of ADAs by anti-TNF exposure. ADA, antidrug antibody; TNF, tumor necrosis factor. Adapted from Yanai et al.[11]

Clinical and Therapeutic Advances

Optimizing Current Therapies The SERENE-UC (Study to Evaluate the Safety and Efficacy of Two Drug Regimens in Subjects with Moderate to Severe Ulcerative Colitis) study was a phase 3, double-blind trial comparing higher vs standard adalimumab dosing regimens for induction and maintenance therapy in adults with moderate to severely active UC. After completion of the 8-week induction study, 757 patients were rerandomized to receive adalimumab 40 mg every week, every other week, or using therapeutic drug monitoring (TDM) regimens.[9] Analysis of the primary endpoint in the intent-to-treat responder population (n=371) demonstrated numerically, but not significantly, higher rates of clinical remission (Full Mayo Score ≤2 with no subscore >1) among patients receiving adalimumab every week than every other week (39.5% vs 29.0%, respectively; *P*=.069) (Figure 2). Weekly maintenance dosing was associated with higher rates of corticosteroid-free patients than every-other-week dosing (74.7% vs 53.3%; *P*=.002), but other secondary efficacy endpoints were similar between groups. The safety profile was similar between treatment arms, and no new long-term safety concerns were identified. Overall, these data reinforce the efficacy of the current US Food and Drug Administration–approved maintenance regimen for adalimumab in UC[10] and demonstrate that more intensive maintenance therapy does not significantly improve outcomes over time. However, it is important to remember that controlled trials such as this do not allow personalized dose adjustments that are frequently needed in clinical practice based on either reactive or proactive TDM.

Given the practical and safety implications of immunogenicity in patients treated with anti–tumor necrosis factor (TNF) agents, Yanai and colleagues examined the rate of consecutive immunogenicity to a second anti-TNF relative to antidrug antibody (ADA) formation against the first agent.[11] In this retrospective cross-sectional study, the immunogenicity rates of 55 patients from 2 US medical centers who switched from 1 anti-TNF agent to another were analyzed and compared with those of the overall ADA rates determined from 1570 tests in the laboratory database. Of 25 patients who developed ADAs to infliximab as their first anti-TNF agent, 7 (28%) developed ADAs against adalimumab after switching to this agent. Seven of 10 (70%) patients with ADAs against adalimumab developed ADAs to infliximab after switching. Regardless of which anti-TNF agent was used first, the rates of consecutive immunogenicity were significantly higher than the overall immunogenicity rates (28% consecutive adalimumab immunogenicity vs 13% overall adalimumab immunogenicity; *P*=.03; 70% consecutive infliximab immunogenicity vs 29% overall infliximab immunogenicity; *P*=.007) (Figure 3). Only 33% of patients were treated with concomitant immunomodulators after switching anti-TNF therapies due to immunogenicity. These findings suggest that patients with consecutive immunogenicity may be predisposed to developing ADAs to anti-TNF therapies, and underscore the need for concomitant immunomodulator therapy in such patients.

Recognizing the need for real-world data, the effects of tofacitinib on endoscopic and histologic outcomes in patients were prospectively evaluated in a cohort of 35 patients with UC refractory to anti-TNF agents and vedolizumab.[12] After treatment with tofacitinib 10 mg twice daily for 8 weeks, the Mayo endoscopic subscore decreased significantly from baseline (*P*=.004). At week 8, 22.9% of patients achieved endoscopic response (Mayo endoscopic subscore ≤1),

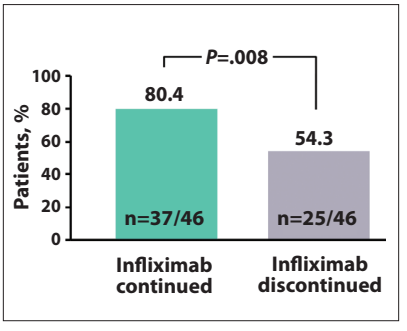

Figure 4. Week 48 remission among patients with baseline Mayo endoscopic subscore of 0 or 1. Adapted from Kobayashi et al.[14]

17.2% achieved endoscopic remission (Mayo endoscopic subscore of 0), and 14.8% achieved histologic remission (numeric Geboes score ≤6). Biologic response (50% decrease in fecal calprotectin or fecal calprotectin <250 mg/g) and remission (fecal calprotectin <250 mg/g at week 8) were achieved in 52.9% and 38.2% of patients, respectively. Multivariate analysis found that higher baseline serum albumin levels and lower Mayo endoscopic subscores were independent predictors of endoscopic and biologic remission. Primary nonresponse to tofacitinib was observed in 10 of 20 (50%) patients with primary nonresponse to 1 anti-TNF agent, 4 of 5 (80%) patients with primary nonresponse to 2 anti-TNF agents, and 3 of 8 (37.5%) patients with primary nonresponse to vedolizumab. These data support the efficacy of tofacitinib in inducing biologic, endoscopic, and histologic remission in patients with refractory UC, although it does not appear to be an alternative treatment strategy for those with primary nonresponse to 2 anti-TNF agents. Commenting on these data, Dr Stephen B. Hanauer noted that "given that tofacitinib is more effective in the anti-TNF–naive populations than those with previous exposure, it is not surprising that in this small series of patients, more refractory patients (based on prior exposure to more than 1 biologic) responded less well than biologic-naive patients."

The impact of combination therapy with immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) was retrospectively evaluated in a cohort of 549 patients (263 with UC, 286 with CD) receiving maintenance therapy with vedolizumab and 363 patients (4 with UC, 359 with CD) receiving ustekinumab maintenance therapy across 3 tertiary centers.[13] Of these, 131 patients receiving vedolizumab and 120 receiving ustekinumab were receiving combination therapy with thiopurines or methotrexate. At week 14, combination therapy did not achieve superior clinical response or remission rates (primary endpoint) compared with either vedolizumab monotherapy (68.2% vs 74.1%, respectively; *P*=.22) or ustekinumab monotherapy (54.6% vs 65.8%; *P*=.08). Similarly, clinical response or remission rates did not differ between treatment groups at week 30 or 54. Combination therapy was not found to improve endoscopic response at 1 year compared with monotherapy. Although these results fail to support a benefit of combining immunomodulators with vedolizumab or ustekinumab, prospective, properly powered studies are needed to define the role of combination therapy in patients treated with non–anti-TNF biologics. Dr Hanauer commented that these results "add to the accumulating real-world and clinical trial data suggesting that there is less impact on outcomes with combination therapy vs monotherapy with ustekinumab and vedolizumab, both of which are inherently less immunogenic than infliximab and adalimumab."

> "This study shows that patients who have a planned withdrawal of the biologic have a 50% chance of flaring. It is my hope that a combination of microbiome and microbiome metabolism analyses could predict whether a patient will stay in a long-lived remission, even after stopping a biologic or a small molecule."
> – Dr Maria T. Abreu

Predicting UC Relapse In the first prospective, randomized trial evaluating the impact of infliximab discontinuation in quiescent UC, 92 patients with UC maintained in clinical remission with infliximab were randomized to continue or discontinue infliximab in a 1:1 ratio.[14] Eligible patients were confirmed to be in clinical remission for longer than 6 months, corticosteroid-free, and had Mayo endoscopic subscores of 0 or 1. At week 48, remission rates were significantly higher in patients who continued infliximab compared with those who discontinued treatment (80.4% vs 54.3%, respectively; *P*=.008) (Figure 4). While the Nancy histologic index and C-

Table 2. Adjusted HRs of Pneumonia and Cox Model Results Adjusted for All Covariates

	Adjusted HR (95% CI)	*P* value
Charlson Comorbidity Index	1.16 (1.14-1.18)	<.001
Influenza vaccination	1.28 (1.19-1.38)	<.001
Narcotic within 60 days prior to index date	1.45 (1.34-1.57)	<.001
Prednisone cumulative (mg/day)	1.02 (1.01-1.03)	<.001
Prednisone within 30 days prior to index date	1.99 (1.78-2.22)	<.001
IBD flare	2.64 (2.38-2.93)	<.001
PPSV23	1.15 (1.07-1.23)	<.001
Medications (5-ASA reference)		
Thiopurines	0.92 (0.81-1.04)	.173
Anti-TNF	1.21 (1.05-1.40)	.01
Thiopurine/anti-TNF combination	1.12 (0.84-1.51)	.439
Vedolizumab	0.74 (0.30-1.80)	.508

5-ASA, 5-aminosalicylate; HR, hazard ratio; IBD, inflammatory bowel disease; PPSV23, pneumococcal polysaccharide vaccine; TNF, tumor necrosis factor. Adapted from Patel et al.[20]

reactive protein levels were predictive of remission at week 48, use of concomitant immunomodulators, serum infliximab trough concentrations, and Mayo endoscopic subscore of 0 at baseline were not. Most (66.7%) of the patients who relapsed achieved remission within 8 weeks of infliximab retreatment. These findings confirm that discontinuation of maintenance infliximab increases the risk of relapse in UC and suggest that endoscopic normalization does not guarantee successful infliximab discontinuation.

The value of various protein, metabolite, or microbial markers in predicting IBD relapse was prospectively explored in a cohort of 164 patients with quiescent IBD (108 with CD, 56 with UC).[15] Quiescent disease was defined as absence of clinical symptoms (Harvey-Bradshaw Index <4, Simple Clinical Colitis Activity Index <2) and endoscopic remission assessed by colonoscopy within the previous year. Serum samples were used to perform metabolomic and proteomic profiling, and stool samples were used for metagenomic sequencing. Multivariate models found 3 protein biomarkers (interleukin [IL]-10, GDNF, and CD8A) and 4 metabolic markers (propionyl-L-carnitine, carnitine, sarcosine, and sorbitol) to be significantly associated (P<.05) with relapse (symptomatic worsening accompanied by elevated inflammatory markers resulting in a change in therapy or IBD-related hospitalization or surgery). High proteomic (odds ratio [OR], 9.11; 95% CI, 1.90-43.61) and metabolomic (OR, 5.79; 95% CI, 1.24-27.11) risk scores independently predicted higher risk of relapse over 2 years. Further, proteomic and metabolomic changes associated with relapse correlated with proinflammatory changes in the microbiome.

Safety of IBD Therapies A number of studies reported at DDW 2020 add to our knowledge of the safety of current IBD therapies. The risk of lymphoma was evaluated among a population-based cohort of IBD patients in Israel (N=37,549), 164 of whom had been diagnosed with lymphoma.[16] Multivariate analysis demonstrated that older age at follow-up start (P=1.3 × 10^{-8}) and recent (up to 6 months) thiopurine exposure (P=.004) were associated with incident lymphoma diagnosis, whereas ever-exposure to thiopurines alone or in combination were not. The association of lymphoma with recent thiopurine exposure is notable given previous studies reporting an increased risk of lymphoma with increasing thiopurine exposure.[17,18] Further, the findings from this cohort differ from previous research that has demonstrated higher lymphoma risk with combination thiopurine and anti-TNF therapy compared with either monotherapy.[19]

The impact of immunosuppressive therapies on the risk of pneumonia was examined in a large nationwide cohort of IBD patients in the Veteran Affairs dataset from 2000 through 2019.[20] Of 56,398 patients with IBD in the database, 3442 (6.1%) developed all-cause pneumonia during a median 8 years of follow-up. Multivariate Cox regression analysis demonstrated an increased risk of pneumonia with exposure to anti-TNF therapy compared with 5-aminosalicylate (5-ASA) alone, higher cumulative corticosteroid dose, and any corticosteroid use in the preceding 30 days (Table 2). In contrast, thiopurines, vedolizumab, or combina-

Table 3. DVT and PE IRs Among Patients in the Tofacitinib Clinical Trial Program

	Induction Cohort (8 weeks)[a]		Maintenance Cohort (52 weeks)[a]			Overall Cohort (≤6.8 years)[a,b]		
	Placebo	Tofacitinib 10 mg BID	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	PD Tofacitinib 5 mg BID	PD Tofacitinib 10 mg BID	Tofacitinib All
N	282	938	198	198	196	198	959	1157
PY	44.8	156.2	100.4	146.2	154.3	664.1	1917.1	2581.3
DVT n (%) IR (95% CI)	1 (0.4) 1.99 (0.1-11.1)	0 (0.0) 0.00 (0.0-2.2)	1 (0.5) 0.97 (0.0-5.4)	0 (0.0) 0.00 (0.0-2.5)	0 (0.0) 0.00 (0.0-2.4)	0 (0.0) 0.00 (0.0-0.5)	1 (0.1) 0.05 (0.0-0.3)	1 (0.1) 0.04 (0.0-0.21)
PE n (%) IR (95% CI)	1 (0.4) 1.98 (0.1-11.0)	0 (0.0) 0.00 (0.0-2.2)	1 (0.5) 0.98 (0.0-5.4)	0 (0.0) 0.00 (0.0-2.5)	0 (0.0) 0.00 (0.0-2.4)	0 (0.0) 0.00 (0.0-0.5)	4 (0.4) 0.20 (0.1-0.5)	4 (0.3) 0.15 (0.0-0.4)

For Overall Cohort analysis, patients were categorized based on the average daily dose of tofacitinib (placebo exposure was not included): PD tofacitinib 5 mg BID (average total daily dose <15 mg) and PD tofacitinib 10 mg BID (average total daily dose ≥15 mg). [a]Events occurring up to 28 days beyond the last dose of the corresponding cohort are included in the analyses. [b]Data as of May 2019 (OLE study database not locked). BID, twice daily; DVT, deep vein thrombosis; IR, incidence rate; N, number of patients; n, unique number of patients with a particular adverse event; OLE, open-label, long-term extension; PD, predominant dose; PE, pulmonary embolism; PY, patient-years. Adapted from Sandborn et al.[22]

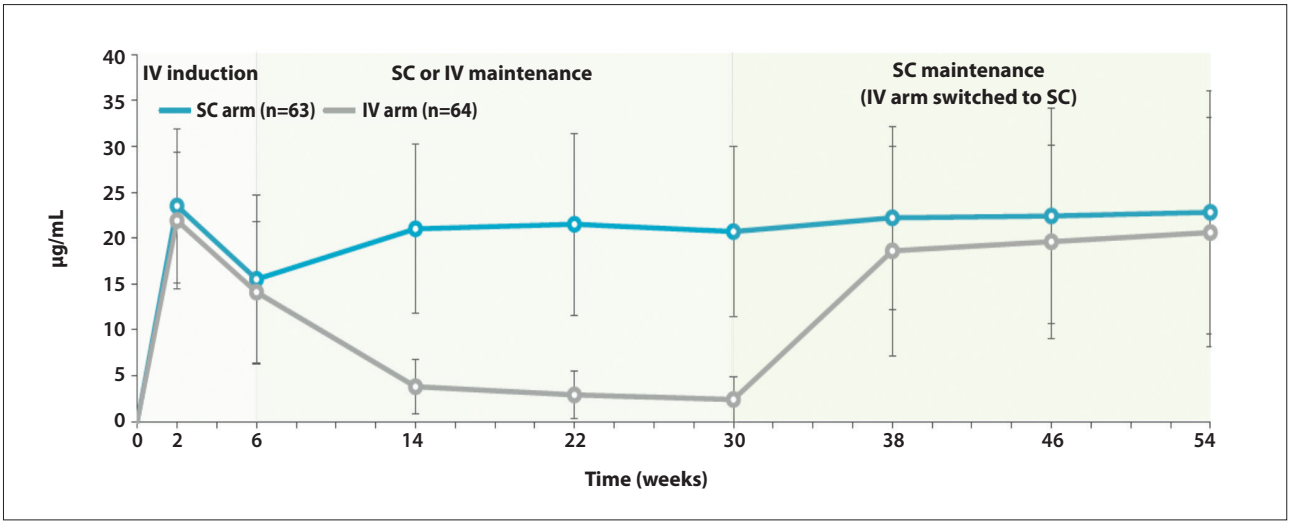

Figure 5. Mean trough (predose) infliximab concentrations with CT-P13 SC or IV. IV, intravenous; SC, subcutaneous. Adapted from Reinisch et al.[26]

tion thiopurine and anti-TNF therapy were not significantly associated with a greater risk of pneumonia. Nonmedication-related factors associated with increased pneumonia risk included older age, male sex, more comorbidities, IBD flares, and higher health care utilization.

In light of recent updates to the tofacitinib prescribing information regarding the risk of thromboembolism,[21] Sandborn and colleagues reported an update on the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in the tofacitinib UC clinical development program.[22] A total of 1157 patients involved in placebo-controlled induction/maintenance studies and/or an open-label, long-term extension (OLE) study were evaluated for DVT and PE, with 2581.3 patient-years of tofacitinib exposure and up to 6.8 years of treatment. Four patients in the Induction and Maintenance Cohorts experienced a DVT or PE, and all were receiving placebo at the time of the event (Table 3). Five patients, all receiving tofacitinib 10 mg twice daily, in the Overall Cohort experienced a thromboembolic event during the OLE study. These events occurred after 7 months or more of treatment, and all patients had risk factors (other than UC) for venous thrombosis. These results indicate that the incidence rates of thromboembolic events in the Overall Cohort have remained stable since last reported.[23]

Looking to the Future Recognizing the therapeutic potential of low doses of IL-2 in immune-mediated diseases as well as in preclinical models of UC,[24] a phase 1b/2a study was conducted to examine the safety and efficacy of this agent when administered subcutaneously to patients with moderate to severely active UC.[25] In this open-label, single-arm trial, 24 patients with UC and a Mayo score of 6 to 12 received daily subcutaneous (SC) IL-2 during a dose-escalation phase followed by treatment with the maximum tolerated dose. The most common (occurring in >10% of patients) adverse events across all doses included injection site reactions and malaise, and no serious adverse events were observed. Ten of 24 (41.6%) patients achieved either response or remission. A dose of 1×10^6 IU/m^2/day was found to be the maximum effective dose, achieving a biologic response and peripheral regulatory T-cell expansion without significant toxicity.

CT-P13 SC, a novel infliximab formulation approved by the European Medicines Agency for use in rheumatoid arthritis, has demonstrated comparable clinical efficacy and safety with CT-P13 intravenous (IV) in a controlled trial involving patients with CD and UC for up to 30 weeks.[26] Reinisch and colleagues reported further data from this trial, characterizing the efficacy, pharmacokinetics, and safety of CT-P13 SC over 1 year. After receiving 5 mg/kg IV loading doses at weeks 0 and 2, patients were randomized at week 6 to either SC 120 mg (patients <80 kg) or 240 mg (patients ≥80 kg) every 2 weeks or to continue 5 mg/kg IV every 8 weeks. At week 30, patients in the IV arm were switched to the SC arm. A total of 105 of 131 randomized patients completed the week 54 visit. Clinical response and remission rates were comparable between the IV and SC arms at week 30 and at week 54 after the remaining IV patients switched to SC. Rates of mucosal healing were also similar between arms at week 54. The overall safety profiles of the formulations were comparable, with the exception of a higher rate of localized injection site reactions in the SC group. Trough (predose) infliximab concentrations in the IV arm increased to levels similar to those in the SC group and were maintained through week 54 (Figure 5). These results support CT-P13 as a viable therapeutic option for use early after induction or in patients switching from IV during maintenance therapy.

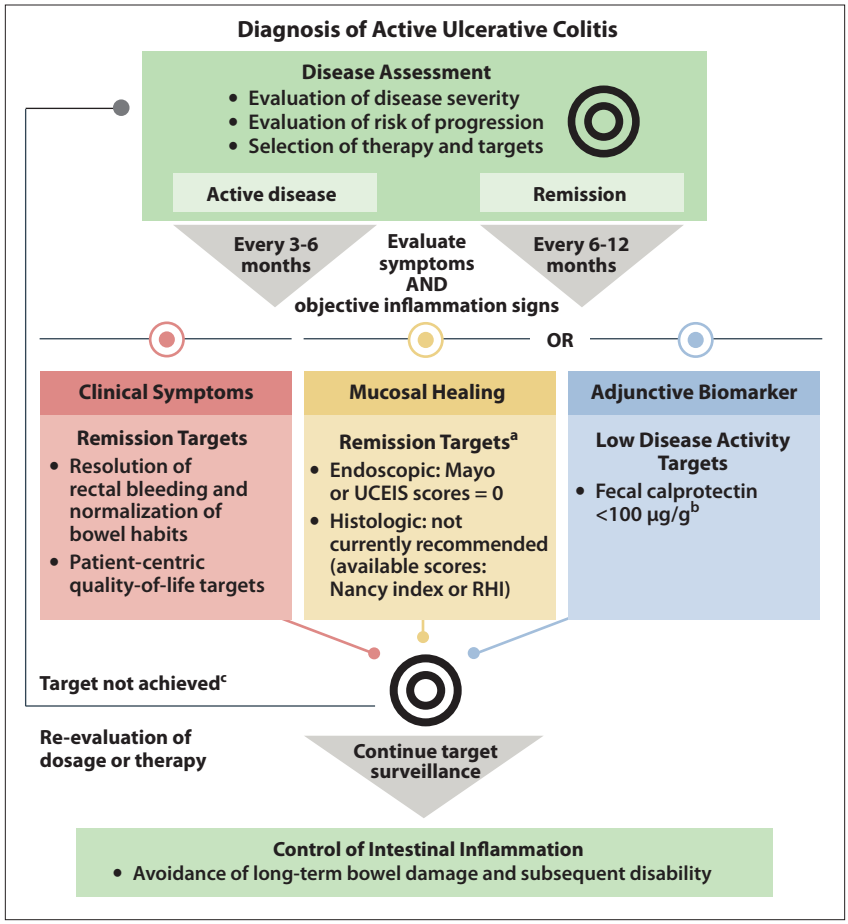

Figure 6. Proposed ulcerative colitis treat-to-target algorithm. [a]Mucosal healing as a treatment target must involve patient decision because of the high burden of monitoring and potential need for therapy escalation despite symptom resolution. [b]Biomarker normalization as a treatment target must involve patient decision because of potential need for therapy escalation despite symptom resolution. [c]If adjunctive biomarkers are not improving or normalizing, mucosal healing targets should be reassessed. RHI, Robarts Histopathology Index; UCEIS, Ulcerative Colitis Endoscopic Index of Severity. Adapted from Ungaro et al.[29]

Update on UC Management

The recognition of the importance of minimizing disease activity early in the disease course, coupled with an increasing ability to measure clinical and objective endpoints, has led to evolving treatment paradigms in UC. A key emerging strategy is a treat-to-target approach, which aims to achieve disease remission by adjusting therapy according to the achievement of treatment response targets.[27-29] This concept has widespread adaptation in other diseases, such as targeting normal blood pressure in patients with hypertension or normal glycosylated hemoglobin in patients with diabetes. From a practical perspective, the treat-to-target strategy requires collaboration between the physician and patient to assess baseline disease characteristics, identify appropriate targets, tailor therapy based on the risk of disease progression, monitor progress, and optimize therapy to reach the goal (Figure 6).[27]

Assessing Disease Severity and Activity

Once a diagnosis of UC is made, assessment of both disease activity and severity are essential in formulating a treatment plan.[30] In differentiating

Table 4. American College of Gastroenterology Guidelines for Severity in Active Ulcerative Colitis

	Remission	Mild	Moderate to Severe	Fulminant
Stools (number/day)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR (mm/hr)	<30	<30	>30	>30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
FC (µg/g)	<150-200	>150-200	>150-200	>150-200
Endoscopy (Mayo subscore)	0-1	1	2-3	3
UCEIS	0-1	2-4	5-8	7-8

The above factors are general guides for disease activity. With the exception of remission, a patient does not need to have all of the factors to be considered in a specific category. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; UCEIS, Ulcerative Colitis Endoscopic Index of Severity. Adapted from Rubin et al.[30]

"A treat-to-target strategy is not a snapshot in the time course of a disease but rather an iterative, ongoing process of assessing the parameter, modifying treatment, subsequent assessment of response, and further modifications until the endpoint is achieved and then maintained. The process does not stop when the target is met but is ongoing to ensure long-term stability."
– Dr Stephen B. Hanauer

these 2 parameters, Dr Hanauer explained that "disease activity can be considered a snapshot in time, capturing clinical signs and symptoms that are independent of ongoing medications or surgeries." Whereas activity does not imply the clinical course, disease severity considers the longitudinal factors associated with the prognosis. Based on the most recent American College of Gastroenterology guidelines on UC management, disease severity in active disease ranges from mild to severe based on a combination of patient-reported outcomes, laboratory values, and endoscopic parameters (Table 4). However, these factors actually reflect disease activity rather than prognosis, aside from the presence of deep ulcers reflected by a Mayo 3 endoscopic subscore. Thus, disease severity reflects not only symptoms, but factors that contribute to the risk of disease progression and influence response to various therapies.

Treatment Targets

Recognizing the disabling nature of UC, treatment goals are increasingly focused on slowing disease progression with the hope of altering the natural history of the condition.[28-30] To that end, treating to symptom resolution alone may leave active disease (ie, mucosal inflammation) and has not been proven sufficient to alter long-term remission or complication rates.[29] To the contrary, a proportion of patients with UC has been shown to have mucosal inflammation without clinical symptoms.[30,31] "With the introduction of endoscopic capabilities and indices that reproduce and validate endoscopic findings in the colon," Dr Hanauer explained, "discrepancies between the severity of symptoms, objective markers of inflammation, and the endoscopic findings became apparent." Moreover, a number of studies have demonstrated that achieving mucosal healing, or endoscopic remission, is associated with improved outcomes in UC, including lower risk of colectomy, lower clinical relapse and hospitalization rates, and reduced rates of dysplasia and colorectal cancer.[32,33] In light of these findings, treatment goals have evolved beyond symptom resolution alone to include sustained control of inflammation, with mucosal healing now widely recognized as an important goal of therapy.[28-30]

"When practitioners choose therapies for patients with UC, it is important to take into consideration not only their disease activity (that is, how sick they are at the time they have active disease), but their prognosis. A practitioner may see a patient with mild activity but a poor prognosis and start that patient on initial therapy with biologic therapy. The recent ACG guidelines for the first time also take into consideration the presence of fecal urgency. In addition, fecal calprotectin and endoscopic disease activity are included. Thus, a conglomerate of endoscopy, symptoms, and biomarkers may help a practitioner decide on appropriate therapeutic interventions."
– Dr Gary R. Lichtenstein

Although the endoscopic aspects of mucosal healing have emerged as a primary treatment goal in UC, the histologic aspects of mucosal healing are just beginning to be appreciated.[29,30,34-37] Histologic healing, defined as microscopic normalization of the colonic mucosa, is a distinct target from endoscopic healing, a measure of endoscopically visible disease activity.[29] Dr Hanauer noted that "with validation of histologic scores in UC, such as the Robarts or Nancy histologic indices and Geboes score, resolution of histologic inflammation has been associated with additional improvements in outcomes." Indeed, a growing number of studies demonstrate that histologic remission in UC is predictive of corticosteroid-free remission, clinical relapse, hospitalization, and corticosteroid use,[30,38] while others have correlated the degree of histologic inflammation with dysplasia and colorectal cancer.[30,39,40] Although more data are needed to identify which histologic indices should be used in research and in clinical practice,

Dr Maria T. Abreu noted that "mucosal healing, which includes both endoscopic and histologic normalization, should be an aspirational goal in treating our patients."

In speaking to the clinical utility of these endpoints, Dr Gary R. Lichtenstein noted that "perfection may be the enemy of excellence." "For example," he continued, "a patient with a previous Mayo score of 4 who is now a Mayo 1 with persistent histologic inflammation and is asymptomatic does not represent a failure of medical therapy. In other words, not all patients evaluated are mandated to have a Mayo 0 and absent histologic inflammation as their treatment endpoint." All endpoints need to be considered in the context of where patients were prior to therapy and which therapies have been used. Dr Lichtenstein concluded, "Thus, although the presence of persistent histologic inflammation in the aforementioned patient may confer a higher risk of disease flare in the subsequent 6 to 12 months, the treatment endpoint achieved in this patient may be considered to be appropriate and the outcome successful."

The clinical utility of adjunctive biomarkers, particularly fecal calprotectin, as targets in UC has grown, with accumulating data demonstrating correlations of low concentrations with the absence of mucosal inflammation and rising concentrations with relapse.[29,30] In contrast, advanced imaging modalities (eg, computed tomography, magnetic resonance, intestinal ultrasound) are useful in staging disease location and evaluating complications, but have not been adequately evaluated or established as surrogate targets for disease severity or response to therapies.[29] Dr Lichtenstein noted that although normalization of biomarkers is desirable, it is not necessarily the final endpoint to achieve, as verification with endoscopy is important. Normal C-reactive protein levels can be seen in patients with active disease[41] as well as in asymptomatic patients with mild mucosal lesions, especially those with isolated involvement of the ileum.[42]

> "Putting these all together has evolved the concept of a deep remission that includes the resolution of symptoms, endoscopic lesions, and biomarkers. Increasing numbers of clinical trials and real-world observational series have continued to support the concept that 'the deeper the remission, the better the long-term course.'"
> – Dr Stephen B. Hanauer

Personalizing Therapy

With the growing effort to slow disease progression, management of UC is increasingly driven by assessing a patient's prognostic factors for aggressive disease.[43-45] With this approach, patients with risk factors for an unfavorable disease course are treated more aggressively after initial diagnosis than patients with fewer risk factors for progression, who may be managed with a conventional step-up approach.[43,45] In patients with limited anatomic involvement and mild endoscopic disease who are believed to have a low risk of colectomy, treatment with oral and/or rectal 5-ASAs with or without oral budesonide is recommended.[30,46] In contrast, more aggressive therapies are recommended for patients with poor prognostic factors such as extensive colitis, deep ulcers, previous requirement for corticosteroids, and failure to respond to conventional treatments. Options for such patients include initiating a thiopurine with a short course of corticosteroids, a biologic agent (anti-TNF agent [infliximab, adalimumab, certolizumab pegol], vedolizumab, or ustekinumab) with or without an immunomodulator, or the oral Janus kinase (JAK) inhibitor tofacitinib.[30,46,47]

With the availability of several classes of biologics and targeted therapies with variable efficacy and safety profiles, positioning different agents in the treatment course of moderate to severe UC can be challenging.[48] Robust data support the efficacy of the anti-TNF therapies in achieving and maintaining clinical and endoscopic remission, improving quality of life, and reducing hospitalizations and surgeries in UC.[30,49-54] 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.[55] Vedolizumab, a gut-selective agent that

> "Perhaps as a result of the age of our patient population, and the fact that tofacitinib is being used primarily in the outpatient setting, the increase in thromboembolic complications seen in rheumatoid arthritis patients has not been seen in UC. This concern has limited the use of tofacitinib in the right population, which would be younger patients who could achieve rapid remission with this agent."
> – Dr Maria T. Abreu

acts by binding the $\alpha_4\beta_7$ integrin,[56,57] has emerged as a first-line agent in this setting due to its efficacy, favorable safety profile, and low rate of immunogenicity.[55,58] Ustekinumab, an anti-p40 antibody that inhibits IL-12 and -23, induces and maintains remission in UC and, like vedolizumab, offers excellent safety with low immunogenicity.[55]

Unlike the biologics, tofacitinib is an oral small molecule inhibitor that has demonstrated a notably rapid onset of action, with some patients in phase 3 trials achieving significant improvement in the partial Mayo score as early as 2 weeks.[59] Dr Lichtenstein emphasized the importance of onset when choosing therapies and added that post hoc analysis of tofacitinib clinical trial data demonstrated benefit within 3 days of use. Given this rapid onset, patients hospitalized with acute severe UC have been successfully treated with tofacitinib.[60] "Although this use in hospitalized patients is currently an off-label use," he noted, "future validation of clinical treatment efficacy in this study population might be of interest to assess in a prospective randomized clinical trial." Key safety concerns with tofacitinib include the risk of infection, particularly reactivation of herpes zoster, hyperlipidemia, and thromboembolic risks.[21,30,59] Data indicating an increased risk of DVT and PE associated with tofacitinib in patients with rheumatoid arthritis recently prompted the addition of a warning to the product labeling.[21] Dr Abreu noted that tofacitinib has been relegated to second- or third-line use due to this thromboembolic risk, an unfortunate positioning "for many patients who could benefit from its mechanism of action and rapid response."

The role of combination therapy in UC continues to be refined. Historically, clinical trials of biologics and the more recent JAK inhibitors enrolled patients with inadequate responses to aminosalicylates, immunosuppressives, or anti-TNF agents. Dr Hanauer noted that "within the context of these trials where patients were refractory to their baseline medications, post hoc analyses did not demonstrate clinical benefits whether or not patients were receiving aminosalicylates or thiopurines (despite higher biologic drug levels and reduced ADAs)." He further explained that these trials were neither powered nor randomized according to baseline therapies. In contrast, subsequent data from trials such as the UC-SUCCESS study that randomized immunosuppressive- and bio-naive patients clearly demonstrated a benefit of combining thiopurines and anti-TNF agents in UC.[61] Commenting on these findings, Dr Abreu noted that thiopurines not only increase the level of these biologics, but provide a complementary mechanism of action to TNF inhibition. Of interest, recent American Gastroenterological Association guidelines on managing moderate to severe UC suggest that vedolizumab or ustekinumab can also benefit from combination with immunosuppressives, a recommendation based on post hoc analyses.[47] Given that prospective, controlled trials have yet to be performed with non-TNF biologics, this recommendation has not been met with universal agreement.

Monitoring Progress

Regular assessment of disease activity is an essential component of a treat-to-target strategy, although the frequency of monitoring varies by parameter and by disease activity and severity.[28-30] According to the STRIDE consensus statement, endpoints should be assessed at least every 3 months in patients with active disease and 6 to 12 months in patients who have achieved remission.[28] Symptoms are the most responsive to change and can be evaluated within days to weeks. Biomarkers such as C-reactive protein and fecal calprotectin can be assessed both short and long term. Expanding on this, Dr Lichtenstein noted that "laboratory evaluation every 4 weeks or less may be needed in patients with an acute flare, while assessments every 12 weeks may be acceptable after patients have normalized after a recent flare or change in therapy." In contrast, endoscopy and histology are longer-term targets that may require many months to demonstrate improvement. In general, patients starting on therapy for UC may generally have endoscopic confirmation of their target after 3 to 6 months,[28] perhaps with an intermediate biomarker. Dr Abreu added that "there is a role for colonoscopy for any major changes in medical therapy, and certainly at baseline to get the extent of disease, including biopsies of inflamed and normal-appearing mucosa."

Optimizing Therapy

With the evolution of validated treatment targets and expanded treatment options, the concept of optimizing therapies based on their pharmacokinetic and pharmacodynamic properties has become an important tool in managing UC. However, as Dr Hanauer noted, "this is not a novel concept in medicine or in IBD. Remember that weight-based dosing of thiopurines has been shown to be inferior to thioguanine levels in improving outcomes and reducing complications, and serum cyclosporine concentrations are useful in monitoring for both efficacy and safety." More recently, however, growing evidence linking high concentrations of biologic agents with favorable outcomes (clinical, biomarker, and endoscopic remission),[62-65] as well as ADAs to worse outcomes (lower serum drug concentrations, reduced clinical response, and infusion reactions),[66,67] has established TDM as an important tool in optimizing UC management. Although much of these data have been obtained in patients on anti-TNF therapies,[62-65] exposure-response relationships have been demonstrated for other biologics, including vedolizumab[68,69] and ustekinumab.[70]

TDM can be used at any point in induction or maintenance therapy, either in a proactive routine fashion when the patient is in remission, or as a reactive strategy to help guide treatment in cases of suboptimal

response.[71] Although most current evidence has explored reactive TDM, recent retrospective data 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.[72] In contrast, the TAXIT (Trough Concentration Adapted Infliximab Treatment) study in patients with CD found that, after initial infliximab dose optimization, the proportion of patients achieving remission at 1 year did not differ between those who received routine proactive TDM and those who received no TDM.[73] Despite these inconsistencies, Dr Abreu noted that proactive monitoring allows for necessary dosing adjustments to be made early in the course of treatment.

Another important aspect of optimizing UC management is to continually reevaluate the patient's medication regimen, adjusting dosing as necessary. For example, Dr Abreu noted, "there are patients who are finally doing well after a severe flare in whom the biologic dose or frequency can be reduced." The decision to discontinue a therapy, however, may be unclear, as definitive data to guide such decisions are lacking.[74-76] Although some studies have explored the impact of infliximab withdrawal on UC relapse, randomized trials assessing the withdrawal of mesalamine, thiopurines, non-TNF biologics, and tofacitinib have not been performed. In the absence of such data, decisions to discontinue treatment are typically made on a case-by-case basis. Recognizing that mesalamine can be discontinued in some patients who achieve remission on a biologic, Dr Abreu commented that there are others "who continue to have some symptoms even on a biologic who can benefit from oral and topical mesalamine." Additionally, it is reasonable to consider discontinuation of either thiopurines or biologics in patients who achieve deep remission on combination therapy, allowing concentrations of each agent to guide the decision. For example, it may be appropriate to stop the thiopurine when infliximab levels are adequate, whereas infliximab may be discontinued in the setting of suboptimal infliximab concentrations but adequate thioguanine levels. Other patient factors, such as age and prognostic factors for relapse, may influence the decision as well. Regardless of which agent is discontinued, Dr Hanauer emphasized, "continued monitoring of symptoms, biomarkers, and endoscopy are necessary to avoid unanticipated disease progression."

Updates on COVID-19 and IBD

Overview of COVID-19

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, where over half of the 41 infected patients had direct contact history with a local seafood market selling live and slaughtered wild animals for food consumption.[77-79] Within months of the first reports in December 2019, the virus had infected thousands of people worldwide and had been declared a global pandemic.[80] At the time of this writing, nearly 18.7 million cases of COVID-19 and over 700,000 deaths have been confirmed worldwide.[81]

Named for its crown-like appearance,[82] SARS-CoV-2 is an enveloped RNA virus that enters target cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in epithelial cells of the lung, small intestine, colon, kidney, liver, pancreas, and blood vessels.[83-86] Transmission occurs primarily person-to-person via respiratory droplets from infected individuals and possibly from contaminated surfaces.[87,88] Manifestations of SARS-CoV-2 infection can range from asymptomatic to mild upper respiratory tract symptoms to life-threatening sepsis and cytokine storm. The most common manifestations among hospitalized patients with COVID-19 are fever and respiratory symptoms, including dry cough and shortness of breath.[88,89] Multiple reports have identified older age and the presence of comorbidities to be risk factors for severe COVID-19 and worse outcomes.[77,90-94]

COVID-19 and the GI Tract

Although research conducted to date has focused on the mechanisms and consequences of SARS-CoV-2 infection in respiratory cells, the wide expression of ACE2 receptors throughout the digestive system, particularly the small intestine and colon, also provides a target for viral invasion.[86,95,96] Accordingly, it has become increasingly clear that a considerable proportion of patients with COVID-19 experience gastrointestinal (GI) symptoms, usually in addition to respiratory symptoms.[96-100] An earlier report involving 204 patients with COVID-19 across hospitals in Hubei province in China found that half of patients reported a digestive symptom, most commonly lack of appetite and diarrhea.[97] Similarly, a multicenter cohort study across 9 US hospitals demonstrated that 61.3% of 318 patients with COVID-19 presented with at least 1 GI symptom, with lack

> "Similar to the general population, patients with IBD should practice social distancing, appropriate use of personal protective equipment, and avoid nonessential travel to minimize potential exposure to other individuals with COVID-19."
> – Dr Gary R. Lichtenstein

of appetite (34.8%), diarrhea (33.7%), and nausea (26.4%) being the most common symptoms.[98] In fact, GI symptoms were the chief complaint in 20% of patients and the initial presenting symptom in 14% of patients. Liver damage related to COVID-19 is also commonly observed, with a meta-analysis of 29 studies reporting a 15% to 20% pooled rate of elevated liver function enzymes among patients with COVID-19.[96]

A number of studies have detected SARS-CoV-2 RNA in stool specimens of infected patients, providing further evidence that the virus can involve the GI tract.[86,89,95,96,100-103] A recent meta-analysis found that 8 studies reported fecal tests that were positive for SARS-CoV-2, with fecal viral RNA shedding detected in 40.5% of patients.[96] Importantly, fecal viral shedding has been reported long after respiratory samples have become negative.[101,103] However, some investigators have found that the viral particles in stool were of insufficient quantities to be infectious.[102] Although these findings raise important questions, more data are needed to confirm the possibility of fecal-oral transmission and inform decisions regarding stool testing in infected patients.[86,95,96,101]

Risk, Clinical Course, and Outcomes of COVID-19 in IBD

The potential for increased susceptibility of patients with IBD to SARS-CoV-2 infection and COVID-19 has been a concern due to the immune-mediated pathogenesis of the condition, frequent treatment with immunosuppressive therapies, and need to be at medical facilities for infusions or endoscopic procedures.[104,105] Although data are limited, one study reported a 0.0025 cumulative incidence of COVID-19 among 6000 patients with IBD in France and Italy, a rate similar to that observed in the general population.[104] Based on the limited published evidence and expert opinion, patients with IBD are not believed to have a baseline increased risk of infection with SARS-CoV-2 or development of COVID-19.[105,106]

Table 5. Multivariate Regression for Outcomes From the SECURE-IBD Cohort

Variable (Referent)	ICU/Vent/Death OR (95% CI) N=517	*P* value
Age	1.04 (1.01-1.06)	.002
Male (female)	1.20 (0.55-2.60)	.65
Diagnosis of CD (UC/IBD unspecified)	0.76 (0.31-1.85)	.54
Active disease (remission)	1.14 (0.49-2.66)	.76
Systemic corticosteroid (none)	6.87 (2.30-20.51)	<.001
Anti-TNF agent (none)	0.90 (0.37-2.17)	.81
Current smoker	0.55 (0.06-4.94)	.59
BMI ≥30	2.00 (0.72-5.51)	.18
Comorbidities (none) 1 ≥2	 1.22 (0.45-3.26) 2.87 (1.05-7.85)	 .70 .04
5-ASA/sulfasalazine (none)	3.14 (1.28-7.71)	.01

5-ASA, 5-aminosalicylate; BMI, body mass index; CD, Crohn's disease; IBD, inflammatory bowel disease; ICU, intensive care unit; OR, odds ratio; SECURE-IBD, Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; TNF, tumor necrosis factor; UC, ulcerative colitis; vent, ventilator use. Adapted from Brenner et al.[77]

Several reports have begun to characterize the clinical course and outcomes of COVID-19 in patients with IBD.[77,90,107] In a prospective observational cohort of patients with IBD and COVID-19 across 24 Italian referral units, 36 of 79 (46%) patients developed COVID-19–related pneumonia, 22 (28%) were hospitalized, 7 (9%) required nonmechanical ventilation, and 6 (8%) died.[90] Age over 65 years, active IBD, and higher Charleston Comorbidity Index score were significantly associated with worse prognosis (ie, higher risk of COVID-19–related pneumonia and death). Similar findings were observed in the first published analysis of data from the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) registry.[77] In this report involving 525 cases from 33 countries, 37 (7%) patients developed severe COVID-19, 161 (31%) were hospitalized, and 16 died, translating to a 3% case fatality rate. Consistent with the Italian cohort, older age and presence of comorbidities were significantly associated with risk of poor outcomes (composite outcome of ICU admission, ventilator support, and/or death) (Table 5). Although the presence of active disease significantly increased the risk of hospitalization or death, it was not associated with ICU admission/ventilator requirement/death. Taken collectively, these findings do not suggest that IBD predisposes patients to aggravated outcomes of COVID-19, and underscore the contribution of age and comorbidities to worse outcomes in IBD patients, as observed in the general population.

Given the increased risk of serious bacterial and viral infections associated with many IBD therapies,[10,21,30,108,109] the impact of these medications on the risk and clinical course of COVID-19 in patients with IBD has been an area of great interest.[77,90,107] To that end, a nationwide retrospective cohort study involving 36 of 37,857 IBD patients in the Veterans' Affairs Healthcare System with COVID-19 observed no increase of COVID-19 associated with thiopurine or anti-TNF therapy.[107] Further, published evidence to date has not demonstrated an association between worse outcomes of COVID-19 and

therapy with thiopurines, anti-TNF agents, or vedolizumab.[77,90] In contrast, evidence published to date has consistently implicated corticosteroids as a risk factor for worse outcomes in patients with IBD and COVID-19.[77,90] In the previously mentioned Italian study, use of corticosteroids was associated with increased risk of COVID-19–related pneumonia (OR, 4.94; 95% CI, 0.95-25.55; *P*=.05) and death (OR, 6.28; 95% CI, 0.89-44.24; *P*=.064).[90] Similarly, multivariate regression analyses of data from the SECURE-IBD registry found the use of systemic corticosteroids associated with an OR of 11.62 for death (95% CI, 2.09-64.74; *P*=.05).[77] Of interest, 5-ASA/sulfasalazine use was also found to be significantly associated with worse outcomes in this population.

Guidance for IBD Management During the Pandemic

In light of the potential implications of COVID-19 on patients with IBD, the American Gastroenterological Association has issued a clinical practice update summarizing available guidance for patients with IBD and their providers.[105] Recognizing that patients with IBD do not appear to be at higher risk of SARS-CoV-2 infection, patients who are not infected are encouraged to maintain their current regimens with the goal of maintaining clinical and endoscopic remission.[105] Despite concerns regarding patients going to infusion centers for delivery of certain therapies, the ongoing use of infusion centers is supported, provided that the center has appropriate COVID-19 screening protocols in place. Specific guidance for patients who are infected with SARS-CoV-2 varies based on the presence and severity of COVID-19 manifestations, but general recommendations include tapering corticosteroids and holding thiopurines, methotrexate, and tofacitinib during the viral illness (Figure 7, Table 6). It is particularly important to investigate the source of GI symptoms in patients with COVID-19 and digestive symptoms, excluding enteric infection and active inflammation. Finally, clinicians who care for patients with IBD are encouraged to submit cases of IBD and confirmed COVID-19 to the SECURE-IBD registry at covidibd.org.

Conclusion

The management of UC has evolved considerably over the past decade

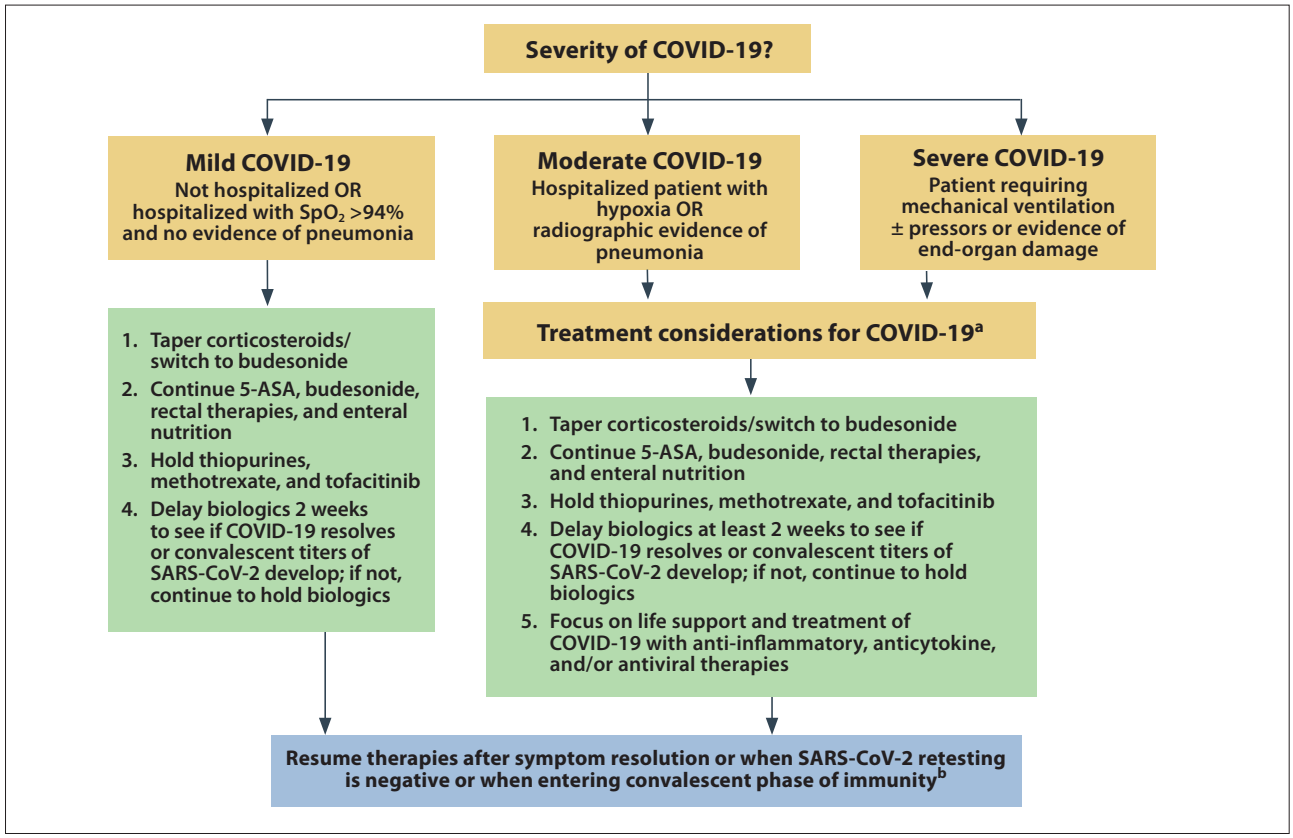

Figure 7. American Gastroenterological Association guidance for managing patients with IBD and COVID-19. [a]Treatment of COVID-19 under investigation; consider therapies that have safety and efficacy in IBD. [b]Clearance of SARS-CoV-2 may enable resumption of IBD therapy; role of serologic antibody testing unclear at the current time. (Viral clearance testing may or may not be possible or appropriate, given local testing capabilities and health system–approved epidemiologic testing strategies during the COVID-19 pandemic.) 5-ASA, 5-aminosalicylate; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, oxygen saturation. Adapted from Rubin et al.[105]

Table 6. American Gastroenterological Association Clinical Practice Update on Management of IBD During the COVID-19 Pandemic: Key Points

1. COVID-19 is the disease caused by the SARS-CoV-2 virus, but patients with IBD do not appear to be at a higher risk for infection with SARS-CoV-2 or development of COVID-19.
2. Patients with IBD who do not have infection with SARS-CoV-2 should not discontinue their IBD therapies and should continue infusion schedules at appropriate infusion centers.
3. Patients with IBD who have known SARS-CoV-2 but have not developed COVID-19 should hold thiopurines, methotrexate, and tofacitinib. Dosing of biologic therapies should be delayed for 2 weeks of monitoring for symptoms of COVID-19.
4. Patients with IBD who develop COVID-19 should hold thiopurines, methotrexate, tofacitinib, and biologic therapies during the viral illness. These can be restarted after complete symptom resolution or, if available, when follow-up viral testing is negative or serologic tests demonstrate the convalescent stage of illness.
5. The severity of the COVID-19 and the severity of the IBD should result in careful risk-benefit assessments regarding treatments for COVID-19 and escalating treatments for IBD.
6. Please submit cases of IBD and confirmed COVID-19 to the SECURE-IBD registry at covidibd.org.

COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SECURE-IBD, Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease. Adapted from Rubin et al.[105]

with growing emphasis on altering the natural history of the condition, recognition of both clinical and objective treatment targets, and availability of new treatment options. Taken collectively, these concepts have paved the way for a treat-to-target strategy in UC aimed at achieving and maintaining remission by adjusting therapies according to treatment targets. To that end, emerging data presented at DDW 2020 continue to add to our understanding of UC, strategies for optimizing its management, and the safety and efficacy of newer therapies. Lastly, clinicians who manage patients with UC are encouraged to keep up with the rapidly expanding evidence regarding COVID-19 and its implications for IBD management, and to report all cases of IBD and COVID-19 to the SECURE-IBD database.

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