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CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis

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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the management of moderate to severe ulcerative colitis (UC). The guideline was developed by the AGA Institute's Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that provides a detailed synthesis of the evidence from which these recommendations were formulated.[1] Development of this guideline and the accompanying technical review was fully funded by the AGA Institute without additional outside funding. Members of the guideline panel and technical review panel were selected by the AGA Governing Board in consultation with the Clinical Guidelines Committee with careful consideration of all Institute of Medicine recommendations for clinical guideline development. Joseph Feuerstein was the guideline panel chair and Siddharth Singh was the methodologist and co-chair of the guideline panel. A patient representative was also included in the development and review process and had no recommended changes. The guideline and accompanying technical review underwent independent peer review, and a 30-day open public comment period; all comments were collated by the AGA staff, and were reviewed and carefully considered by the guideline panel and technical review teams, respectively. Changes were incorporated in revised documents, and where changes were not accepted, a thoughtful response document was created. After the public comment period, 2 pivotal clinical trials (VARSITY, UNIFI) were published and a critical safety update on tofacitinib was issued by the US Food and Drug Administration (FDA). At the recommendation of the Clinical Guidelines Committee, the technical review and clinical guidelines were updated to incorporate this new evidence as presented here. In accordance with the Clinical Guidelines Committee policies, all clinical guidelines are reviewed annually at the AGA Clinical Guideline Committee meeting for new information. The next update for these guidelines is anticipated in 3 years from publication.

UC is a chronic inflammatory bowel disease with peak onset in early adulthood.[2] Untreated, the natural history of the disease is one of relapsing and remitting mucosal inflammation. Based on population-based cohort studies, the majority of patients with UC have a mild to moderate course, generally most active at diagnosis and then in varying periods of remission or mild activity. Approximately 15% patients may experience an aggressive course, and 20% of these patients may require hospitalization for severe disease activity.[2,3] The 5- and 10-year cumulative risk of colectomy is 10%–15%, primarily limited to patients with moderate to severe disease activity; a subset of hospitalized patients with acute severe ulcerative colitis (ASUC) have short-term colectomy rates of 25%–30%.[3] Predictors of an aggressive disease course and colectomy are the following: young age at diagnosis (<40 years old), extensive disease, severe endoscopic activity (presence of large and/or deep ulcers), presence of extra-intestinal manifestations, early need for corticosteroids, and elevated inflammatory markers.[4] For this guideline and the accompanying technical review, moderate to severe UC is defined based on the Truelove and Witts criteria and Mayo Clinic score (Table 1).[4–6] After excluding concomitant infections (such as *Clostridium difficile*), patients with moderate to severe disease are those who are dependent on or refractory to corticosteroids, have severe endoscopic disease activity (presence of ulcers), or are at high risk of colectomy. When reported, Mayo Clinic scores of 6–12 with an endoscopic subscore of 2 or 3 were considered moderate to severe disease. ASUC in this guideline is defined as hospitalized patients with the following Truelove and Witts criteria: ≥6 bloody bowel movements/day with at least 1 marker of systemic toxicity, including heart rate >90 beats/min, temperature >37.8°C, hemoglobin <10.5 g/dL, and/or erythrocyte sedimentation rate –30 mm/h.[6]

There are a number of different drug classes for long-term management of moderate to severe UC, including

Abbreviations used in this paper: **AGA, American Gastroenterological Association; 5-ASA, 5-aminosalicylate; ASUC, acute severe ulcerative colitis; CI, confidence interval; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; UC, ulcerative colitis.**

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Table 1. Disease Severity Scoring Systems

Variable	Truelove and Witts criteria		
	Mild	Severe	Fulminant
No. of stools/d	<4	>6	>10
Blood in stool	Intermittent	Frequent	Continuous
Temperature, °C	Normal	>37.5	>37.5
Pulse, *beats/min*	Normal	>90	>90
Hemoglobin	Normal	<75% normal	Transfusion required
Erythrocyte sedimentation rate, *mm/h*	≤30	>30	>30
Colonic features on radiograph	None	Air, edematous wall, thumbprinting	Colonic dilation
Clinical signs	None	Abdominal tenderness	Abdominal distention and tenderness

Variable	Mayo score for UC				
	Definition	Score	Variable	Definition	Score
Stool pattern	Normal no. of daily bowel movements	0	Endoscopic findings	Normal/inactive colitis	0
	1–2 more bowel movements than normal	1		Erythema, decreased vascularity	1
	3–4 more bowel movements than normal	2		Friability, marked erythema, erosions	2
	5 or more bowel movements than normal	3		Ulcerations, severe friability, spontaneous bleeding	3
Most severe rectal bleeding of the day	None	0	Physician Global Assessment	Normal	0
	Blood streaks seen in the stool less than half of the time	1		Mild colitis	1
	Blood in most stool	2		Moderate colitis	2
	Pure blood passed	3		Severe colitis	3

TNF-α antagonists, anti-integrin agent (vedolizumab), Janus kinase inhibitor (tofacitinib), interleukin 12/23 antagonist (ustekinumab), and immunomodulators (thiopurines, methotrexate).[7] In general, most drugs that are initiated for induction of remission are continued as maintenance therapy, if they are effective. This clinical practice is considered standard of care in this guideline and it is assumed that if a drug (excluding corticosteroids and cyclosporine) is started for and is effective for induction of remission or response, it will be continued for maintenance of remission.

This guideline addresses the medical management of adult outpatients with moderate to severe UC, as well as the medical management of adult hospitalized patients with ASUC. The guideline focuses on immunomodulators, biologics, and small molecules for induction and maintenance of remission (for moderate to severe UC) and decreasing the risk of colectomy (for ASUC). As noted, unless otherwise specified, we do not present separate recommendations for induction and maintenance of remission. The drugs are listed in order of FDA approval unless specifically mentioned. The first 7 questions are focused on the medical management of adult outpatients with moderate to severe UC; the subsequent 4 questions are focused on adult patients hospitalized with ASUC, focusing on initial management, and rescue therapy in cases of corticosteroid-refractory disease. We acknowledge challenges in defining moderate disease activity and severity, with variable definitions in clinical practice, and an understanding of this entity may be enhanced reading the AGA guideline on the management of mild to moderate UC.[8] This guideline does not address surgical management of moderate to severe UC or ASUC. Therapeutic drug monitoring to guide the use of biologic therapy has been addressed in separate AGA guidelines.[9] The guideline is intended for the use of gastroenterology providers, primary care providers, surgeons, patients, and policymakers.

For this guideline, critical outcomes for decision-making for adults with moderate to severe UC were induction and maintenance of remission, and for hospitalized adults with ASUC was short-term colectomy risk (within 3 months of hospitalization), and are reported in the evidence profiles. Important outcomes of interest were induction and maintenance of endoscopic remission, maintenance of corticosteroid-free remission, serious adverse events (including serious infections and malignancy), and treatment tolerability (drug discontinuation due to adverse events). These were considered in evidence synthesis especially if inadequate or conflicting data was observed for critical outcomes. Safety considerations with these medications have been synthesized in the accompanying technical review. In the recommendations presented in this guideline, estimates of effects of different medications are presented as the risk for failure to induce or maintain remission, that is, a relative risk (RR) or odds ratio (OR) <1 suggests that the drug under consideration is more effective than the comparison drug or placebo for induction or maintenance of remission.

This guideline was developed using a process described elsewhere.[10] Briefly, the AGA process for developing clinical practice guidelines incorporate Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[11] and best practices as outlined by the Institute of Medicine.[12] GRADE methodology was used to

prepare the background information for the guideline and the accompanying technical review.[1] Optimal understanding of the guideline will be enhanced by reading the applicable portions of the technical review. The guideline panel and the authors of the technical review met face to face on December 14, 2018 to discuss the findings from the technical review. The guideline authors subsequently formulated the guideline recommendations using the GRADE evidence-to-decision framework guidance. New evidence was presented to the guideline panel by the technical review team on October 16, 2019, and was reviewed and approved in a virtual face-to-face meeting on November 1, 2019. Although the quality of evidence (Table 2) was a key factor in determining the strength of the recommendations (Table 3), the panel also considered the balance between benefit and harm of interventions, patients' values and preferences, and overall resource utilization. The recommendations, quality of evidence, and strength of recommendations are summarized in Table 4.

Table 2. GRADE Definitions of Quality and Certainty of the Evidence

Quality grade	Definition
High	We are very confident that the true effect lies close to the estimate of the effect
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low	Our confidence in the estimate is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect
Evidence gap	Available evidence is insufficient to determine true effect

Recommendation

1. In adult outpatients with moderate to severe ulcerative colitis, the AGA recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment. *(Strong recommendation, moderate quality evidence)*

The panel recommends treating adult outpatients with moderate to severe UC with infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment for the induction and maintenance of remission. There were 16 randomized controlled trials (RCTs) comparing the TNF-α antagonists, vedolizumab, tofacitinib, and ustekinumab to placebo (see technical review). Induction of remission was assessed at 6–8 weeks and maintenance of remission was evaluated at 30–54 weeks. All active interventions were superior to placebo for induction of remission, regardless of prior biologic exposure (infliximab: relative risk [RR], 2.85; 95% confidence interval [CI], 2.11–3.86; adalimumab: RR, 1.62; 95% CI, 1.15–2.29; golimumab: RR, 2.49; 95% CI, 1.58–3.93; vedolizumab: RR, 2.22; 95% CI, 1.36–3.64; tofactinib: RR, 3.22; 95% CI, 2.03–5.08; and ustekinumab: RR, 2.91; 95% CI, 1.72–4.94). Likewise, all active interventions were superior to placebo for maintenance of remission (infliximab: RR, 2.25; 95% CI, 1.67–3.05; adalimumab: RR, 2.28; 95% CI, 1.52–3.42; golimumab: RR, 1.88; 95% CI, 1.32–2.68; vedolizumab: RR, 2.31; 95% CI, 1.63–3.28; tofactinib 5 mg twice daily: RR, 3.09; 95% CI, 1.99–4.79; and ustekinumab: RR, 1.83; 95% CI, 1.33–2.49). All medications were well-tolerated with low rates of serious adverse events in both trials of induction and maintenance therapy, not significantly different from

Table 3. GRADE Definitions on Strength of Recommendation and Guide to Interpretation

Strength of recommendation	Wording in the guideline	For the patient	For the clinician
Strong	"The AGA recommends…"	Most individuals in this situation would want the recommended course and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests…"	The majority of individuals in this situation would want the suggested course, but many would not.	Different choices would be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
No recommendation	"The AGA makes no recommendation…"	—	The confidence in the effect estimate is so low that any effect estimate is speculative at this time.

Table 4. Summary of Recommendations of the AGA Clinical Guidelines Committee for the Management of Moderate to Severe Ulcerative Colitis

Recommendations	Strength of recommendation	Quality of evidence
1. In adult outpatients with moderate to severe UC, the AGA recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment. (Medications are ordered based on year of approval by the US FDA.)	Strong	Moderate
2a. In adult outpatients with moderate to severe UC who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab rather than adalimumab, for induction of remission.	Conditional	Moderate
Comment: Patients, particularly those with less severe disease, who place higher value on the convenience of self-administered subcutaneous injection, and a lower value on the relative efficacy of medications, may reasonably chose adalimumab as an alternative.		
2b. In adult outpatients with moderate to severe UC who are naïve to biologic agents, the AGA recommends that tofacitinib only be used in the setting of a clinical or registry study. (No recommendation, knowledge gap)	No recommendation	Knowledge gap
Comment: Updated FDA recommendations (July 26, 2019) on indications for use of tofacitinib in UC recommends its use only after failure of or intolerance to TNF-α antagonists.		
2c. In adult outpatients with moderate to severe UC who have previously been exposed to infliximab, particularly those with primary nonresponse, the AGA suggests using ustekinumab or tofacitinib rather than vedolizumab or adalimumab for induction of remission.	Conditional	Low
3a. In adult outpatients with active moderate to severe UC, the AGA suggests against using thiopurine monotherapy for induction of remission.	Conditional	Very low
3b. In adult outpatients with moderate to severe UC in remission, the AGA suggests using thiopurine monotherapy rather than no treatment for maintenance of remission.	Conditional	Low
3c. In adult outpatients with moderate to severe UC, the AGA suggests against using methotrexate monotherapy for induction or maintenance of remission.	Conditional	Low
4a. In adult outpatients with active moderate to severe UC, the AGA suggests using biologic monotherapy (TNF-α antagonists, vedolizumab, or ustekinumab) or tofacitinib rather than thiopurine monotherapy for induction of remission.	Conditional	Low
4b. In adult outpatients with moderate to severe UC in remission, the AGA makes no recommendation in favor of or against using biologic monotherapy or tofacitinib rather than thiopurine monotherapy for maintenance of remission.	No recommendation	Knowledge gap
5a. In adult outpatients with moderate to severe UC, the AGA suggests combining TNF-α antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate rather than biologic monotherapy.	Conditional	Low
Comment: Patients, particularly those with less severe disease, who place higher value on the safety of biologic monotherapy and lower value on the efficacy of combination therapy may reasonably chose biologic monotherapy.		
5b. In adult outpatients with moderate to severe UC, the AGA suggests combining TNF-α antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate rather than thiopurine monotherapy.	Conditional	Low
6. In adult outpatients with moderate to severe UC, the AGA suggests early use of biologic agents with or without immunomodulator therapy rather than gradual step up after failure of 5-ASA.	Conditional	Very low
Comment: Patients, particularly those with less severe disease, who place higher value on the safety of 5-ASA therapy and lower value on the efficacy of biologic agents or tofacitinib may reasonably chose gradual step therapy with 5-ASA therapy.		
7. In adult outpatients with moderate to severe UC who have achieved remission with biologic agents and/or immunomodulators or tofacitinib, the AGA suggests against continuing 5-ASA for induction and maintenance of remission.	Conditional	Very low
8. In hospitalized adult patients with ASUC, the AGA suggests using intravenous methylprednisolone dose equivalent of 40–60 mg/d rather than higher doses of intravenous corticosteroids.	Conditional	Very low
9. In hospitalized adult patients with acute severe UC without infection, the AGA suggests against adjunctive antibiotics.	Conditional	Very low
10. In hospitalized adult patients with ASUC refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine.	Conditional	Low
11. In hospitalized adult patients with acute severe UC being treated with infliximab, the AGA makes no recommendation on routine use of intensive vs standard infliximab dosing.	No recommendation	Knowledge gap

placebo. Importantly, the recommended induction dose of tofacitinib is 10 mg twice daily for 8 weeks; in select cases with modest response to initial 8-week therapy, high-dose tofacitinib may be considered for a total of 16 weeks. For long-term maintenance, tofacitinib 5 mg twice daily is recommended for most patients; a higher dose may be considered in patients who lose response at the 5-mg twice-daily dose after careful deliberation of risks and benefits of

the medication. At higher doses, an unexpected increase in risk of pulmonary embolism and all-cause mortality has been observed.

The overall quality of evidence for this recommendation was moderate for both induction and maintenance of remission. Although the majority of the studies were registration trials sponsored by industry, there was no important bias, inconsistency, or indirectness. The evidence was rated down for imprecision due to the lower number of events (<200) for all comparisons, failing to achieve the optimal information size.

2a. In adult outpatients with moderate to severe ulcerative colitis who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab rather than adalimumab, for induction of remission. *(Conditional recommendation, moderate quality evidence)*
Comment: Patients, particularly those with less severe disease, who place higher value on the convenience of self-administered subcutaneous injection, and a lower value on the relative efficacy of medications, may reasonably chose adalimumab as an alternative.

2b. In adult outpatients with moderate to severe ulcerative colitis who are naïve to biologic agents, the AGA recommends that tofacitinib only be used in the setting of a clinical or registry study. *(No recommendation, knowledge gap)*
Comment: Updated FDA recommendations (July 26, 2019) on indications for use of tofacitinib in ulcerative colitis recommend its use only after failure of, or intolerance to TNF-α antagonists.

In adult outpatients with moderate to severe UC naïve to biologic agents, the guideline panel suggests using infliximab or vedolizumab rather than adalimumab for induction of remission. Based on updated FDA document on approved indication for tofacitinib use only in patients after failure of, or intolerance to TNF-α antagonists, the guideline panel recommends that any use of tofacitinib in biologic-naïve patients with UC be closely monitored in the setting of a clinical or registry study. Currently, both infliximab and vedolizumab are intravenous medications that require infusions, which may be inconvenient to some patients. For these patients, particularly those with less severe disease who value the convenience of self-administered injection therapy, adalimumab may be a reasonable alternative option as first-line biologic therapy.

In the head-to-head trials comparing vedolizumab vs adalimumab in patients with moderate to severe UC (VARSITY), rate of clinical remission at 52 weeks was significantly higher in vedolizumab-treated patients vs adalimumab-treated patients (34.2% vs 24.3%; RR, 1.41; 95% CI, 1.10–1.81) among biologic-naïve patients. For all other comparisons, evidence on comparative efficacy was derived from a network meta-analysis.[13] Network meta-analysis can help assess comparative efficacy of several interventions and synthesize evidence across a network of RCTs, especially if there is weak (or absent) direct evidence.[14] Such indirect comparisons of competing interventions, adjusted by a common control, such as placebo, can partially take account of prognostic characteristics of patients in different trials. The analysis included 15 RCTs with a total of 3747 biologic-naïve patients with moderate to severe UC, treated with infliximab (4 trials, 667 patients), adalimumab (4 trials, 1046 patients), golimumab (2 trials, 586 patients), vedolizumab (3 trials, 630 patients), tofacitinib (2 trials, 520 patients), and ustekinumab (1 trial, 298 patients) were included (see technical review). For this body of evidence for induction therapy, trial design, participant characteristics, interventions, comparators, and outcomes for trials of infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab were deemed reasonably similar to facilitate indirect comparison. In contrast, trials of tofacitinib were deemed dissimilar because they used a strict rectal bleeding score of 0 for outcome assessment (in contrast to other trials, which allowed rectal bleeding score of 0 or 1 in outcome assessment). See the technical review and technical review Tables 3–5 for full details regarding this analysis.[1] On network meta-analysis, there was moderate confidence in estimates demonstrating the superiority of infliximab over adalimumab (Odds ratio [OR], 2.10; 95% CI, 1.16–3.79) (evidence rated down for serious imprecision). It is important to note that in these clinical trials, treatment was not optimized to suggested drug concentrations; it is possible that the efficacy of infliximab, adalimumab, and golimumab may be comparable in patients who achieve adequate drug concentrations, given their similar mechanism of action.

2c. In adult outpatients with moderate to severe ulcerative colitis who have previously been exposed to infliximab, particularly those with primary nonresponse, the AGA suggests using ustekinumab or tofacitinib, rather than vedolizumab or adalimumab, for induction of remission. *(Conditional recommendation, low quality evidence)*
Comment: Patients, particularly those with less severe disease, who place higher value on the potential safety of medications, and a lower value on the relative efficacy of medications, may reasonably chose vedolizumab as an alternative.

In adult outpatients with moderate to severe UC who have previously been exposed to infliximab, especially those with primary nonresponse, the guideline panel suggests using ustekinumab or tofacitinib rather than vedolizumab or adalimumab for induction of remission.

In the VARSITY trial, approximately 21% of patients had received prior treatment with a TNF-α antagonist other than adalimumab. In these patients, there was no significant difference in rates of achieving clinical remission at week 52 (20.3% vs 16.0%), and the overall body of evidence was deemed to be low quality (rated down for very serious imprecision). A separate network meta-analysis was also performed comparing trials of different agents in patients with moderate to severe UC, who had previously been exposed to TNF-α antagonists. The network meta-analysis included 7 RCTs with 1580 patients with prior exposure to TNF-α antagonists.[13] Infliximab and golimumab were excluded because the published studies included

biologic-naïve patients only (see technical review Table 5).[1] Of note, all these comparisons were rated down for intransitivity. Prior treatment exposure and response is an important effect modifier. Study-level estimates did not report what proportion of patients had exposure to more than one TNF-α antagonist and whether patients had exposure to multiple different classes of biologics. There was low confidence in estimates supporting higher efficacy of tofacitinib and ustekinumab over adalimumab (tofacitinib vs adalimumab: OR, 11.05; 95% CI, 1.79–68.41; ustekinumab vs adalimumab: OR, 10.71; 95% CI, 2.01–57.20) and over vedolizumab (tofacitinib vs vedolizumab: OR, 6.18; 95% CI, 1.00–38.00; ustekinumab vs vedolizumab: OR, 5.99; 95% CI, 1.13–31.76) for induction of clinical remission in patients with prior exposure to TNF-α antagonists.

The guideline panel was explicit in stating that these conditional recommendations apply for patients with prior exposure to infliximab only. Given prior evidence supporting superiority of infliximab over adalimumab or golimumab in biologic-naïve patients with moderate to severe UC and lack of direct evidence in adalimumab- or golimumab-exposed patients, benefit of switching to vedolizumab, ustekinumab, or tofacitinib over infliximab in patients with prior exposure to adalimumab or golimumab, is uncertain. As noted in AGA's therapeutic drug monitoring guidelines, switching out of class may be reasonable in case of lack of response, despite achieving adequate drug concentration.[9]

Data for maintenance of remission could not be reliably synthesized using network meta-analysis due to significant differences in clinical trial designs—trials of infliximab and adalimumab were treat-straight through trials, whereas maintenance trials of golimumab, vedolizumab, tofacitinib, and ustekinumab re-randomized responders to induction therapy—and lack of stratification of data by prior biologic exposure. However, as with standard clinical practice, once a drug is initiated for induction of remission, if effective, it is typically continued for maintenance of remission as well.

3a. In adult outpatients with active moderate to severe ulcerative colitis, the AGA suggests against using thiopurine monotherapy for INDUCTION of remission. *(Conditional recommendation, very low quality of evidence)*

3b. In adult outpatients with moderate to severe ulcerative colitis in remission, the AGA suggests using thiopurine monotherapy, rather than no treatment, for MAINTENANCE of remission. *(Conditional recommendation low quality of evidence)*

The panel suggests against using thiopurine monotherapy for induction of remission in adult outpatients with active moderate to severe UC. However, in patients who have achieved remission (typically induced with corticosteroids), the panel suggests using thiopurine monotherapy rather than no treatment for maintenance of remission.

There were 3 trials comparing thiopurines vs placebo and 2 trials comparing thiopurines vs 5-aminosalicylates (5-ASA) for inducing corticosteroid free remission.[15–19] In 4 of 5 trials, patients were considered corticosteroid-dependent, unable to taper corticosteroids below 10–20 mg/d without relapsing. In contrast to modern clinical trials, different disease activity indices were used in these studies, outcome of corticosteroid-free remission was assessed at variable intervals from 4 weeks to 52 weeks, and in patients with active disease started simultaneously on thiopurines and corticosteroids, it was unclear whether remission was induced by corticosteroids or thiopurines. Although thiopurines were associated with a higher rate of corticosteroid-free clinical remission compared to placebo or 5-ASA (RR, 1.25; 95% CI, 1.01–1.56), the overall quality of evidence was deemed very low due to serious risk of bias, imprecision, and indirectness (outcome definition and assessment). Based on the slow onset of action of thiopurines, they are unlikely to be effective as monotherapy for induction of remission in patients with active disease, in the absence of corticosteroids. Therefore, based on uncertainty of evidence, the guideline panel opted to suggest against the use of thiopurines for induction of clinical remission in patients with active moderate to severe UC.

For maintenance of remission, 4 trials comparing thiopurines vs placebo and 3 trials comparing thiopurines vs 5-ASA were included.[16,17,19–23] Maintenance of remission was defined as prevention of relapse after corticosteroid-induced remission (5 trials) or as the ability to maintain a corticosteroid-free remission in patients on long-standing thiopurine therapy (2 trials), evaluated between 6 and 18 months. On meta-analysis, thiopurines were more effective than placebo or 5-ASA for prevention of disease relapse (RR, 0.61; 95% CI, 0.49–0.77) among patients with inactive UC (in remission). Quality of evidence was rated as low due to risk of bias and imprecision.

3c. In adult outpatients with moderate to severe ulcerative colitis, the AGA suggests against using methotrexate monotherapy for induction or maintenance of remission. *(Conditional recommendation, low quality evidence)*

The guideline panel suggests against the use of methotrexate monotherapy for induction or maintenance of remission for adult outpatients with moderate to severe UC.

Two trials compared methotrexate vs placebo and 1 trial compared methotrexate vs 5-ASA for induction of remission.[24,25] In the pivotal METEOR trial, all patients were on 10–40 mg/d of corticosteroids with or without active disease.[24] The primary outcome was corticosteroid-free remission between weeks 12 and 30. On meta-analysis, there was no significant difference in rates of inducing remission with methotrexate compared to placebo (RR, 1.31; 95% CI, 0.89–1.94). The quality of evidence was rated as very low due to very serious indirectness (different dosing regimens and modes of administration, variable definition of clinical remission, and inability to truly assess

whether remission was induced by corticosteroids or methotrexate), and serious imprecision. For maintenance of remission, 2 trials compared methotrexate vs placebo and 1 compared methotrexate vs 5-ASA.[17,24,25] Similar to induction, there was no difference between methotrexate and placebo/5-ASA for maintenance of remission (RR, 1.01; 95% CI, 0.79–1.29). The quality of evidence was rated as very low due to serious indirectness, and very serious imprecision.

4a. In adult outpatients with active moderate to severe ulcerative colitis, the AGA suggests using biologic monotherapy (TNF-α antagonists, vedolizumab, ustekinumab) rather than thiopurine monotherapy for INDUCTION of remission. *(Conditional recommendation, low quality evidence)*

4b. In adult outpatients with moderate to severe ulcerative colitis in remission, the AGA makes no recommendation in favor of, or against, using biologic monotherapy (TNF-α antagonists, vedolizumab, or ustekinumab), rather than thiopurine monotherapy for MAINTENANCE of remission. *(No recommendation, knowledge gap)*

The panel conditionally suggests use of biologic monotherapy rather than thiopurine for induction of remission. The panel makes no recommendation in favor of or against using biologic monotherapy over thiopurine monotherapy for maintenance of remission.

Evidence was informed by a 3-arm clinical trial (UC-SUCCESS) comparing infliximab vs azathioprine vs combination therapy of infliximab with azathioprine,[26] as well as indirect evidence based on trials comparing individual medications with placebo. While UC-SUCCESS was designed as an induction and maintenance trial to evaluate the comparative efficacy of monotherapy vs combination therapy in biologic-naïve adult outpatients with moderate to severe UC, the trial was discontinued prematurely by the sponsor before intended enrollment and without completion of the maintenance phase.[26] In this trial, there was no difference between infliximab monotherapy and azathioprine monotherapy for achieving corticosteroid-free remission at week 16 (RR, 0.96; 95% CI, 0.53–1.72), albeit based on very low quality evidence. Infliximab monotherapy was superior to thiopurine monotherapy for achieving endoscopic remission, an important outcome. In addition, based on prior evidence synthesis from PICO (population, intervention, comparator, and outcome) questions 1 and 3 and corresponding recommendations, AGA recommends using biologic agents (TNF-α antagonists, vedolizumab, or ustekinumab) over placebo (moderate quality evidence), whereas it suggests against using thiopurine monotherapy, for induction of remission (very low quality evidence) in adult outpatients with moderate to severe UC.

Because UC-SUCCESS was terminated prematurely,[26] no head-to-head trials informed comparative efficacy of biologic monotherapy vs thiopurines for maintenance of remission. As in PICO questions 1 and 3, both strategies have been recommended for maintenance of remission, over no treatment. Recognizing lack of evidence, the panel makes no recommendation in favor of or against biologic monotherapy rather than thiopurine monotherapy, for maintenance of remission. Physician judgment factoring in patients' clinical status, safety profile of different agents, and costs and convenience of therapy may be used to inform choice of agents.

5a. In adult outpatients with moderate to severe ulcerative colitis, the AGA suggests combining TNF-α antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate, rather than biologic monotherapy. *(Conditional recommendation, low quality evidence)*

Comment: Patients, particularly those with less severe disease, who place higher value on lower risk of adverse events with biologic monotherapy, and lower value on the relative efficacy of combination therapy, may reasonably chose biologic monotherapy.

5b. In adult outpatients with moderate to severe ulcerative colitis, the AGA suggests combining TNF-α antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate, rather than thiopurine monotherapy. *(Conditional recommendation, low quality evidence)*

The guideline panel suggests combining TNF-α antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate over biologic monotherapy, or thiopurine monotherapy, in adult outpatients with moderate to severe UC. However, in patients, particularly those with less severe disease, who place higher value on safety and tolerability of pharmacotherapy may reasonably chose biologic monotherapy.

Combination therapy of infliximab with thiopurine compared to infliximab monotherapy was evaluated in UC-SUCCESS, a single 3-arm double-blind double-dummy RCT in biologic-naïve patients with UC.[26] As noted here, this trial was terminated prematurely before planned enrollment and before completion of maintenance trial. Patients were randomized to infliximab monotherapy, azathioprine monotherapy, or combined infliximab and azathioprine therapy.[26] Combination therapy was more effective for inducing a corticosteroid-free remission at week 16 compared to infliximab monotherapy (RR, 1.78; 95% CI, 1.08–1.94). No trials compared combination therapy of other TNF-α antagonists, vedolizumab, or ustekinumab with immunomodulators vs biologic monotherapy. Because adding immunomodulators to biologic agents improves pharmacokinetics of the biologic agent (increasing trough concentration and decreasing immunogenicity), the guideline panel extrapolated this indirect evidence favoring combination therapy of thiopurines and infliximab to other TNF-α antagonists, vedolizumab, or ustekinumab, particularly in patients with unfavorable pharmacokinetics (more severe disease, higher inflammatory burden, low albumin, and higher body mass index), even though the immunogenicity of newer biologic agents may be lower than infliximab.[27]

Evidence supporting the use of combination therapy vs immunomodulator monotherapy is also based on UC-SUCCESS.[26] In this trial, combination of infliximab and thiopurines was superior to thiopurine monotherapy for achieving corticosteroid-free remission at week 16 (RR, 1.70; 95% CI, 1.04–2.78).

No clinical trial comparing combination therapy with biologic monotherapy for maintenance of remission was identified. Very low quality evidence from a retrospective French study of 82 patients in remission on combination therapy, suggested that continuing combination infliximab and azathioprine was superior to de-escalating to infliximab monotherapy.

Overall, quality of evidence for infliximab-based combination therapy vs infliximab monotherapy and vs thiopurine monotherapy for induction of remission was rated as moderate quality (rated down for imprecision). No trials comparing combination therapy of other TNF-α antagonists (adalimumab, golimumab), vedolizumab, or ustekinumab with thiopurines (or methotrexate) vs biologic monotherapy were identified. Extrapolating from evidence supporting the use of combination of therapy with infliximab, acknowledging lower risk of immunogenicity with newer biologic agents, evidence of other agents was rated as low quality, due to indirectness. Quality of evidence for maintenance of remission was rated as very low due to the observational evidence and serious imprecision.

6. In adult outpatients with moderate to severe ulcerative colitis, the AGA suggests early use of biologic agents with or without immunomodulator therapy, rather than gradual step up after failure of 5-ASA. *(Conditional recommendation, very low quality evidence)*

Comment: Patients, particularly those with less severe disease, who place higher value on the safety of 5-ASA therapy, and lower value on the efficacy of biologic agents, may reasonably choose gradual step therapy with 5-ASA therapy.

The guideline panel suggests early use of biologics with or without immunomodulator therapy, or tofacitinib rather than gradual step-up therapy after failure of 5-ASA in patients with moderate to severe disease activity at high risk of colectomy. However, patients with less severe disease who place higher value on the safety profile of 5-ASA therapy and lower value on the overall efficacy of biologics may choose to start with 5-ASA therapy.

There were no studies identified that compared a strategy of upfront biologic-based therapy or tofacitinib vs gradual step-up therapy (introducing biologic-based therapy or tofacitinib only after failure of 5-ASA), or that compared biologic-based therapy vs 5-ASA–based therapy, in patients with moderate to severe UC at high risk of colectomy. Three studies compared thiopurines vs 5-ASA, in corticosteroid-exposed patients with UC.[17,20,23] On meta-analysis, thiopurines achieved higher rates of corticosteroid-free remission than 5-ASA. Indirectly extrapolating the data from PICO questions 3 and 4 suggests that biologic-based therapy will likely be more effective than 5-ASA–based therapy. Importantly, 5-ASAs have not been specifically studied in patients with moderate to severe disease activity, and their use is limited to patients with mild to moderate disease activity. Delaying effective treatment to induce remission in patients with moderate to severe UC at high risk of colectomy may be harmful due to ongoing untreated active disease, increasing risk of UC-related complications, hospitalization, colectomy, and overall inferior quality of life.

The overall quality of evidence supporting this recommendation was rated as very low due to serious indirectness and imprecision.

7. In adult outpatients with moderate to severe ulcerative colitis who have achieved remission with biologic agents and/or immunomodulators, or tofacitinib, the AGA suggests against continuing 5-ASA for induction and maintenance of remission. *(Conditional recommendation, very low quality evidence)*

The guideline panel suggests against continuation of 5-ASA in adult outpatients with moderate to severe UC for induction and maintenance of remission, who have previously failed 5-ASA and have been escalated to a biologic agent and/or immunomodulators or tofacitinib.

In a randomized clinical trial, patients with moderate to severe UC in corticosteroid-free clinical, endoscopic, and histologic remission on azathioprine and olsalazine were randomized to either continuation of azathioprine with olsalazine or de-escalation to azathioprine alone.[28] In 2 years of follow-up, there were no differences in risk of relapse between the 2 groups (RR, 1.02; 95% CI, 0.77–1.34). There were no studies of systematic withdrawal of 5-ASA in biologic- or tofacitinib-treated patients with moderate to severe UC. Indirect evidence from subgroup analysis of RCTs comparing rates of induction and maintenance of remission in patients who were vs were not concomitantly on 5-ASA at trial entry was used.[29] On meta-analysis, there was no differences in rates of inducing or maintaining clinical remission in TNF-α antagonist–treated or tofacitinib-treated patients who were vs were not on concomitant 5-ASA at trial entry (induction: RR, 0.94; 95% CI, 0.74–1.18; maintenance: RR, 0.92; 95% CI, 0.78–1.09). Of note, these trials did not assess effect of systematic withdrawal of 5-ASAs in biologic-treated or tofacitinib-treated patients. Overall quality of evidence was rated as low due to imprecision and indirectness of evidence.

This recommendation did not factor in whether continuing 5-ASAs may or may not have a chemoprotective benefit against colorectal cancer in patients with UC. While studies have variably shown an association between 5-ASA use and lower risk of colorectal cancer in patients with UC,[30,31] recent data suggests that chronically active disease is a risk factor for colon cancer and that sustained remission is protective regardless of the type of therapy used.[32]

Management of Hospitalized Patients With Acute Severe Ulcerative Colitis

8. In hospitalized adult patients with acute severe ulcerative colitis, the AGA suggests using intravenous methylprednisolone dose equivalent of 40 to 60 mg/d rather than higher doses of intravenous corticosteroids. *(Conditional recommendation, very low quality evidence)*

The guideline panel suggests using intravenous corticosteroids at doses equivalent to 40–60 mg/d of methylprednisolone rather than higher doses of intravenous corticosteroids to decrease risk of colectomy in hospitalized adults with ASUC.

Intravenous corticosteroids are the mainstay of management of hospitalized adults with ASUC. There were no head-to-head trials comparing different doses of corticosteroids in hospitalized patients with ASUC. In a systematic review evaluating the risk factors for colectomy in patients with ASUC, Turner and colleagues[33] observed that mean methylprednisolone dose was 68 mg/d (range, 40–100 mg) in hospitalized patients with ASUC; on meta-regression after controlling for baseline disease severity, there was no correlation between corticosteroid dose and risk of colectomy ($R^2 < 0.01$). In included trials, different intravenous corticosteroid regimens (different formulations given once daily vs multiple times daily vs as continuous infusion) were used, and none was superior to others. Based on models estimating risk and risk factors for colectomy in patients with ASUC, corticosteroid trials of 3–5 days are suggested; continued use of corticosteroids beyond 7 days has not been shown to be effective in nonresponding patients.[33,34]

Overall quality of evidence was rated as very low due to observational nature of evidence and indirectness in approach to comparing efficacy.

9. In hospitalized adult patients with acute severe ulcerative colitis without infections, the AGA suggests against adjunctive antibiotics. *(Conditional recommendation, very low quality of evidence)*

The guideline panel suggests against the routine use of adjunctive antibiotics for the treatment of ASUC in patients without gastrointestinal or extra-intestinal infections.

Four RCTs comparing antibiotics vs no antibiotics/placebo for the treatment of ASUC were identified.[35–38] Different antibiotics were used, with durations ranging from 5 to 10 days. On meta-analysis, the addition of antibiotics was not superior to no antibiotics for decreasing short-term risk of colectomy in patients with ASUC (RR, 0.79; 95% CI, 0.46–1.35). After exclusion of 1 trial of oral vancomycin that was positive but used an insensitive test to exclude concomitant *C difficile* infection, overall summary estimate for adjunctive antibiotics was close to unity (RR, 0.95; 95% CI, 0.55–1.64).

The quality of evidence was rated very low due to serious risk of bias, serious imprecision, and inconsistency, given the diverse group of antibiotics used in the studies.

10. In hospitalized adult patients with acute severe ulcerative colitis refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine. *(Conditional recommendation, low quality evidence)*

The guideline panel suggests using either infliximab or cyclosporine in hospitalized adult patients with ASUC refractory to a 3- to 5-day trial of intravenous corticosteroids.

One RCT compared infliximab to placebo in 45 patients with ASUC refractory to intravenous corticosteroids.[39] In this trial, infliximab was superior to placebo in decreasing the risk of colectomy within 90 days of hospitalization (RR, 0.44; 95% CI, 0.22–0.87). Patients were given a single dose of 5 mg/kg infliximab without further induction or maintenance doses. Likewise, intravenous cyclosporine (4 mg/kg) was compared to placebo in a single small RCT in corticosteroid-refractory patients with ASUC.[40] In this trial, there was a trend favoring cyclosporine over placebo (RR, 0.61; 95% CI, 0.18–2.01). In a subsequent RCT, cyclosporine dose 2 mg/kg/d was comparable to 4 mg/kg/d, with conceivably a superior safety profile with lower dose.[41] In 2 head-to-head trials comparing infliximab vs cyclosporine, there was no significant difference in short-term risk of colectomy between standard-dose induction therapy with infliximab vs cyclosporine in hospitalized patients with corticosteroid-refractory ASUC (RR, 1.00; 95% CI, 0.72–1.40).[42,43] Long-term follow-up of these trials also suggest similar findings. Over a median follow-up of 4.5 years of participants in the CYSIF trial, 1- and 5- year colectomy-free survival rates were 70.9% and 61.5% in patients treated with cyclosporine initially and 69.1% and 65.1%, respectively, in patients randomized to infliximab ($P = .97$). Importantly, in these trials, randomized treatment was offered for 12–14 weeks, after which treatment decisions were deferred to treating physicians. After the initial randomization period, 1- and 5-year cumulative use of infliximab in cyclosporine-treated patients was 45.7% and 57.1%, respectively; in contrast, only 4 infliximab-treated patients switched to cyclosporine.[42,43]

Overall quality of evidence supporting the use of infliximab or cyclosporine over placebo for ASUC refractory to intravenous corticosteroids was rated as moderate quality (imprecision) or low quality (very serious imprecision), respectively. Evidence supporting the comparability of infliximab and cyclosporine decreasing risk of short-term colectomy in hospitalized patients with corticosteroid-refractory ASUC was rated as low quality (open-label trials with high risk of bias, and imprecision).

11. In hospitalized adult patients with acute severe UC, refractory to intravenous corticosteroids, being treated with infliximab, the AGA makes no recommendation on routine use of intensive vs standard infliximab dosing. *(No recommendation, knowledge gap)*

The guideline panel makes no recommendation regarding routine use of intensive vs standard infliximab dosing in adult patients hospitalized with ASUC refractory to intravenous corticosteroids.

There were no RCTs comparing different dosing regimens in patients hospitalized with ASUC. Five observational studies compared outcomes in patients hospitalized with ASUC refractory to intravenous corticosteroids, being treated with different infliximab regimens.[44–47] Intensive dosing regimens included either shortened interval between the infliximab dosing (<2 weeks, dose stacking) and/or induction with higher-dose infliximab (10 mg/kg) either upfront or at time of dose stacking, without a standard protocol. On meta-analysis of these observational studies, there was no significant difference in the short-term risk of colectomy intensive vs standard infliximab dosing regimens (RR, 1.61; 95% CI, 0.74–3.52). In 2 studies, upfront induction with higher-dose infliximab (10 mg/kg) was superior to dose stacking with standard doses (5 mg/kg), with lower risk of colectomy (RR, 0.24; 95% CI, 0.08–0.68). Overall, quality of evidence was rated as very low quality due to serious risk of bias, inconsistency, and imprecision.

Biologically, patients with corticosteroid-refractory ASUC have a high inflammatory burden that may result in accelerated consumption and fecal wasting of infliximab, resulting in low serum concentrations and immunogenicity.[48] Additionally, given that the drug is albumin-bound and many of these patients are malnourished in the setting of ASUC, the systemic drug concentration of biologics may be lower. Hence, it is plausible that intensive regimens may be more effective than standard induction with infliximab. However, this entire body of observational evidence is confounded by disease severity, wherein patients at intrinsically higher risk of colectomy, or those who have inadequate response to standard induction dose are treated with more intensive regimens. As a result, given the lack of robust evidence in this setting to guide therapy, this remains a knowledge gap in need of further research to better guide therapy for the ideal induction regimens for infliximab in hospitalized patients with ASUC refractory to intravenous corticosteroids.

Summary

These practice recommendations for the management of moderate to severe UC were developed using the GRADE framework and in adherence to the standards established by the Institute of Medicine for the development of trustworthy guidelines.[11,12] The goal of this guideline is to promote high-quality, high-value evidence-based care for patients with moderate to severe UC.

Current evidence supports use of infliximab, adalimumab, golimumab, vedolizumab, and tofacitinib for the induction and maintenance of remission in moderate to severe UC. Thiopurine monotherapy should not be used for induction of remission, but may be considered for maintenance of remission; in contrast, methotrexate monotherapy, orally or subcutaneously, should not be used for induction or maintenance of remission. Network meta-analysis suggests that infliximab and vedolizumab may be preferred first-line therapy in biologic-naïve patients rather than standard-dose adalimumab or golimumab, with limited evidence to inform appropriate positioning of tofacitinib. In patients with prior exposure to infliximab, particularly those with primary nonresponse to induction therapy, vedolizumab or tofacitinib may be preferred over adalimumab or golimumab. Combination therapy of a biologic agent with an immunomodulator is more effective than monotherapy with either agent, although patients, particularly those with less severe disease and those averse to side effects from medications, may opt for monotherapy. In patients with moderate to severe disease activity at high risk of colectomy, biologic agents with or without an immunomodulator, or tofacitinib, should be used early rather than gradual step-up therapy after failure of 5-ASA. Patients in remission with biologic agents and/or immunomodulators or tofacitinib after prior failure of 5-ASA, may discontinue 5-ASA.

Among hospitalized patients with ASUC, after excluding alternative etiologies, intravenous methylprednisolone doses of 40–60 mg/d or equivalent are the mainstay of therapy. Routine use of adjunctive antibiotics in patients without infections is not recommended. Patients who are refractory to a 3- to 5-day trial of intravenous corticosteroids and who prefer ongoing medical management may be treated with either infliximab or cyclosporine. In patients being treated with infliximab, no recommendation can be made regarding routine use of intensive vs standard infliximab dosing.

Areas for Future Research

The guideline panel identified multiple knowledge gaps and areas for future research in patients with moderate to severe UC. With the increasing number of different drug classes available to treat UC, there is a clear need for identifying biomarkers predictive of response to individual therapies, to facilitate optimal positioning of therapies; in addition, head-to-head trials will directly inform comparative efficacy, and strengthen quality of evidence derived from network meta-analyses. Besides efficacy, safety is an important consideration with different therapies, and different treatment strategies offer distinct risk to benefit profiles. A comprehensive personalization of therapy based on key treatment attributes (efficacy, safety, speed of onset of action, co-interventions, and convenience) is warranted to optimally inform shared decision-making. There is limited evidence regarding the utility and duration of combination therapy of biologics and immunomodulators in patients with UC, particularly with newer agents with lower immunogenicity and with better optimization of biologic agents through therapeutic drug monitoring. Treatment targets with UC are in evolution. It is unclear how well targeting an integrated clinical and biomarker remission compares to endoscopic remission, and whether there may be incremental benefit to treating to a target of histologic remission. Finally, there is considerable paucity of evidence

on optimally using existing therapies and novel treatment options for hospitalized patients with ASUC who are refractory to intravenous corticosteroids. The management of these patients, at very high-risk of colectomy in the short-term, also need to be prioritized.

References

1. **Singh S, Allegretti JR**, Siddique SM, et al. AGA Technical review on the management of moderate to severe ulcerative colitis. Gastroenterology 2019;158:1465–1496.
2. Fumery M, Singh S, Dulai PS, et al. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. Clin Gastroenterol Hepatol 2018; 16:343–356 e3.
3. Narula N, Marshall JK, Colombel JF, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. Am J Gastroenterol 2016;111:477–491.
4. Dassopoulos T, Cohen RD, Scherl EJ, et al. Ulcerative colitis care pathway. Gastroenterology 2015;149:238–245.
5. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–1629.
6. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955;2:1041–1048.
7. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. Lancet 2017;389:1756–1770.
8. Ko CW, Singh S, Feuerstein JD, et al. American Gastroenterological Association Institute guideline on the management of mild-to-moderate ulcerative colitis. Gastroenterology 2019;156:748–764.
9. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology 2017;153:827–834.
10. American Gastroenterological Association. AGA Institute Clinical Practice Guideline Development Process. Bethesda, MD: American Gastroenterological Association, 2018.
11. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol 2013;11:329–332.
12. Institute of Medicine. Clinical Practice Guidlines We Can Trust. Washington, DC: National Academies Press, 2011.
13. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis. Clin Gastroenterol Hepatol 2020; Jan 13 [Online ahead of print]. https://doi.org/10.1016/j.cgh.2020.01.008.
14. Cipriani A, Higgins JP, Geddes JR, et al. Conceptual and technical challenges in network meta-analysis. Ann Intern Med 2013;159:130–137.
15. Caprilli R, Carratu R, Babbini M. Double-blind comparison of the effectiveness of azathioprine and sulfasalazine in idiopathic proctocolitis. Preliminary report. Am J Dig Dis 1975;20:115–120.
16. Jewell DP, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. Br Med J 1974; 4:627–630.
17. Mate-Jimenez J, Hermida C, Cantero-Perona J, et al. 6-Mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. Eur J Gastroenterol Hepatol 2000;12:1227–1233.
18. Rosenberg JL, Wall AJ, Levin B, et al. A controlled trial of azathioprine in the management of chronic ulcerative colitis. Gastroenterology 1975;69:96–99.
19. Sood A, Midha V, Sood N, et al. Role of azathioprine in severe ulcerative colitis: one-year, placebo-controlled, randomized trial. Indian J Gastroenterol 2000;19:14–16.
20. Ardizzone S, Maconi G, Russo A, et al. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut 2006;55:47–53.
21. Hawthorne AB, Logan RF, Hawkey CJ, et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. BMJ 1992;305:20–22.
22. Sood A, Kaushal V, Midha V, et al. The beneficial effect of azathioprine on maintenance of remission in severe ulcerative colitis. J Gastroenterol 2002;37:270–274.
23. Sood A, Midha V, Sood N, et al. Azathioprine versus sulfasalazine in maintenance of remission in severe ulcerative colitis. Indian J Gastroenterol 2003;22:79–81.
24. Herfarth H, Barnes EL, Valentine JF, et al. Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. Gastroenterology 2018;155:1098–1108.e9.
25. Oren R, Arber N, Odes S, et al. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. Gastroenterology 1996;110:1416–1421.
26. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014;146:392–400.e3.
27. Vermeire S, Gils A, Accossato P, et al. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol 2018;11:1756283X17750355.
28. Mantzaris GJ, Sfakianakis M, Archavlis E, et al. A prospective randomized observer-blind 2-year trial of azathioprine monotherapy versus azathioprine and olsalazine for the maintenance of steroid-dependent ulcerative colitis. Am J Gastroenterol 2004;99:1122–1128.
29. Singh S, Proudfoot JA, Dulai PS, et al. No benefit of concomitant 5-aminosalicylates in patients with ulcerative colitis escalated to biologic therapy: pooled analysis of individual participant data from clinical trials. Am J Gastroenterol 2018;113:1197–1205.
30. Nguyen GC, Gulamhusein A, Bernstein CN. 5-aminosalicylic acid is not protective against colorectal cancer in inflammatory bowel disease: a meta-analysis of non-referral populations. Am J Gastroenterol 2012; 107:1298.

31. O'Connor A, Packey CD, Akbari M, et al. Mesalamine, but not sulfasalazine, reduces the risk of colorectal neoplasia in patients with inflammatory bowel disease: an agent-specific systematic review and meta-analysis. Inflamm Bowel Dis 2015;21:2562–2569.
32. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case–control study. Clin Gastroenterol Hepatol 2013;11:1601–1608. e4.
33. Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol 2007;5:103–110.
34. Seo M, Okada M, Yao T, et al. Evaluation of the clinical course of acute attacks in patients with ulcerative colitis through the use of an activity index. J Gastroenterol 2002;37:29–34.
35. Chapman RW, Selby WS, Jewell DP. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. Gut 1986;27:1210–1212.
36. Dickinson RJ, O'Connor HJ, Pinder I. Double blind controlled trial of oral vancomycin as adjunctive treatment in acute exacerbations of idiopathic colitis. Gut 1985;26:1380–1384.
37. Mantzaris GJ, Hatzis A, Kontogiannis P, et al. Intravenous tobramycin and metronidazole as an adjunct to corticosteroids in acute, severe ulcerative colitis. Am J Gastroenterol 1994;89:43–46.
38. Mantzaris GJ, Petraki K, Archavlis E, et al. A prospective randomized controlled trial of intravenous ciprofloxacin as an adjunct to corticosteroids in acute, severe ulcerative colitis. Scand J Gastroenterol 2001; 36:971–974.
39. Jarnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128:1805–1811.
40. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330:1841–1845.
41. Van Assche G, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology 2003;125:1025–1031.
42. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet 2012;380:1909–1915.
43. Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. Lancet Gastroenterol Hepatol 2016;1:15–24.
44. Choy MC, Seah D, Gorelik A, et al. Predicting response after infliximab salvage in acute severe ulcerative colitis. J Gastroenterol Hepatol 2018;33:1347–1352.
45. Gibson DJ, Heetun ZS, Redmond CE, et al. An accelerated infliximab induction regimen reduces the need for early colectomy in patients with acute severe ulcerative colitis. Clin Gastroenterol Hepatol 2015; 13:330–335 e1.
46. Govani SM, Waljee AK, Stidham RW, et al. Accelerated dosing of infliximab prevents colectomy within 90 days in only half of patients with severe ulcerative colitis. Gastroenterology 2016;150:S106.
47. Shah SC, Naymagon S, Cohen BL, et al. There is significant practice pattern variability in the management of the hospitalized ulcerative colitis patient at a tertiary care and IBD referral center. J Clin Gastroenterol 2018; 52:333–338.
48. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology 2015; 149:350–355 e2.

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