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GUIDELINES

AGA Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis

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BACKGROUND & AIMS: This American Gastroenterological Association (AGA) living guideline is intended to support practitioners in the pharmacological management of moderate-to-severe ulcerative colitis (UC). **METHODS:** A multidisciplinary panel of content experts and guideline methodologists used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to prioritize clinical questions, identify patient-centered outcomes, conduct an evidence synthesis, and develop recommendations on the pharmacological management of moderate-to-severe UC. **RESULTS:** The AGA guideline panel made 14 recommendations. In adult outpatients with moderate-to-severe UC, the AGA recommends the use of infliximab, golimumab, vedolizumab, tofacitinib, upadacitinib, ustekinumab, ozanimod, etrasimod, risankizumab, and guselkumab, and suggests the use of adalimumab, filgotinib, and mirikizumab over no treatment. In patients who are naïve to advanced therapies, the AGA suggests using a higher-efficacy medication (eg, infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, and guselkumab) or an intermediate-efficacy medication (eg, golimumab, ustekinumab, tofacitinib, filgotinib, and mirikizumab) rather than a lower-efficacy medication (eg, adalimumab). In patients who have previously been exposed to 1 or more advanced therapies, particularly tumor necrosis factor (TNF)-α antagonists, the AGA suggests using a higher-efficacy medication (eg, tofacitinib, upadacitinib, and ustekinumab) or an intermediate-efficacy medication (eg, filgotinib, mirikizumab, risankizumab, and guselkumab) rather than a lower-efficacy medication (eg, adalimumab, vedolizumab, ozanimod, and etrasimod). In adult outpatients with moderate-to-severe UC, the AGA suggests against using thiopurine monotherapy for induction of remission, but suggests using thiopurine monotherapy over no treatment for maintenance of (typically corticosteroid-induced) remission. The AGA suggests against using methotrexate monotherapy, for induction or maintenance of remission. In adult outpatients with moderate-to-severe UC, the AGA suggests the use of infliximab, adalimumab, and golimumab in combination with an immunomodulator over corresponding monotherapy. However, the AGA makes no recommendation in favor of, or against, the use of non-TNF antagonist biologics in combination with an immunomodulator over non-TNF biologic alone. In patients with UC who are in corticosteroid-free clinical remission for at least 6 months on combination therapy of TNF antagonists and an immunomodulator, the AGA suggests against withdrawal of TNF antagonists, but makes no recommendation in favor of, or against, withdrawing immunomodulators. In adult outpatients with moderate-to-severe UC, who have failed 5-aminosalicylates, and have escalated to therapy with immunomodulators or advanced therapies, the AGA suggests stopping 5-aminosalicylates. Finally, in adult outpatients with moderate-severe UC, the AGA suggests early use of advanced therapies and/or immunomodulator therapy, rather than gradual step-up after failure of 5-aminosalicylates. The panel also proposed key implementation considerations for optimal use of these medications and identified several knowledge gaps and areas for future research. **CONCLUSIONS:** This guideline provides a comprehensive, patient-centered approach to the pharmacological management of patients with moderate-to-severe UC.

Keywords: Inflammatory Bowel Disease; Network Meta-Analysis; Evidence Synthesis; Positioning.

Ulcerative colitis (UC) affects nearly 2 million individuals in the United States and millions more worldwide.[1,2] It has a protracted relapsing-remitting course with up to one-fifth of patients requiring colectomy and

Abbreviations used in this paper: **AGA, American Gastroenterological Association; 5-ASA, 5-aminosalicylate; CD, Crohn's disease; CMD, clinically meaningful difference; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IBD, inflammatory bowel disease; IL, interleukin; IV, intravenous; JAK, Janus kinase; NMA, network meta-analysis; OR, odds ratio; PICO, population, intervention, comparator, and outcomes; RCT, randomized controlled trial; RR, relative risk; SC, subcutaneous; S1P, sphingosine-1-phosphate; TNF, tumor necrosis factor; UC, ulcerative colitis.**

Most current article

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one-third requiring hospitalization for management of their disease.[3] Effective control of inflammatory activity is important to reduce disease-related morbidity. An important component of this effective control is an informed approach for therapy selection as first or subsequent therapy. The past 2 decades have witnessed a significant expansion in the therapeutic armamentarium for moderate-to-severe UC. In the nearly 2 decades since the approval of the first biologic therapy (ie, infliximab) for UC in 2005, there have been 11 additional advanced therapies approved for treatment of moderate-to-severe UC in the United States. Importantly, 7 of these medications, including 2 novel therapeutic classes, were approved since the publication of the most recent American Gastroenterological Association (AGA) guideline for treatment of moderate-to-severe UC in 2020.[4] Two approved treatments addressed in prior guidelines (ie, infliximab and vedolizumab) have also received approval for subcutaneous administration, and some drugs are available as biosimilars. Thus, the AGA prioritized updating the prior guidelines to provide recommendations for the pharmacological management of moderate-to-severe UC.

Guideline Objectives and Scope

These guidelines are intended to apply to patients with moderate-to-severe UC disease activity. This is conventionally defined based on the severity of rectal bleeding and diarrhea. According to the 2-item patient-reported outcome disease activity scale, a stool frequency score $\geq$2, and rectal bleeding score $\geq$2 suggests moderate-to-severe UC disease activity.[5] Endoscopically, moderate-to-severe UC is indicated by the presence of diffuse erythema, friability, erosions (Mayo endoscopic subscore 2), or spontaneous bleeding or ulcerations (Mayo endoscopic subscore 3). The objective of this guideline was to provide guidance for the pharmacological management of moderate-to-severe UC in outpatients. In addition to patients with moderate-to-severe symptoms, these recommendations are also intended to apply to patients with mildly active symptoms, but prognostic signs that predict adverse disease course, including high burden of inflammation with severe endoscopic disease activity, corticosteroid dependence, or who experience significant impact of disease on quality of life. These guidelines also apply to those with moderate-to-severe proctitis. The recommendations in these guidelines do not apply to hospitalized patients with acute severe UC.

The AGA has developed these guidelines as living guidelines, given rapid evolution in the field.[6] A *living guideline* is defined as one that allows for optimization of guidelines during the development process with updating of individual recommendations based on the availability of new evidence. Recommendations will only be made for treatments that have received regulatory approval for use in the United States or Europe.

Target Audience

The target audience of these guidelines includes gastroenterologists, advanced practice providers (ie, nurse practitioners or physician assistants), primary care providers, patients, and policy makers. These guidelines are meant to be broad recommendations for management of patients with moderate-to-severe UC and are not intended to address the intricacies of individual patients. Provider experience and patient values and preferences can inform treating providers and patients to reasonably choose alternative treatment options.

Methods

Overview

This document represents official recommendations from the AGA. It was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for therapeutic strategies and adheres to best practices in guideline development, per the direction provided by the National Academy of Medicine.[7] The development of this document is fully supported by the AGA Institute.

Guideline Panel Composition and Conflicts of Interest

Members of the guideline panel were selected based on clinical and methodological expertise and experience, and after review of all conflicts of interest in a comprehensive vetting process. The multidisciplinary guideline panel included gastroenterologists with expertise in inflammatory bowel disease (IBD) and guideline methodologists. Panel members disclosed all conflicts of interest, which were defined and categorized per AGA policies and the National Academy of Medicine and Guidelines International Network standards.[7,8] No guideline panel member was excused from participation in the process owing to disqualifying conflict. A full list of conflicts can be accessed at AGA's National Office in Bethesda, MD.

Formulation of Clinical Questions and Outcome Measurement

Using the PICO format, which frames a clinical question by defining a specific population (P), intervention (I), comparator (C), and outcomes (O), the team finalized 12 questions to be addressed (Table 1). The AGA Governing Board approved the final set of questions and statements in September 2023. Consistent with AGA's prior guidelines on the pharmacological management of moderate-to-severe UC,[4] induction and maintenance of clinical remission were considered critical outcomes for decision making, whereas achieving endoscopic remission, endoscopic improvement, corticosteroid-free remission, serious adverse events, serious infections, and treatment tolerability (drug discontinuation due to adverse events) were considered important outcomes. Clinical remission was most commonly measured using the Mayo Clinic score, an index with scores ranging from 0 to 12, based on measures of stool frequency, rectal bleeding, physician global assessment, and endoscopic disease activity.[9] Scores of 6–12 correspond to moderate-to-severe disease activity, whereas clinical remission is most consistently defined as Mayo Clinic score $<$3, with no individual subscore $>$1. In earlier trials, alternative cutoffs of Mayo Clinic score–defined remission and alternative disease activity indices, such as Powell-Tuck Index, Baron endoscopy score, and others, were used.[10] In these trials, if clinical and endoscopic

Table 1. Focused Questions and Corresponding PICO Questions Addressed in the Guidelines

Question no.	Focused question	PICO question			
		Patients	Intervention	Comparator	Critical outcomes
1 (Living)	In adult outpatients with moderate- to-severe UC, what is the efficacy of TNF antagonists (infliximab, adalimumab, golimumab), vedolizumab, ustekinumab, JAK-inhibitors (tofacitinib, filgotinib, upadacitinib), S1P receptor modulators (ozanimod, etrasimod) and IL23 antagonists (mirikizumab, risankizumab, guselkumab), for induction and maintenance of remission in patients with moderate-severe UC?	Adult outpatients with moderate-to-severe UC	TNF antagonists (infliximab, adalimumab, golimumab) Vedolizumab Ustekinumab JAK-inhibitors (tofacitinib, filgotinib, upadacitinib) S1P receptor modulators (ozanimod, etrasimod) IL23 antagonists (mirikizumab, risankizumab, guselkumab)	Placebo	Induction of clinical remission Maintenance of clinical remission
2 (Living)	In adult outpatients with moderate- to-severe UC who are *naïve to advanced therapies*, what is the comparative efficacy of infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib, filgotinib, upadacitinib, ozanimod, etrasimod, mirikizumab, Risankizumab, and guselkumab for induction and maintenance of remission?	Adult outpatients with moderate-to-severe UC who are naïve to advanced therapies	Infliximab Adalimumab Golimumab Vedolizumab Ustekinumab Tofacitinib Filgotinib Upadacitinib Ozanimod Etrasimod Mirikizumab Risankizumab Guselkumab	Placebo or another active comparator	Induction of clinical remission Maintenance of clinical remission
3 (Living)	In adult outpatients with moderate-to-severe UC who *have been exposed to advanced therapies,* what is the comparative efficacy of infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib, filgotinib, upadacitinib, ozanimod, etrasimod, mirikizumab, risankizumab, and guselkumab for induction and maintenance of remission?	Adult outpatients with moderate-to-severe UC who have been exposed to advanced therapies	Infliximab Adalimumab Golimumab Vedolizumab Ustekinumab Tofacitinib Filgotinib Upadacitinib Ozanimod Etrasimod Mirikizumab Risankizumab Guselkumab	Placebo or another active comparator	Induction of clinical remission Maintenance of clinical remission

Table 1. Continued

Question no.	Focused question	PICO question			
		Patients	Intervention	Comparator	Critical outcomes
4	In adult outpatients with moderate- to-severe UC, what is the efficacy of immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of remission?	Adult outpatients with moderate-to-severe UC	Thiopurines (azathioprine, mercaptopurine) Methotrexate (oral or SC)	Placebo (or 5-ASA)	Achieving remission Prevention of relapse (≈maintenance of remission)
5 (Living)	In adult outpatients with moderate- to-severe UC, is combination therapy of TNF antagonists with an immunomodulator (thiopurines or methotrexate) superior to TNF monotherapy or immunomodulator monotherapy for induction and maintenance of remission?	Adult outpatients with moderate-to-severe UC	Combination therapy with a TNF antagonist and an immunomodulator (thiopurines or methotrexate)	TNF antagonist monotherapy Immunomodulator monotherapy (thiopurines or methotrexate)	Induction of clinical remission Maintenance of clinical remission
6 (Living)	In adult outpatients with moderate-to-severe UC, is combination therapy of a non-TNF biologic with an immunomodulator (thiopurines or methotrexate) superior to TNF monotherapy or immunomodulator monotherapy for induction and maintenance of remission?	Adult outpatients with moderate-to-severe UC	Combination therapy with a non-TNF antagonist biologic and an immunomodulator (thiopurines or methotrexate)	Non-TNF antagonist biologic monotherapy Immunomodulator monotherapy (thiopurines or methotrexate)	Induction of clinical remission Maintenance of clinical remission
7 (Living)	In adult outpatients with moderate-to-severe UC in steroid-free remission on combination therapy of biologic + immunomodulator, is discontinuation of (1) an immunomodulator or (2) discontinuation of a biologic, superior to continuation of combination therapy?	Adult outpatients with moderate-to-severe UC in steroid-free remission on combination therapy	Discontinuation of an immunomodulator Discontinuation of a biologic	Continuation of combination therapy	Prevention of relapse
8	In adult outpatients with moderate-to-severe UC, is top-down therapy superior to step therapy for induction and maintenance of remission?	Adult outpatients with moderate-to-severe UC	Top-down therapy Upfront use of advanced therapies and/or immunomodulator therapy Upfront use of biologic-based combination therapy	Step therapy Acceleration to advanced therapy only after failure of 5-ASA Initial use of immunomodulator or advanced therapy	Induction of clinical remission Maintenance of clinical remission •

Table 1. Continued

Question no.	Focused question	PICO question			
		Patients	Intervention	Comparator	Critical outcomes
9	In adult outpatients with moderate-to-severe UC with prior failure of 5-ASA, currently being treated with immunomodulators or advanced therapy, is continuing 5-ASA superior to stopping 5-ASA for inducing and maintaining remission?	Adult outpatients with moderate-to-severe UC with prior failure of 5-ASA, currently being treated with immunomodulators or advanced therapy	Continuation of 5-ASA	Stopping 5-ASA	Induction of clinical remission Maintenance of clinical remission

NOTE. Questions in the "living" mode will be reviewed every 6 months for new evidence. Evidence synthesis will be updated when new phase 3 or phase 4 data of a relevant intervention or new agents become publicly available, there is change in regulatory guidance, or there are large studies suggesting meaningful change in safety of existing therapies or treatment strategies.

outcomes were reported separately, then data on clinical remission were used for analysis. Although randomized controlled trials (RCTs) also variably report clinical response outcomes, attaining clinical remission is the primary treatment target in moderate-to-severe UC and thus was the primary outcome used to grade evidence and inform absolute and comparative treatment efficacy.

Estimating Absolute Magnitude of Benefit

To provide a synthesis of the risks and benefits of different interventions, and to calculate absolute effect estimates, the panel relied on pooled clinical remission rates on placebo. In RCTs with advanced therapies, the rate of induction of clinical remission with placebo was set at 10%, and maintenance of clinical remission was set at 15%. In trials of thiopurines that reported steroid-free remission as an outcome, pooled rates across placebo arms were used. For comparisons against no treatment, the guideline panel set a clinically meaningful difference (CMD) threshold of 10%, based on consensus. If the effect size was below this CMD threshold, then benefit was deemed to be trivial. For comparisons between 2 active therapies, the guideline panel set a CMD threshold of 5%, based on consensus, that is, we considered the difference between an active agent vs comparator as "important" if the absolute risk difference of achieving remission crossed the CMD threshold of >50 per 1000 patients treated (5%).

Search Strategy, Study Selection Criteria, and Data Abstraction

A comprehensive search of Ovid MEDLINE, Embase, and Wiley Cochrane Library, using a combination of controlled vocabulary terms and relevant keywords (Supplementary Table 1), from inception to November 21, 2023, was conducted by an experienced medical librarian, with input from the guideline methodologist. The search was updated on September 1, 2024. In addition, we reviewed references of previous guidelines and consensus statements, conference proceedings, and press releases on novel advanced therapies. Content experts provided insights into ongoing studies. All searches were limited to human subjects and English language. For evidence synthesis, RCTs conducted in adults with moderate-to-severe UC (corresponding to relevant PICOs) were included. If RCT-level evidence was not available for specific PICOs, then observational studies were considered to inform evidence. Due to the relatively recent approval of several of the medications under consideration, there is a paucity of real-world data regarding their use, both for effectiveness and safety outcomes. The minimum trial duration for induction and maintenance therapy was 4 weeks and 24 weeks, respectively. Efficacy trials exclusively in patients with Crohn's disease (CD) were excluded (except for data on combination therapy and treatment de-escalation); if a trial included both patients with UC and CD, it was included only if results were stratified by disease type or if >70% of participants had UC. Because safety outcomes are not well-informed by RCTs, representative large cohort studies and high-quality systematic reviews and meta-analyses were used to inform risk of serious infections and malignancy with different therapies. In addition, studies on issues of racial, ethnic, and social disparities and issues of general health equity pertinent to the topic were identified. Data

abstraction was conducted in duplicate, independently by 2 sets of investigators, with disagreements or questions of accuracy resolved by discussion and consensus.

Statistical Analysis

For trials of induction and maintenance therapy, outcomes were abstracted and reported as induction of clinical remission (in patients with active disease), and maintenance of remission (in patients with quiescent disease at trial entry), respectively. All analyses were conducted using true intention-to-treat analysis; patients lost to follow-up or excluded from analysis for other reasons were deemed to be treatment failures. Pooled relative risk (RR) or odds ratios (OR) and 95% CI were calculated using the Mantel-Haenszel fixed-effects model (in the absence of conceptual heterogeneity and if fewer than 5 studies) or the DerSimonian-Laird random-effects model.[11] First, pooled RR estimates were derived from pooled clinical trials for each individual therapy; these risk estimates are influenced both by efficacy of individual therapies and placebo rates in each of these trials. These RR estimates were then applied to a standardized placebo rate that represented the pooled placebo rate across all phase 2 and phase 3 RCTs in moderate-to-severe UC. The absolute risk difference derived from this was then used to inform strength of evidence for efficacy for each treatment. Use of a pooled standardized placebo response rates minimizes the effect of variable placebo rates across each trial, while still being informed by the efficacy of each treatment from the parent RCTs and enhances generalizability. This choice of pooled placebo rates is consistent with prior AGA guidelines for management of UC and CD and recommendations from GRADE. Statistical heterogeneity was assessed using the I^2 statistic.[12] Small study effects were examined using funnel plot symmetry and Egger's regression test, although it is important to recognize that these tests are unreliable when the number of studies is fewer than 10.[13] Direct comparisons were performed using Comprehensive Meta-Analysis, version 2.0. Due to a paucity of head-to-head trials of active agents, to inform comparative efficacy of different pharmacological interventions, we performed network meta-analysis (NMA) using the frequentist approach, with the statistical package "netmeta" (version 9.0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 4.0.2). Details of the NMA are reported in the accompanying 2024 AGA Evidence Synthesis document on comparative efficacy of different advanced therapies for management of moderate-to-severe UC that has been co-published in the Journal.

Certainty of Evidence

The quality of evidence was judged using the GRADE framework.[14] Briefly, using this approach, evidence from RCTs starts at high quality and evidence from observational studies starts at low quality (Supplementary Table 2). This evidence can be further rated down for risk of bias in the evidence, indirectness, inconsistency, imprecision, and publication bias. In selected cases, particularly for observational studies, evidence may be rated up if a large treatment effect is observed, if there is a dose–response relationship, or if all plausible confounding and bias would reduce a demonstrated effect or suggest a spurious effect if no effect was observed. Evidence profiles were developed for each intervention using the GRADEpro Guideline Development Tool (https://gradepro.org).

For questions of comparative efficacy of different pharmacological interventions, we used GRADE approach for NMA. Details are reported in the accompanying 2024 AGA Evidence Synthesis document that has been co-published in the Journal. In this evaluation, we considered the difference between an active agent vs comparator as "important" if the absolute risk difference of achieving remission crossed the CMD threshold of >50 per 1000 patients treated (5%), and "trivial" if the absolute risk difference was between 0 and 50 per 1000 patients treated. In using NMA for evidence synthesis, we relied on direct evidence when it was available from head-to-head comparisons and provided at least moderate certainty evidence. If there were no direct comparisons between 2 interventions or if the evidence from direct comparisons was very low or low certainty evidence, then effect estimates from the NMA were used.

Translating Evidence to Recommendations

Based on the GRADE Evidence-to-Decision framework, the guideline panel weighed the magnitude of, and balance between, the benefit and harms of interventions, patients' values and preferences, and the domains of feasibility, acceptability, and resource requirements and the impact on health equity.[15] The panel reached a consensus for all guideline statements. The certainty of evidence and the strength of recommendation are provided for each clinical question. Based on GRADE methodology, we labeled recommendations as "strong" or "conditional." The phrase "we recommend" indicates strong recommendations and the phrase "we suggest" indicates conditional recommendations and provide the suggested interpretation of strong and weak recommendations for patients, clinicians, and health care policy makers (Table 2). In addition, the panel provided broad overarching, as well as recommendation-specific implementation considerations to provide context and facilitate real-world use and adoption of these recommendations, based on evidence and their clinical experience and practice.

Review Process

This guideline was submitted for public comment and external peer review and was approved by the AGA Governing Board. The accompanying 2024 AGA Evidence Synthesis document focusing on comparative efficacy of different advanced therapies underwent conventional peer review.

Recommendations

A summary of all the recommendations is provided in Table 3 and discussed below. Broad overarching considerations for implementing these recommendations in clinical practice are discussed below and in Table 4. Two clinical decision support tools, which may assist clinicians in making pharmacological management decisions for patients with ulcerative colitis, are presented in Figures 1 and 2.

Safety of Pharmacological Therapies for Moderate-to-Severe Ulcerative Colitis

The guideline panel rated the safety of pharmacological therapies as an important but not critical outcome for decision making. It is important to note that clinical trials are selective in enrollment, and often have short follow-up. Data

Table 2. Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessment, Development and Evaluation Framework

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with their values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will involve various stakeholders. Performance measures should assess whether decision making is appropriate.

from these trials are often not able to adequately assess the safety of different therapies. Hence, we reviewed large cohort studies and published systematic reviews and meta-analyses to understand comparative safety of different advanced therapies in patients with UC. In a systematic review and meta-analysis of 20 head-to-head studies comparing risk of infections among different advanced therapies for treatment of IBD, Solitano and colleagues[16] observed that vedolizumab was associated with a 32% lower risk of serious infections compared with tumor necrosis factor (TNF) antagonists in patients with UC with minimal heterogeneity. In patients with CD, ustekinumab was associated with 51% lower risk of serious infections compared with TNF antagonists, and 60% lower risk compared with vedolizumab. There have been limited comparative safety studies of new small molecule drugs, including Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) receptor modulators, in patients with IBD. In a US administrative claims-based study, Cheng et al[17] did not observe any significant difference in the risk of all or serious infections between 305 patients with IBD treated with tofacitinib vs 19,096 patients treated with TNF antagonists. In contrast, in the large ORAL surveillance trial in older adults (aged 50 years or older) with rheumatoid arthritis and at least 1 cardiovascular risk factor, tofacitinib was associated with a higher risk of serious and opportunistic infections compared with TNF antagonists.[18] There are limited real-world data on the safety of newer advanced therapies like S1P receptor modulators and interleukin (IL) 23 antagonists, particularly in patients with UC. Comparative safety studies of JAK inhibitors with non-TNF antagonist biologics are sparse. Across studies, most consistent risk factors for serious infections are disease-related (eg, high disease activity, inadequate disease control, and need for corticosteroids and opioids) and individual patient–related (eg, advanced age, frailty and comorbidities)[17,19–24]

TNF antagonists have also been associated with increased risk of lymphoma and melanoma. In a French population-based study, Lemaitre and colleagues[25] estimated the annual incidence of lymphoma in patients treated with TNF antagonist monotherapy vs unexposed patients to be 0.41 per 1000 person-years vs 0.26 per 1000 person-years; after adjusting for potential confounders, the risk of lymphoma was 2.4 times higher in patients treated with TNF antagonist monotherapy. This risk was comparable with the risk observed in patients treated with thiopurine monotherapy. Patients exposed to combination therapy had a 6-fold increased risk of lymphoma compared with unexposed patients, and 2.3–2.5 times higher risk compared with patients exposed to monotherapy with either agent. The US Food and Drug Administration (FDA) has issued a black box warning on the increased risk of malignancy with TNF antagonists (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf). Currently, there is a paucity of population-representative data to inform risk estimates related to malignancy for other classes of advanced therapies.

Overall, the guideline panel felt that although advanced therapies, particularly TNF antagonists, JAK inhibitors and S1P receptor modulators, may be associated with increased risk of serious infections, the magnitude of increased risk is small for most patients with moderate-to-severe UC, and overall balance significantly favored benefits over harms with these agents for most patients. In addition, active disease and ongoing corticosteroid use to control symptoms are important determinants of safety outcomes; consequently the efficacy of treatments in achieving remission, particularly steroid-free remission, is important in reducing overall likelihood of infections for patients. Where there are individual patient characteristics pertaining to treatment safety that may influence selection of therapy, they are discussed below.

Table 3. Executive Summary of Recommendations for the Management of Adult Outpatients With Moderate-to-Severe Ulcerative Colitis

Recommendation
Use and positioning of advanced therapies
1. In adult outpatients with moderate-to-severe UC, the *AGA recommends* the use of infliximab, golimumab, vedolizumab, tofacitinib,[a] upadacitinib,[a] ustekinumab, ozanimod, etrasimod, risankizumab and guselkumab over no treatment. *[Strong recommendation, moderate to high certainty of evidence]*
2. In adult outpatients with moderate-to-severe UC, the *AGA suggests* the use of adalimumab, filgotinib[a] or mirikizumab over no treatment. *[Conditional recommendation, moderate certainty of evidence]*
Implementation considerations: • JAK inhibitors (tofacitinib, filgotinib, upadacitinib) have restricted use in advanced therapy-naïve patients. The FDA label recommends the use of JAK inhibitors in patients with prior failure or intolerance to TNF antagonists. In Europe, the European Medicines Agency recommends cautious use of JAK inhibitors as a first-line agent in patients at risk for adverse cardiovascular outcomes, including age 65 years or older, current or previous long-term smokers, a history of cardiovascular disease (such as heart attack or stroke), and a history of cancer. • Biosimilars of infliximab, adalimumab, and ustekinumab can be considered equivalent to their originator drug in their efficacy in terms of therapy selection • SC formulations of infliximab and vedolizumab have shown comparable efficacy to the respective IV maintenance doses • In patients, particularly those with severe disease, extended induction regimens (for up to 16 wk) or dose escalation upon may be beneficial for certain agents
3. In adult outpatients with moderate-to-severe UC who are *naïve to advanced therapies*, the *AGA suggests* using a HIGHER efficacy medication (infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib,[a] risankizumab, guselkumab) OR an INTERMEDIATE efficacy medication (golimumab, ustekinumab, tofacitinib,[a] filgotinib,[a] mirikizumab), rather than a LOWER efficacy medication (adalimumab). *[Conditional recommendation, low certainty of evidence]*
Implementation considerations: • Individual patient factors (eg, age, comorbidities, frailty, pregnancy, adherence) and preferences (eg, route of administration, ease of access) should be incorporated within a shared decision framework in selection of advanced therapies. • JAK inhibitors have restricted use in advanced therapy–naïve patients. The FDA label recommends the use of JAK inhibitors in patients with prior failure or intolerance to TNF antagonists. In Europe, the European Medicines Agency recommends cautious use of JAK inhibitors as a first-line agent in patients at risk for adverse cardiovascular outcomes including age 65 years or older, current or previous long-term smokers, a history of cardiovascular disease (such as heart attack or stroke), and a history of cancer. JAK inhibitors may be associated with higher risk of major adverse cardiovascular events and cancer than TNF antagonists in older adults with cardiovascular risk factors (eg, smoking, prior cardiovascular disease). • Vedolizumab and anti-IL therapies may be associated with a lower rate of infectious complications than TNF antagonists. They may be preferred in patients who may be at higher risk of immunosuppression-related infections or malignancies. • There are limited data on the safety of JAK inhibitors and S1P receptor modulators in pregnancy. These drugs should be avoided in women of childbearing age contemplating pregnancy.
4. In adult outpatients with moderate-to-severe UC who have previously been exposed to 1 or more advanced therapies, particularly TNF antagonists, the *AGA suggests* using a HIGHER efficacy medication (tofacitinib, upadacitinib, ustekinumab) OR an INTERMEDIATE efficacy medication (filgotinib, mirikizumab, risankizumab, guselkumab), rather than a LOWER efficacy medication (adalimumab, vedolizumab, ozanimod, etrasimod). *[Conditional recommendation, low certainty of evidence]*
Implementation considerations: • Individual patient factors (eg, age, comorbidities, frailty, pregnancy, adherence) and preferences (eg, route of administration, ease of access) should be incorporated within a shared decision framework in selection of advanced therapies. • Vedolizumab and anti-IL therapies may be associated with a lower rate of infectious complications than TNF antagonists. They may be preferred in patients who may be at higher risk of immunosuppression-related infections or malignancies. • There are limited data on the safety of JAK inhibitors and S1P receptor modulators in pregnancy. These drugs should be avoided in women of childbearing age contemplating pregnancy. • JAK inhibitors may be associated with higher risk of major adverse cardiovascular events and cancer than TNF antagonists in older adults with cardiovascular risk factors (smoking, prior cardiovascular disease). • Lower-efficacy medications may require longer duration of treatment for response in patients with multiple prior biologic failures. • While there is no direct RCT evidence, observational studies demonstrate that infliximab and golimumab are effective in inducing remission in patients with prior exposure to advanced therapies.
Use of immunomodulators
5. In adult outpatients with moderate-to-severe UC, the AGA suggests AGAINST using thiopurine monotherapy for induction of remission. *[Conditional recommendation, very low certainty of evidence]*
6. In adult outpatients with moderate-to-severe UC in remission, the AGA suggests using thiopurine monotherapy, rather than no treatment, for maintenance of remission, typically induced by corticosteroids. *[Conditional recommendation, low certainty of evidence]*
7. In adult outpatients with moderate-to-severe UC, the AGA suggests AGAINST using methotrexate monotherapy, for induction or maintenance of remission. *[Conditional recommendation, low certainty of evidence]*

Table 3. Continued

Recommendation
Combination therapy of biologics and immunomodulators
8. In adult outpatients with moderate-to-severe UC, the AGA suggests the use of infliximab in combination with an immunomodulator over infliximab or an immunomodulator alone. *[Conditional recommendation, moderate certainty of evidence]*
9. In adult outpatients with moderate-to-severe UC, the AGA suggests the use of adalimumab or golimumab in combination with an immunomodulator over adalimumab, golimumab or immunomodulator monotherapy. *[Conditional recommendation, low certainty of evidence]*
10. In adult outpatients with moderate-to-severe UC, the AGA makes no recommendation in favor of, or against the use, of non-TNF antagonist biologics in combination with an immunomodulator over non-TNF biologic alone. *[No recommendation, knowledge gap]*
De-escalation of therapy
11. In patients with UC who are in corticosteroid-free clinical remission for at least 6 months on combination therapy of TNF antagonists and an immunomodulator, the AGA makes no recommendation in favor of withdrawing immunomodulators or continuing combination therapy. *[No recommendation, knowledge gap]*
12. In patients with UC who are in corticosteroid-free clinical remission for at least 6 months on combination therapy of TNF antagonists and an immunomodulator, the AGA suggests AGAINST withdrawal of TNF antagonists. *[Conditional recommendation, very low certainty of evidence]*
13. In adult outpatients with moderate-to-severe UC, who have failed 5-ASAs, and have escalated to therapy with immunomodulators or advanced therapies, the AGA suggests stopping 5-ASAs. *[Conditional recommendation, low certainty of evidence]* Implementation considerations: • A subset of patients who have significant but not complete response with advanced therapies or immunomodulators may benefit from ongoing 5-ASAs to achieve remission. This may be particularly important for patients with residual proctitis who may benefit from adding rectal 5-ASA. • The independent benefit of long-term 5-ASAs in preventing colorectal cancer in patients with IBD is has not been robustly demonstrated.
Step therapy
14. In adult outpatients with moderate-severe UC, the AGA suggests early use of advanced therapies with or without immunomodulator therapy, rather than gradual step up after failure of 5-ASAs. *[Conditional recommendation, very low certainty of 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 immunosuppressive therapies, may reasonably choose gradual step therapy with 5-ASA therapy.

[a]In the United States, the FDA label recommends use of JAK inhibitors in patients with prior failure or intolerance to TNF antagonist therapy.

Table 4. Key Overarching Considerations in the Management of Adult Outpatients With Moderate-to-Severe Ulcerative Colitis

Key consideration
Patients should have confirmation of active inflammation based on UC-related symptoms, biomarkers, and/or endoscopic evaluation before starting advanced therapies.
Patients should have both general and therapy-specific pretreatment workup before initiation of such treatments. These include screening for hepatitis B and tuberculosis exposure before any biologic or advanced small molecule treatments, thiopurine methyl transferase testing before initiation of thiopurines, and a baseline electrocardiogram before use of S1P receptor modulators. There are other treatment- and patient-specific tests that should be performed in accordance with the labels from regulatory agencies.
It is important to evaluate for factors influencing risk of treatment-related complications, including assessment of comorbidities, frailty, and functional status and concomitant medications, and assessment of thromboembolic and cardiovascular risk factors.
In order to decrease risk of serious infections with immunosuppressive therapies, vaccination against influenza, pneumococcal pneumonia, and herpes zoster (particularly before S1P receptor modulator or JAK inhibitor use) should be considered.
Initiation of advanced therapy should be followed by monitoring for symptomatic response within 3 mo of initiation, symptomatic and biochemical remission within 3–6 mo, and endoscopic improvement/ remission within 6–12 mo.
On-treatment monitoring for potential toxicity from immunosuppressive therapies, such as periodic monitoring of hemogram, chemistries, and transaminases, should be performed, according to drug label.

Figure 1. *Clinical Decision Support Tool*: use and positioning of advanced therapies in the management of adult outpatients with moderate-to-severely-active ulcerative colitis.

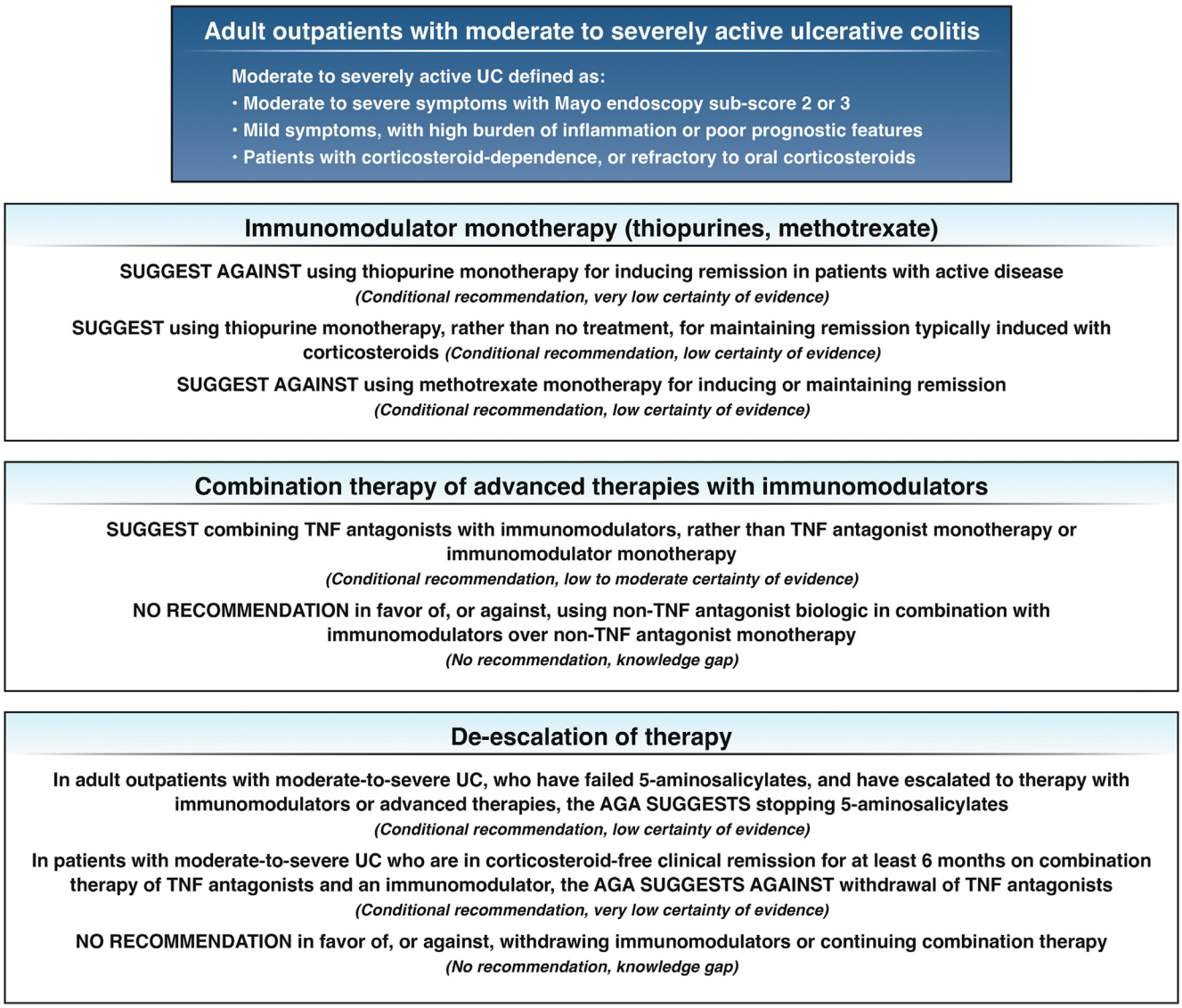

Figure 2. *Clinical Decision Support Tool*: use of combination therapy and immunomodulator therapy, and de-escalation of therapy in management of adult outpatients with moderate-to-severely-active ulcerative colitis.

Question 1: What is the *efficacy of advanced therapies* for induction and maintenance of remission in patients with moderate-to-severe UC?

Recommendations:

- **In adult outpatients with moderate-to-severe UC, the *AGA recommends* the use of infliximab, golimumab, vedolizumab, tofacitinib,[a] upadacitinib,[a] ustekinumab, ozanimod, etrasimod, risankizumab, and guselkumab over no treatment. *[Strong recommendation, moderate to high certainty of evidence]***
- **In adult outpatients with moderate-to-severe UC, the *AGA suggests* the use of adalimumab, filgotinib[a] or mirikizumab over no treatment. *[Conditional recommendation, moderate certainty of evidence]***

[a]In the United States, the FDA label recommends use of JAK inhibitors in patients with prior failure or intolerance to TNF antagonists.

Implementation Considerations

1. JAK inhibitors (eg, tofacitinib, filgotinib, and upadacitinib) have restricted use in advanced therapy–naïve patients. The FDA label recommends the use of JAK inhibitors in patients with prior failure or intolerance to TNF antagonists. In Europe, the European Medicine Agency recommends cautious use of JAK inhibitors as a first-line agent in patients at risk for adverse cardiovascular outcomes, including those aged 65 years or older, current or previous long-term smokers, a history of cardiovascular disease (such as heart attack or stroke), and a history of cancer.
2. Biosimilars of infliximab, adalimumab, and ustekinumab can be considered equivalent to their originator drug in their efficacy in terms of therapy selection.
3. Subcutaneous formulations of infliximab and vedolizumab have shown comparable efficacy to the respective intravenous maintenance doses.
4. In patients, particularly those with severe disease, extended induction regimens (for up to 16 weeks) or dose escalation upon may be beneficial for certain agents.

Summary and Certainty of Evidence

The data examining the efficacy of advanced therapies against placebo were derived from 38 phase 2 or phase 3 RCTs of approved treatments for moderate-to-severe UC. This comprised 13 trials of TNF antagonists (5 infliximab,[26–29] 5 adalimumab,[30–33] 3 golimumab[34–36]), 3 trials of anti-integrins (3 vedolizumab[37–39]), 1 trial of ustekinumab,[40] 5 trials anti-IL23 antibodies (2 mirikizumab,[41,42] 1 risankizumab,[43] and 2 guselkumab[44–46]), 5 trials of S1P receptor modulators (2 ozanimod,[47,48] 3 etrasimod[49,50]), and 8 trials of JAK inhibitors (3 upadacitinib,[51,52] 3 tofacitinib,[53,54] and 2 filgotinib[55]). Of the included RCTs, the trials of ustekinumab, filgotinib, upadacitinib, ozanimod, etrasimod, mirikizumab, risankizumab, and guselkumab were all new since the previous 2020 guideline evidence synthesis.[56] For infliximab and vedolizumab, new information since the 2020 guideline included efficacy of the subcutaneous formulations of each drug for maintenance of remission. For adalimumab, additional data on efficacy were available in the placebo controlled RCT comparing adalimumab and etrolizumab.[30] All trials were conducted in patients with moderate-to-severe UC and compared efficacy against placebo. Patient characteristics, including severity, were broadly comparable across all trials; however, later trials had a larger proportion of patients with multiple biologic failures before study entry. These are summarized in greater detail in the accompanying evidence synthesis document. Most trials provided information on both biologic-naïve and biologic-exposed patients, except for trials of infliximab and golimumab, which included only biologic-naïve patients. Trials of biosimilars (eg, infliximab and adalimumab) or alternate modes of delivery, such as subcutaneous injections (eg, infliximab and vedolizumab) were also included when applicable.

Data on the efficacy of each agent vs placebo for induction and maintenance of clinical remission are shown in Supplementary Figures 1–13. The corresponding GRADE evidence profile with certainty of evidence for each agent is shown in Tables 5–9. Overall, upadacitinib was superior to placebo for inducing and maintaining clinical remission with high certainty of evidence. Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, filgotinib, ustekinumab, ozanimod, etrasimod, mirikizumab, risankizumab, and guselkumab were superior to placebo with moderate certainty of evidence.

Benefits and Harms

In order to make recommendations, it is critical to examine the benefits and harms of choosing an intervention over a comparator. Overall, given the multiplicity of treatments available for moderate-to-severe UC and the importance of making informed, evidence-based, and cost-effective choices, the panel established a CMD of 10% over placebo to suggest at least a moderate desirable effect with the intervention. Infliximab, golimumab, vedolizumab, ustekinumab, tofacitinib, ozanimod, etrasimod, risankizumab, and guselkumab were deemed to have moderate desirable effect, whereas upadacitinib was deemed to have a large desirable effect ($\geq$20%). In contrast, adalimumab, mirikizumab, and filgotinib were deemed to have trivial to small desirable effect over no intervention because the magnitude of benefit was below the prespecified CMD. All active interventions were deemed to have trivial undesirable effects relative to no intervention, given the low risk of treatment-related serious adverse events with these therapies, such as serious infections and malignancy. Importantly, the panel considered potential harms of no intervention to include risks associated with untreated disease that could negatively impact quality of life, functional status, lead to greater need for corticosteroids, and themselves could increase the risk of serious infections and, in some instances, malignancy such as colorectal cancer. The GRADE evidence-

Table 5. GRADE Evidence Profile Comparing Tumor Necrosis Factor Antagonists (Infliximab, Adalimumab, and Golimumab) With Placebo for Induction and Maintenance of Remission in Patients With Moderate-to-Severe Ulcerative Colitis

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with infliximab				
Infliximab compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	50/438 (11.4%)	142/437 (32.5%)	2.70 (2.01–3.61)	170 more per 1000 (from 101 more to 261 more)	875 (5 RCTs)	⨁⨁⨁◯[c] MODERATE
Maintenance of clinical remission (CRITICAL)	78/478 (16.3%)	235/627 (37.5%)	2.17 (1.73–2.71)	176 more per 1000 (from 110 more to 257 more)	1105 (5 RCTs)	⨁⨁⨁⨁ HIGH
Adalimumab compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	59/616 (9.6%)	141/753 (18.7%)	1.84 (1.37–2.48)	84 more per 1000 (from 37 more to 148 more)	1369 (5 RCTs)	⨁⨁⨁◯[d] MODERATE
Maintenance of clinical remission (CRITICAL)	29/342 (8.5%)	84/425 (19.8%)	2.25 (1.50–3.37)	188 more per 1000 (from 75 more to 356 more)	767 (2 RCTs)	⨁⨁⨁◯[c,e] MODERATE
Golimumab compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	23/320 (7.2%)	58/324 (17.9%)	2.46 (1.56–3.90)	146 more per 1000 (from 56 more to 290 more)	644 (2 RCTs)	⨁⨁⨁◯[c,e] MODERATE
Maintenance of clinical remission (CRITICAL)	36/185 (19.5%)	67/183 (36.6%)	1.71 (1.19–2.44)	107 more per 1000 (from 28 more to 216 more)	368 (2 RCTs)	⨁⨁⨁◯[c,e,f] MODERATE

[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).
[d]Rated down for serious imprecision because magnitude of benefit is below the 100 per 1000 absolute benefit rate of clinically meaningful difference threshold over placebo, identified by the guideline panel.
[e]Lower limit of 95% of absolute effect crosses the clinically meaningful difference threshold of drug over placebo.
[f]Although statistical heterogeneity was noted, with use of fixed effects meta-analysis, estimate was largely driven by larger, high-quality trials.

Table 6. GRADE Evidence Profile Comparing Vedolizumab With Placebo for Induction and Maintenance of Remission in Patients With Moderate-to-Severe Ulcerative Colitis

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with vedolizumab				
Vedolizumab compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	18/231 (7.8%)	68/389 (17.5%)	2.09 (1.28–3.43)	109 more per 1000 (from 28 more to 243 more)	620 (2 RCTs)	⨁⨁⨁◯[c,d] MODERATE
Maintenance of clinical remission (CRITICAL)	41/224 (18.3%)	146/323 (45.2%)	2.41 (1.78–3.27)	212 more per 1000 (from 117 more to 340 more)	547 (3 RCTs)	⨁⨁⨁◯[c] MODERATE

[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).
[d]Lower limit of 95% of absolute effect crosses the clinically meaningful difference threshold of drug over placebo for induction of clinical remission outcome.

to-decision judgments for use of all advanced therapies over no intervention is shown in Table 10.

Rationale and Implementation Considerations

The panel surmised that patient characteristics were broadly similar across the clinical trials, although the later clinical trials were more enriched with biologic-refractory patients. The panel recognized the heterogeneity in the response of placebo-treated patients across the trials, which could affect the magnitude of RR reduction. Consequently, absolute risk differences informing strength of evidence for each agent were made against a standardized placebo response rate that represented an average across trials.

As noted earlier, in the implementation of the guideline recommendations, it is important to factor in patient-related factors to guide selection of therapy. These include assessment of patient risk for immunosuppression-related complications, including infections or prior malignancy, presence of extraintestinal manifestations or other disease-complications that may influence therapy, and patient preference for route of administration.

Three biosimilars for infliximab, 10 for adalimumab, and 1 for ustekinumab have been approved for use for moderate-to-severe UC in the United States. In RCTs, switching from parent to biosimilar infliximab was not associated with higher rates of relapse.[57] In observational studies, most patients tolerated a switch to a biosimilar without an increase in loss of response or adverse events.[58,59] Thus, in patients newly starting or on established therapy with infliximab, adalimumab, or ustekinumab, treatment outcomes with originator or biosimilar in most situations may be comparable. There is no increase in the risk of immunogenicity because of this switch; existing drug assays are accurate in measuring biosimilar trough levels with therapeutic thresholds interchangeable with originator drug.[60]

Subcutaneous (SC) formulations of infliximab and vedolizumab have been approved as maintenance therapy for patients with moderate-to-severe UC. Phase 3 RCT-enrolled patients with moderate to severely active UC to receive open-label infliximab biosimilar (CT-P13) 5 mg/kg intravenously (IV) at weeks 0, 2, and 6.[61] Responders were randomized to receive either CT-P13 120 mg SC or placebo every 2 weeks for up to week 52. At the end of the trial, the rates of clinical remission were higher with CT-P13 (43.2%) compared with placebo (20.8%). The VISIBLE 1 trial examined the efficacy of SC vedolizumab after 2 IV induction doses to standard IV maintenance therapy with vedolizumab or placebo.[62] At week 52, the rates of remission were similar with SC vedolizumab (46.2%) and IV vedolizumab (42.6%) and higher than placebo (14.3%). Real-world experience suggests high acceptability and comparable effectiveness with switching from IV to SC formulations.[63] The guideline panel felt that SC formulations of infliximab and vedolizumab are acceptable alternatives to IV maintenance therapy for most patients. Dosing considerations should be factored in for patients with severely active disease, high body mass index, and those on dose-escalated regimens.

Emerging data suggest that in some patients, particularly those with severe disease, an extended induction regimen is necessary to improve rates of clinical response, particularly with JAK inhibitors. Among patients who did not respond to

Table 7. GRADE Evidence Profile Comparing Interleukin-12/23 Antagonist (Ustekinumab) and Interleukin-23 Antagonists (Mirikizumab, Risankizumab, Guselkumab) With Placebo for Induction and Maintenance of Remission in Patients With Moderate-to-Severe Ulcerative Colitis

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with ustekinumab				
Ustekinumab compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	17/319 (5.3%)	50/322 (15.5%)	2.91 (1.72–4.94)	191 more per 1000 (from 72 more to 394 more)	641 (1 RCT)	⨁⨁⨁◯[b,c] MODERATE
Maintenance of clinical remission (CRITICAL)	42/175 (24.0%)	77/176 (43.8%)	1.82 (1.33–2.49)	123 more per 1000 (from 50 more to 224 more)	351 (1 RCT)	⨁⨁⨁◯[b,c] MODERATE

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with mirikizumab				
Mirikizumab compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	42/357 (11.8%)	224/930 (24.1%)	1.94 (1.43–2.63)	94 more per 1000 (from 43 more to 163 more)	1287 (2 RCTs)	⨁⨁⨁◯[d] MODERATE
Maintenance of clinical remission (CRITICAL)	49/205 (23.9%)	216/436 (49.5%)	2.04 (1.57–2.65)	156 more per 1000 (from 86 more to 247 more)	641 (2 RCTs)	⨁⨁⨁◯[c] MODERATE

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with risankizumab				
Risankizumab compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	20/325 (6.2%)	132/650 (18.5%)	3.30 (2.10–5.18)	230 more per 1000 (from 110 more to 418 more)	975 (1 RCT)	⨁⨁⨁◯[b] MODERATE
Maintenance of clinical remission (CRITICAL)	46/183 (25.1%)	180 mg: 72/179 (40.2%) 360 mg: 71/186 (38.2%)	180 mg: 1.60 (1.18–2.18) 360 mg: 1.52 (1.11–2.07)	180 mg: 90 more per 1000 (from 27 more to 177 more) 360 mg: 78 more per 1000 (from 17 more to 160 more)	548 (1 RCT)	180 mg: ⨁⨁⨁◯[d] MODERATE 360 mg: ⨁⨁⨁◯[d] MODERATE

Table 7. Continued

Outcomes	Study event rates [n/N (%)] Risk with placebo	Risk with guselkumab	Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
Guselkumab compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	32/385 (8.3%)	121/522 (23.2%)	2.82 (1.95–4.08)	182 more per 1000 (from 95 more to 308 more)	907 (2 RCTs)	⨁⨁⨁◯[c] MODERATE
Maintenance of clinical remission (CRITICAL)	36/190 (18.9%)	100 mg q8w: 85/188 (45.2%) 200 mg q4w: 95/190 (50.0%)	100 mg q8w: 2.39 (1.71–3.33) 200 mg q4w: 2.64 (1.90–3.66)	100 mg q8w: 209 more per 1000 (from 107 more to 350 more) 200 mg q4w: 246 more per 1000 (from 135 more to 399 more)	568 (1 RCT)	180 mg: ⨁⨁⨁◯[b] MODERATE 360 mg: ⨁⨁⨁◯[b] MODERATE

q4w, every 4 weeks; q8w, every 8 weeks.
[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]Rated down for imprecision because optimal information size not met (<200 events).
[c]Lower limit of 95% of absolute effect crosses the clinically meaningful difference threshold of drug over placebo for induction of clinical remission outcome.
[d]Rated down for serious imprecision because magnitude of benefit is below the 100 per 1000 absolute benefit rate of clinically meaningful difference threshold over placebo, identified by the guideline panel.

the 10-mg twice daily dose of tofacitinib at week 8 in the OCTAVE trial, 52% achieved clinical response at week 16 after extended induction with 10-mg twice daily dosing for an additional 8 weeks.[64] Of these, 56.1% maintained clinical remission at 36 months. Nearly one-half (48%) of patients who failed to respond to the initial 8-week induction regimen with upadacitinib 45 mg/d responded to an additional 8 weeks of induction therapy.[65] More than one-half of these patients maintained clinical response at 1 year. Similarly, an additional 3 IV induction doses of mirikizumab showed benefit in patients with incomplete response to the first 3 weeks' induction dosing.[66]

Patients, particularly those with severe disease, may also require maintenance therapy at a higher dose. In a study of de-escalation of tofacitinib to the 5-mg twice daily maintenance dose, approximately 29% of patients who were de-escalated required an increase in dose back to 10 mg twice daily with clinical response recapturable in only 63% of patients.[67] Similarly in the OCTAVE trials, 25% of patients who were de-escalated were not able to remain in remission on the lower maintenance dose.[68] Thus, a subset of patients may require being maintained at a higher dose. Because some of the risk of adverse effects associated with tofacitinib, particularly shingles and venous thromboembolism are greater at the higher dose, it is important to monitor such patients carefully for these events and adopt preventive strategies to minimize their risk.

Question 2: In adult outpatients with moderate-to-severe UC who are *naïve to advanced therapies*, what is comparative efficacy of different advanced therapies?

Recommendation:

- **In adult outpatients with moderate-to-severe UC who are *naïve to advanced therapies*, the *AGA suggests* using a HIGHER efficacy medication (infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib,[a] risankizumab, guselkumab) OR an INTERMEDIATE efficacy medication (golimumab, ustekinumab, tofacitinib,[a] filgotinib,[a] mirikizumab), rather than a LOWER efficacy medication (adalimumab). *[Conditional recommendation, low certainty of evidence]***

[a]In the United States, the FDA label recommends use of JAK inhibitors in patients with prior failure or intolerance to TNF antagonist therapy.

Implementation Considerations

1. Individual patient factors (eg, age, comorbidities, frailty, pregnancy, adherence) and preferences (eg, route of administration, ease of access) should be incorporated

Table 8. GRADE Evidence Profile Comparing Janus Kinase Inhibitors (Tofacitinib, Upadacitinib, Filgotinib) With Placebo for Induction and Maintenance of Remission in Patients With Moderate-to-Severe Ulcerative Colitis

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with tofacitinib				
Tofacitinib compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	19/282 (6.7%)	177/938 (18.9%)	3.23 (2.05–5.08)	223 more per 1000 (from 105 more to 408 more)	1220 (3 RCTs)	⨁⨁⨁◯[c] MODERATE
Maintenance of clinical remission (CRITICAL)	22/198 (11.1%)	5 mg bid: 68/198 (34.3%) 10 mg bid: 80/197 (40.6%)	5 mg bid: 3.09 (1.99–4.79) 10 mg bid: 3.65 (2.38–5.61)	5 mg bid: 313 more per 1000 (from 149 more to 569 more) 10 mg bid: 397 more per 1000 (from 207 more to 692 more)	593 (1 RCT)	5 mg bid: ⨁⨁⨁◯[c] MODERATE 10 mg bid: ⨁⨁⨁◯[c] MODERATE

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with upadacitinib				
Upadacitinib compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	14/374 (3.7%)	208/716 (29.1%)	7.15 (4.26–11.99)	615 more per 1000 (from 326 more to 1000 more)	1090 (3 RCTs)	⨁⨁⨁⨁ HIGH
Maintenance of clinical remission (CRITICAL)	18/149 (12.1%)	15 mg/d: 63/148 (42.6%) 30 mg/d: 80/154 (51.9%)	15 mg/d: 3.52 (2.20–5.65) 30 mg/d: 4.30 (2.72–6.81)	15 mg/d: 378 more per 1000 (from 180 more to 698 more) 30 mg/d: 495 more per 1000 (from 258 more to 871 more)	451 (1 RCT)	15 mg/d: ⨁⨁⨁◯[c] MODERATE 30 mg/d: ⨁⨁⨁◯[c] MODERATE

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with filgotinib				
Filgotinib compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	27/279 (9.7%)	94/507 (18.5%)	1.88 (1.27–2.80)	88 more per 1000 (from 27 more to 180 more)	786 (2 RCTs)	⨁⨁⨁◯[d] MODERATE

Table 8. Continued

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with filgotinib				
Maintenance of clinical remission (CRITICAL)	23/188 (12.2%)	100 mg/d: 41/172 (23.8%) 200 mg/d: 74/198 (37.4%)	100 mg/d: 1.77 (0.98–3.19) 200 mg/d: 3.36 (1.87–6.04)	100 mg/d: 115 more per 1000 (from 3 fewer to 328 more) 200 mg/d: 354 more per 1000 (from 131 more to 756 more)	558 (1 RCT)	100 mg/d: ⨁⨁⨁◯[d] MODERATE 200 mg/d: ⨁⨁⨁◯[c] MODERATE

bid, twice per day.
[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).
[d]Rated down for serious imprecision because magnitude of benefit is below the 100 per 1000 absolute benefit rate of clinically meaningful difference threshold over placebo, identified by the guideline panel.

within a shared decision framework in selection of advanced therapies.

2. JAK inhibitors have restricted use in advanced therapy-naïve patients. The FDA label recommends the use of JAK inhibitors in patients with prior failure or intolerance to TNF antagonists. In Europe, the European Medicines Agency recommends cautious use of JAK inhibitors as a first-line agent in patients at risk for adverse cardiovascular outcomes, including age 65 years or older, current or previous long-term smokers, a history of cardiovascular disease (such as heart attack or stroke), and a history of cancer. JAK inhibitors may be associated with higher risk of major adverse cardiovascular events and cancer than TNF antagonists in older adults with cardiovascular risk factors (eg, smoking, prior cardiovascular disease).

3. Vedolizumab and anti-IL therapies may be associated with a lower rate of infectious complications than TNF antagonists. They may be preferred in patients who may be at higher risk of immunosuppression-related infections or malignancies.

4. There are limited data on the safety of JAK inhibitors and S1P receptor modulators in pregnancy. These drugs should be avoided in women of childbearing age contemplating pregnancy.

Summary and Certainty of Evidence

The positioning of therapies is a critical component of management of moderate-to-severe UC. Recognizing the paucity of head-to-head trials, the panel relied on NMA to inform comparative efficacy of different agents. The accompanying evidence synthesis document summarizes in detail the results of the NMA. Briefly summarizing the results of the NMA for induction of clinical remission in patients with moderate-to-severe UC who are naïve to advanced therapies, several pair-wise comparisons between 2 active treatments met the *a priori* threshold for superiority (CMD $\geq$5%). Infliximab has a possibly important benefit in achieving remission compared with adalimumab, mirikizumab, tofacitinib, and filgotinib, with a low certainty of evidence. Golimumab, similarly, has possibly important benefit over adalimumab, filgotinib, and tofacitinib, with a low certainty of evidence. Vedolizumab achieves a possibly important benefit compared with adalimumab (including from the head-to-head VARSITY trial[38]) and tofacitinib with a low certainty of evidence. Ozanimod demonstrated a possibly important benefit over adalimumab, mirikizumab, tofacitinib, and filgotinib, while etrasimod demonstrated a possibly important benefit over filgotinib, with a low certainty of evidence. Risankizumab likely has important benefit compared with filgotinib with moderate certainty evidence and possibly important benefit compared with adalimumab, ustekinumab, mirikizumab, and tofacitinib. Guselkumab demonstrated a possibly important benefit over adalimumab, mirikizumab, tofacitinib, and filgotinib with low certainty of evidence. Upadacitinib demonstrated a likely important benefit over infliximab, adalimumab, vedolizumab, ustekinumab, mirikizumab, etrasimod, tofacitinib, and filgotinib, with moderate certainty of evidence, and possibly important benefit over golimumab and ozanimod with a low certainty of evidence. Analyses of endoscopic improvement after induction showed findings broadly consistent with induction of clinical remission. It

Table 9. GRADE Evidence Profile Comparing Sphingosine-1-Phosphate Receptor Modulators (Ozanimod, Etrasimod) With Placebo for Induction and Maintenance of Remission in Patients With Moderate-to-Severe Ulcerative Colitis

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with ozanimod				
Ozanimod compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	17/281 (6.0%)	90/496 (18.1%)	2.97 (1.80–4.90)	197 more per 1000 (from 80 more to 390 more)	777 (2 RCTs)	⨁⨁⨁◯[c,d] MODERATE
Maintenance of clinical remission (CRITICAL)	46/292 (15.8%)	99/297 (33.3%)	2.09 (1.54–2.84)	163 more per 1000 (from 81 more to 276 more)	589 (2 RCTs)	⨁⨁⨁◯[c,d] MODERATE
Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with etrasimod				
Etrasimod compared with placebo for moderate-to-severe UC						
Induction of clinical remission (CRITICAL)	38/314 (12.1%)	160/577 (27.7%)	2.23 (1.61–3.09)	123 more per 1000 (from 61 more to 209 more)	891 (3 RCTs)	⨁⨁⨁◯[c,d] MODERATE
Maintenance of clinical remission (CRITICAL)	11/144 (7.6%)	94/289 (32.5%)	4.26 (2.36–7.69)	489 more per 1000 (from 204 more to 1000 more)	433 (1 RCT)	⨁⨁⨁◯[c] MODERATE

[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).
[d]Lower limit of 95% of absolute effect crosses the clinically meaningful difference threshold of drug over placebo.

was difficult to compare the efficacy of treatments for maintenance of clinical remission through an NMA approach because of heterogeneity in the trial design. The only head-to-head trial was the VARSITY trial, in which 769 patients with moderate-to-severe UC were randomized to receive either vedolizumab (n = 383) or adalimumab (n = 386).[38] At week 52, a higher rate of clinical remission was observed in the vedolizumab-treated patients (31.3%) compared with adalimumab (22.5%). Corticosteroid-free remission rates, however, were higher with adalimumab (21.8%) compared with vedolizumab (12.6%). On NMA of treat-straight-through trials, etrasimod demonstrated likely important benefit over infliximab and possibly important benefit over adalimumab.

Benefits and Harms

No significant differences in the risk of infections and serious adverse events between different agents in previous network meta-analyses of clinical trials.[16] In observational studies, vedolizumab was associated with a lower risk of serious infections compared with TNF antagonists in patients with UC[69,70]; there was paucity of evidence for comparative safety of other agents. Thus, they may be

Table 10. GRADE Evidence-to-Decision Framework for Use of All Advanced Therapies Over No Intervention for the Management of Patients With Moderate-to-Severe Ulcerative Colitis

Domain	Criteria	Judgment					
Problem	Is the problem a priority?	No	Probably no	Probably yes	Yes	Varies	Do not know
Desirable effects	How substantial are the desirable anticipated effects?	**Trivial to small** ***ADA, FILG, MIRI***		**Moderate** ***IFX, GLM, VEDO, UST, TOFA, OZA, ETRA, RISA, GUS***	Large ***UPA***	Varies	Do not know
Undesirable effects	How substantial are the undesirable anticipated effects?	**Trivial** ***IFX, ADA, GLM, VEDO, UST, TOFA, FILG, UPA, OZA, ETRA, MIRI, RISA, GUS***	Small	Moderate	Large	Varies	Do not know
Certainty of evidence	What is the overall certainty of the evidence of effects	Very low		Low	**Moderate** ***IFX, ADA, GLM, VEDO, UST, TOFA, FILG, OZA, ETRA, MIRI, RISA, GUS***	**High** ***UPA***	No included studies
Values	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability		**No important uncertainty or variability**
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Favors comparison/ control	Probably favors comparison	Does not favor either comparison or intervention	**Probably favors intervention** ***ADA, FILG, MIRI***	**Favors intervention** ***IFX, GLM, VEDO, UST, TOFA, UPA, OZA, ETRA, RISA, GUS***	Varies/Do not know
Resource use	Is the incremental cost small relative to the net benefits?	No	**Probably no**	Uncertain	Probably yes	Yes	Uncertain

Table 10. Continued

Domain	Criteria	Judgment					
Equity	What would be the impact on health inequities?	Increased	**Probably increased**	Probably no impact	Probably reduced	Reduced	Varies/Do not know
Acceptability	Is the option acceptable to key stakeholders?	No	Probably no	Probably yes	**Yes**	Varies	Do not know
Feasibility	Is the option feasible to implement?	No	Probably no	Probably yes	**Yes**	Varies	Do not know

NOTE. Clinically meaningful difference threshold of drug over placebo was set at 10%. Judgments made by guideline panel are in bold. Specific decisions for each medication are in italic.
ADA, adalimumab; ETRA, etrasimod; FILG, filgotinib; GLM, golimumab; GUS, guselkumab; IFX, infliximab; MIRI, mirikizumab; OZA, ozanimod, RISA, risankizumab; TOFA, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VEDO, vedolizumab.

preferred among agents of similar efficacy in patients particularly vulnerable to infectious complications, such as the older frail adult or those with recent malignancy, excluding nonmelanoma skin cancers. Specific safety considerations regarding pregnancy and lactation are discussed in the Implementation Considerations below. Overall, the panel established a CMD of 5% over an active intervention to suggest at least a moderate desirable effect with the intervention relative to the comparator; for most comparisons, this risk difference was between 5% and 15%. Only upadacitinib was deemed to have a large desirable effect exceeding 20% for comparisons against infliximab, adalimumab, vedolizumab, ustekinumab, mirikizumab, etrasimod, tofacitinib, and filgotinib. The panel deemed that even though there may be small differences in the relative risk of adverse events with different medications, the overall magnitude of these undesirable effects with all medications was trivial. Hence, decision making for recommendations was driven primarily by comparative efficacy, rather than safety, in most instances.

Rationale and Implementation Considerations

With the availability of multiple drugs within a class for several therapeutic mechanisms, there are emerging data suggesting differences in efficacy even within a therapeutic class. Consequently, the panel made recommendations specific to individual drugs rather than to classes. Rather than relying only on active comparisons showing important benefit over a comparison through NMA, the guideline panel took a more pragmatic and holistic approach to create "efficacy buckets" that grouped together treatments with similar magnitude of treatment benefit. The efficacy buckets were informed by magnitude of absolute risk difference (over placebo) in the phase 3 RCTs, as well as comparative efficacy in the NMA. Treatments were generally considered high efficacy if they demonstrated a CMD $\geq$5% in direct or network head-to-head comparison (if no direct evidence available), a p-score in the NMA of 0.49 or higher, and an absolute benefit of $\geq$15% over placebo in phase 3 RCT among biologic-naïve patients. Recognizing several medications have only recently been approved and there is paucity of real-world evidence on their absolute and comparative effectiveness, the panel took a more conservative approach on creating efficacy buckets. Applying the above criteria, the guideline panel classified infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, and guselkumab as high-efficacy medications, and golimumab, ustekinumab, tofacitinib, filgotinib, and mirikizumab were labeled moderate-efficacy medications, and adalimumab was rated as having lower efficacy. The panel debated the relative weight of efficacy during induction and maintenance phases to inform comparative effectiveness and relative positioning. Given the recognized adverse impact of corticosteroid therapy and the importance of achieving steroid-free remission early as a treatment end point, the panel prioritized the relative efficacy of treatments in achieving clinical remission at the end of the induction as primary determinant of relative positioning of

treatments. However, patients and providers may reasonably select medications based on strength of maintenance efficacy, particularly in the setting of other patient or disease factors (such as comorbidity) that may influence treatment choice.

The panel recognized the varying recommendations for use of JAK inhibitors as first-line treatment in different regions of the world. In the United States, the FDA label recommends use of JAK inhibitors in patients with prior failure or intolerance to TNF antagonists. In Europe, the European Medicines Agency recommends cautious use of JAK inhibitors as a first-line agent in patients at risk for adverse cardiovascular outcomes, including age 65 years and older, current or previous long-term smokers, a history of cardiovascular disease (such as heart attack or stroke), and a history of cancer. Restriction for use of JAK inhibitors first line is largely informed by data from the ORAL Surveillance study.[18] This study compared the safety of tofacitinib (5 mg or 10 mg twice daily) to TNF antagonist therapy among patients with rheumatoid arthritis aged 50 years or older who also had cardiovascular risk factors (such as prior cardiovascular disease or cigarette smoker [current or past], hypertension, high-density lipoprotein cholesterol level of $<$40 mg/dL, diabetes mellitus, family history of premature coronary heart disease, extra-articular rheumatoid arthritis, or history of coronary artery disease). In this cohort, over a median follow-up of 4 years, patients using tofacitinib, particularly at the 10-mg twice daily dose, had a higher risk of major adverse cardiovascular events, including venous thromboembolism and cancer. In regions where JAK inhibitors may be used as first-line therapy in biologic-naïve patients, upadacitinib can be considered a high-efficacy medication and tofacitinib and filgotinib are considered moderate-efficacy medications. In patients at high risk of major adverse cardiovascular events, JAK inhibitors should be used cautiously.

For patients who desire an oral route of administration, an S1P receptor modulator or JAK inhibitor may be a preferred therapeutic agent. Large prospective registries have demonstrated that maternal use of TNF antagonists or other biologics during pregnancy is not associated with a significant increase in risk of adverse pregnancy or early childhood outcomes.[71,72] Although there are limited data on newer anti-IL23 inhibitors (ie, mirikizumab, risankizumab, and guselkumab), it can be reasonably expected that their safety profile during pregnancy will be similar to ustekinumab. In contrast to above, there is a paucity of data on small molecule treatments, including JAK inhibitors and S1P receptor modulators, with animal data suggesting potential adverse pregnancy effects at doses much higher than used for treatment of IBD.[73] Thus, in women of childbearing age actively contemplating pregnancy, we recommend avoiding JAK inhibitors and S1P receptor modulators and selecting an alternate therapeutic option when possible.

The relative positioning of different therapies was informed primarily by comparative efficacy in inducing clinical remission, which was defined by the panel *a priori* as a critical outcome of interest. The panel recognized that other patient-important end points, including achieving corticosteroid-free remission, maintenance of clinical remission, and avoiding surgery and hospitalization, as well as objective outcomes, such endoscopic and histologic healing, are important treatment goals for moderate-to-severe UC. The heterogeneity in trial designs (responder re-randomization or treat-straight-through) prevented robust comparisons for treatments for longer-term end points. Where data were available, relative efficacy for maintenance end points was broadly consistent with induction data. Similarly, data on achievement of endoscopic improvement were also consistent with clinical remission end points. There was a lack of systematic reporting of other end points, particularly for older clinical trials that precluded using such data to inform relative positioning.

Question 3: In adult outpatients with moderate-to-severe UC who have been *exposed to advanced therapies*, what is the comparative efficacy of different advanced therapies?

Recommendation:

- **In adult outpatients with moderate-to-severe UC who have previously been exposed to 1 or more advanced therapies, particularly TNF antagonists, the *AGA suggests* using a HIGHER efficacy medication (tofacitinib, upadacitinib, ustekinumab) OR an INTERMEDIATE efficacy medication (filgotinib, mirikizumab, risankizumab, guselkumab), rather than a LOWER efficacy medication (adalimumab, vedolizumab, ozanimod, etrasimod). *[Conditional recommendation, low certainty of evidence]***

Implementation Considerations

1. Individual patient factors (eg, age, comorbidities, frailty, pregnancy, adherence) and preferences (eg, route of administration, ease of access) should be incorporated within a shared decision framework in selection of advanced therapies.
2. Vedolizumab and anti-IL therapies may be associated with a lower rate of infectious complications than TNF antagonists. They may be preferred in patients who may be at higher risk of immunosuppression-related infections or malignancies.
3. There are limited data on the safety of JAK inhibitors and S1P receptor modulators in pregnancy. These drugs should be avoided in women of childbearing age contemplating pregnancy.
4. JAK inhibitors may be associated with higher risk of major adverse cardiovascular events and cancer than TNF antagonists in older adults with cardiovascular risk factors (eg, smoking and prior cardiovascular disease).

5. Lower-efficacy medications may require longer duration of treatment for response in patients with multiple prior biologic failures.
6. While there is no direct RCT evidence, observational studies demonstrate that infliximab and golimumab are effective in inducing remission in patients with prior exposure to advanced therapies.

Summary and Certainty of Evidence

The body of evidence for comparative effectiveness of individual therapy in patients exposed to advanced therapies is summarized in the accompanying NMA. There was a single head-to-head randomized trial (VARSITY) comprising a small number (21%) of previously biologic-exposed patients comparing vedolizumab and adalimumab in moderate-to-severe UC.[38] This trial noted no difference between the 2 agents in maintaining clinical remission (20.3% vs 16.0%) in this subpopulation. Thus, most of the evidence for relative positioning was informed by the NMA, as well as direct evidence from the phase 2 and phase 3 RCTs. In this synthesis, tofacitinib, filgotinib, upadacitinib, ustekinumab, mirikizumab, risankizumab, and guselkumab demonstrated likely important benefit in achieving clinical remission compared with no treatment, with a moderate certainty of evidence. Among active comparisons, upadacitinib likely has important benefit over adalimumab, vedolizumab, filgotinib, etrasimod, mirikizumab, risankizumab, and guselkumab, with a moderate certainty of evidence, and possibly important benefit over ozanimod. Tofacitinib also demonstrated likely important benefit over adalimumab, vedolizumab, and etrasimod, and possible important benefit over ozanimod and mirikizumab, with a low certainty of evidence. Ustekinumab demonstrated a likely important benefit over adalimumab, vedolizumab, ozanimod, etrasimod, and mirikizumab, with a moderate certainty of evidence. Risankizumab was associated with possibly important benefit over adalimumab, vedolizumab, and etrasimod with a low certainty of evidence. Guselkumab was associated with likely important benefit over adalimumab, with moderate certainty of evidence, and possibly important benefit over vedolizumab and etrasimod, with low certainty of evidence. Notably, there was no RCT for infliximab or golimumab in patients with prior exposure to biologics.

Benefits and Harms

The comparative safety of individual therapeutic agents is discussed above in Questions 1 and 2 and Safety of Pharmacological Therapies section. Overall, the panel established a CMD $\geq$5% over an active intervention to suggest at least a moderate desirable effect with the intervention relative to the comparator; for most comparisons, this risk difference was between 5% and 10%. Tofacitinib, upadacitinib, and ustekinumab demonstrated a large desirable effect exceeding 30% for relevant comparisons. The panel deemed that even though there may be small differences in the risk of adverse events with different medications, the overall magnitude of these undesirable effects with all medications was trivial. Importantly, although observational studies suggest lower risk of serious infection with vedolizumab compared with TNF antagonists, inadequate disease control is also associated with increased risk of infections.[23] In these instances, any potential safety benefit of more targeted advanced therapies must be balanced against differences in treatment efficacy. This is particularly relevant for biologic-exposed patients, where safer drugs (such as vedolizumab) were rated lower in efficacy than other, less-targeted mechanisms.

Rationale and Implementation Considerations

The panel recognized differences in treatment efficacy between drugs within the same therapeutic class. Consequently, recommendations were made specifically for drugs rather than by therapy class. As in the biologic-naïve population, rather than relying only on active comparisons showing important benefits over a comparator in an NMA, the guideline panel took a more pragmatic and holistic approach to create efficacy buckets that grouped together treatments with similar magnitude of treatment benefit. The efficacy buckets were informed by magnitude of absolute risk difference (over placebo) in the phase 3 RCTs, as well as comparative efficacy in the NMA. Treatments were generally considered high efficacy if they demonstrated a CMD of $\geq$5% in direct or network head-to-head comparisons (if no direct evidence available), a p-score in the NMA $\geq$0.49, and an absolute benefit of $>$10% over placebo in phase 3 RCTs among biologic-exposed patients. Based on these criteria, tofacitinib, upadacitinib, and ustekinumab were considered higher-efficacy medications; filgotinib, mirikizumab, risankizumab, and guselkumab were considered intermediate-efficacy medications; and adalimumab, vedolizumab, ozanimod, and etrasimod were considered lower-efficacy medications in biologic-exposed patients with moderate-to-severe UC.

The panel recognized several considerations for the interpretation of data in the biologic-exposed patients. Of the studies that examined efficacy in biologic-exposed patients, $>$90% of patients had exposure to TNF antagonists. Up to one-half of the patients in the later treatment trials were also exposed to vedolizumab or other therapeutic mechanisms. Given this, no recommendations could be made for patients who had specifically failed only prior non-TNF advanced therapies. Recommendations were also made broadly for biologic-exposed patients, but the number of prior biologic failures may impact treatment efficacy. In the phase 3 randomized trial of ozanimod against placebo, ozanimod was significantly more effective than placebo in achieving clinical remission, with rates of 23% (vs 7%) and 17% (vs 8%) in biologic-naïve and single biologic–exposed patients. In contrast, in patients who had been on 2 or more biologics previously, ozanimod was no more effective than placebo (4% vs 3%) in inducing clinical remission. However, the efficacy of ozanimod in achieving clinical remission at week 52 was similar for the biologic-naïve, 1 biologic, and 2 or more biologic-exposed patients, with all differences being greater than placebo.[74] Thus, in patients with multiple prior biologic failures, a longer duration of

treatment may be required for clinical benefit for treatments in the lower-efficacy category. As noted above, there are limited data on use of JAK inhibitors or S1P receptor modulators during pregnancy. Thus, other agents should be preferred over them when possible in women contemplating pregnancy. These decisions should be made on an individual case-by-case basis, recognizing the impact of uncontrolled disease on fertility and pregnancy outcomes and using personalized risk–benefit thresholds.

The differences in trial designs between the various agents precluded our ability to compare efficacy in maintaining clinical remission or endoscopic improvement to inform positioning. There are no RCTs that examined infliximab or golimumab in patients with prior biologic exposure. However, observational studies have demonstrated effectiveness of both these agents in this setting and it is reasonable to consider them in patients with prior TNF antagonist exposure, particularly those who discontinued prior therapy due to intolerance and/or immunogenicity.[75,76]

Question 4: In adult outpatients with moderate-to-severe UC, what is the efficacy of immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of clinical remission?

Recommendations:

- **In adult outpatients with moderate-to-severe UC, the AGA suggests AGAINST using thiopurine monotherapy for induction of remission. *[Conditional recommendation, very low certainty of evidence]***
- **In adult outpatients with moderate-to-severe UC in remission, the AGA *suggests* using thiopurine monotherapy, rather than no treatment, for maintenance of remission, typically induced by corticosteroids. *[Conditional recommendation, low certainty of evidence]***
- **In adult outpatients with moderate-to-severe UC, the AGA *suggests* AGAINST using methotrexate monotherapy, for induction or maintenance of remission. *[Conditional recommendation, low certainty of evidence]***

Summary and Certainty of Evidence

Since the last guideline published was in 2020, we identified 1 new RCT comparing mercaptopurine with placebo for achieving corticosteroid-free remission at 52 weeks.[77] In this trial, patients with active UC despite 5-aminosalicylates (5-ASAs) were randomized 1:1 to therapeutic drug monitoring-guided mercaptopurine vs placebo for 52 weeks; all patients received corticosteroids for the first 8 weeks. The primary end point of corticosteroid-free clinical remission was achieved by 14 of 29 patients treated with mercaptopurine compared with 3 of 30 patients treated with placebo. Including this trial, we identified 4 trials comparing thiopurines with placebo and 2 trials comparing thiopurines with 5-ASA for inducing corticosteroid-free remission. In 4 of 6 trials, patients were considered corticosteroid-dependent, unable to taper corticosteroids below 10–20 mg/d without relapsing. In contrast to more recent clinical trials, different disease activity indices were used in these studies, and the outcome of corticosteroid-free remission was assessed at variable intervals from 4 weeks to 52 weeks. In patients with active disease, patients were started simultaneously on thiopurines and corticosteroids, and it was unclear whether remission was induced by corticosteroids or thiopurines or the combination of both. Thiopurines were associated with a higher rate of achieving corticosteroid-free clinical remission compared with placebo or 5-ASA (RR, 1.41; 95% CI, 0.91–2.18) (Supplementary Figure 14). However, the overall quality of evidence was deemed very low due to serious risk of bias, imprecision, and indirectness (outcome definition and assessment) (Table 11). On limiting analysis to studies where outcome was assessed at 26 weeks or more, thiopurines were associated with a higher rate of corticosteroid-free clinical remission compared with placebo or 5-ASA (RR, 2.62; 95% CI, 0.99–6.96).

Since the last guideline published in 2020, we did not identify any new RCTs examining the efficacy of thiopurines in preventing relapse in patients with quiescent UC.[56] For maintenance of remission, we identified 4 trials comparing thiopurines with placebo and 3 trials comparing thiopurines with 5-ASA. 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 decreasing risk of disease relapse (RR, 0.61; 95% CI, 0.49–0.77) among patients with inactive UC (in remission) (Supplementary Figure 14). There was low certainty of evidence due to risk of bias and imprecision (Table 11).

Since the last guideline published in 2020, we did not identify any new RCTs examining the efficacy of methotrexate for induction or maintenance of remission in patients with UC.[56] Two trials compared methotrexate with placebo and 1 trial compared methotrexate with 5-ASA for induction of remission. In the METEOR trial, all patients were on 10–40 mg/d of corticosteroids with or without active disease. 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 with placebo (RR, 1.31; 95% CI, 0.89–1.94) (Supplementary Figure 15). The certainty 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 (Table 12). For maintenance of remission, 2 trials compared methotrexate with placebo and 1 compared methotrexate with 5-ASA. Similar to induction, there was no difference between methotrexate and placebo or 5-ASA for maintenance of remission (RR, 1.01; 95% CI, 0.79–1.29)

Table 11. GRADE Evidence Profile Comparing Thiopurines vs No Thiopurines for Achieving Steroid-Free Remission, and Preventing Relapse in Patients With Steroid-Dependent Moderate-to-Severe Ulcerative Colitis

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk without thiopurines	Risk with thiopurines				
Thiopurines compared with no thiopurines for moderate-to-severe UC						
Achieving clinical remission (CRITICAL)	57/127 (55.7%)	86/134 (68.6%)	1.41 (0.91–2.18)	184 more per 1000 (from 40 fewer to 530 more)	261 (6 RCTs)	⨁◯◯◯[c,d,e] VERY LOW
Relapse after achieving remission (CRITICAL)	90/146 (61.6%)	59/157 (37.6%)	0.61 (0.49–0.77)	240 fewer per 1000 (from 314 fewer to 142 more)	303 (7 RCTs)	⨁⨁◯◯[c,e] LOW

[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for risk of bias (inadequate blinding).
[d]Rated down for indirectness (not truly induction of remission, because majority of patients received corticosteroids for inducing remission; outcomes in 1/5 trials not standardized)
[e]Rated down for imprecision due to low event rate.

Table 12. GRADE Evidence Profile Comparing Methotrexate vs No Methotrexate for Achieving Steroid-Free Remission, and Preventing Relapse in Patients With Steroid-Dependent Moderate-to-Severe Ulcerative Colitis

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk without methotrexate	Risk with methotrexate				
Methotrexate compared with no methotrexate for moderate-to-severe UC						
Achieving clinical remission (CRITICAL)	30/96 (31.3%)	40/102 (39.2%)	1.31 (0.89–1.94)	97 more per 1000 (from 34 fewer to 294 more)	198 (3 RCTs)	⨁◯◯◯[c,d] VERY LOW
Relapse after achieving remission (CRITICAL)	39/60 (65.0%)	44/65 (67.7%)	1.01 (0.79–1.29)	7 more per 1000 (from 136 fewer to 189 more)	125 (3 RCTs)	⨁◯◯◯[c,d] VERY LOW

[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for indirectness (different modes of administering methotrexate, majority of patients received corticosteroids for inducing remission).
[d]Rated down for very serious imprecision with very wide CIs.

(Supplementary Figure 15). The certainty of evidence was rated as very low due to serious indirectness, and very serious imprecision (Table 12).

Benefits and Harms

Short- and long-term adverse effects of thiopurines and methotrexate are well-recognized, including risk of bone marrow suppression, hepatotoxicity (including liver fibrosis with long-term use of methotrexate), nonmelanoma skin cancer and lymphoma, especially with thiopurines.[78] Besides the direct risks associated with these therapies, risks associated with use of ineffective therapies and delay in initiation of more effective therapies also need to be considered when evaluating potential harms of intervention.

Rationale and Implementation Considerations

Thiopurines have a slow onset of action, so they have conventionally been used as maintenance agents rather than as induction agents. In the trials of thiopurine therapy in patients with active UC, outcomes were usually assessed 26 weeks or beyond (in 4 trials), in contrast to more recent trials and clinical practice of induction therapy, where response to induction therapy is generally assessed within 8–12 weeks. Real-world cohort studies have confirmed the effectiveness of thiopurines in maintaining steroid-free remission and reducing the risk of colectomy in patients with UC.[79] Thiopurines are inexpensive and convenient to take as oral medications and may be particularly useful for maintaining long-term remission in resource-limited settings. Methotrexate, particular SC dosing, may be effective for inducing and maintaining remission in patients with CD; the reason for its lack of efficacy in patients with UC is not well understood. Of note, in the contemporary era of advanced therapies, recruitment to trials of methotrexate was challenging, with METEOR recruiting 111 patients over 6 years (2007–2013) and MERIT-UC recruiting 84 patients over 5 years (2012–2016).

Question 5: In adult outpatients with moderate-to-severe UC, what is the efficacy of combination therapy with immunomodulator (thiopurines, methotrexate) and TNF antagonists in comparison to TNF antagonists alone for induction and maintenance of clinical remission?

Recommendations:

- **In adult outpatients with moderate-to-severe UC, the AGA *suggests* the use of infliximab in combination with an immunomodulator over infliximab or an immunomodulator alone. *[Conditional recommendation, moderate certainty of evidence]***
- **In adult outpatients with moderate-to-severe UC, the AGA *suggests* the use of adalimumab or golimumab in combination with an immunomodulator over adalimumab, golimumab or immunomodulator monotherapy. *[Conditional recommendation, low certainty of evidence]***

Summary and Certainty of Evidence

We did not identify any new RCT that provided direct evidence for combination immunomodulator-TNF antagonist therapy in moderate-to-severe UC since the last guideline.[56] The UC-SUCCESS trial provides direct evidence for this recommendation.[80] This RCT randomized patients with moderate-to-severe UC to receive infliximab alone (n = 77), azathioprine alone (n = 76), or a combination of both agents (n = 78). At week 16, the primary end point of corticosteroid-free clinical remission was achieved by 39.7% of patients receiving combination therapy compared with 22.1% of infliximab-treated patients and 23.7% of azathioprine-treated patients. A higher rate of mucosal healing was observed in the combination therapy group (62.8%) compared with infliximab (54.6%) or azathioprine (36.8%). This translated to an absolute difference in clinical remission rate of 170 per 1000 for combination therapy compared with infliximab alone (Table 13) and 159 per 1000 for combination therapy compared with immunomodulator alone (Table 14).

Benefits and Harms

In the UC-SUCCESS trial, there was no difference in the rate of serious infections between the combination therapy group compared with those receiving infliximab monotherapy (OR, 0.33; 95% CI, 0.01–7.86). In observational studies, there was a higher risk of lymphoma with combination therapy compared with TNF antagonist monotherapy. In a national study from France, the risk of lymphoma was higher in patients receiving combination therapy compared with TNF-antagonist monotherapy (HR, 2.53; 95% CI, 1.35–4.77) or thiopurine monotherapy (HR, 2.35; 95% CI, 1.31–4.22).[25] Thus, the increase in efficacy with combination therapy must be balanced against the risk of therapy-related adverse events. Patients, particularly with more moderate (rather than severe) disease, may reasonably elect to use TNF antagonist monotherapy over combination therapy balancing risks and benefits.

Rationale and Implementation Considerations

In addition to direct evidence from the UC-SUCCESS study, indirect evidence in support of combination therapy is also derived from moderate-to-severe CD. In the landmark SONIC trial of immunomodulator-naïve patients with CD, a combination of azathioprine and infliximab therapy was associated with higher rates of corticosteroid-free clinical remission at week 26 compared with those receiving infliximab or azathioprine alone.[80] Although the COMMIT trial did not demonstrate benefit of methotrexate added to infliximab in patients with CD, patients receiving combination therapy had a higher infliximab trough level and lower rates of anti-infliximab antibody positivity.[81] Thus, it is reasonable to infer, given their similar broad mechanisms of immunosuppression, that there is an additive benefit to use of methotrexate in combination with TNF antagonists. There are less direct data demonstrating the benefit of combination therapy with adalimumab or golimumab. In the DIAMOND trial, a combination of azathioprine and

Table 13. GRADE Evidence Profile Comparing Infliximab + Immunomodulators vs Infliximab Monotherapy for Achieving Steroid-Free Remission in Patients With Moderate-to-Severe Ulcerative Colitis

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with infliximab monotherapy	Risk with combination therapy				
Combination therapy with infliximab + immunomodulators compared with infliximab monotherapy for moderate- to-severe UC						
Achieving clinical remission (CRITICAL)	17/78 (21.8%)	31/80 (38.8%)	1.78 (1.08–2.94)	170 more per 1000 (from 17 more to 423 more)	158 (1 RCT)	⨁⨁⨁◯[c] MODERATE

NOTE. No trial of maintenance therapy comparing TNF-α antagonists + immunomodulators vs TNF-α antagonist monotherapy was identified.
[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).

Table 14. GRADE Evidence Profile Comparing Infliximab + Immunomodulators vs Immunomodulator Monotherapy for Achieving Steroid-Free Remission in Patients With Moderate-to-Severe Ulcerative Colitis

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with immunomodulator	Risk with combination therapy				
Combination therapy with infliximab + immunomodulators compared with immunomodulator monotherapy for moderate-to-severe UC						
Achieving clinical remission (CRITICAL)	18/79 (22.8%)	31/80 (38.8%)	1.70 (1.04–2.78)	159 more per 1000 (from 9 more to 406 more)	159 (1 RCT)	⨁⨁⨁◯[c] MODERATE

NOTE. No trial of maintenance therapy comparing TNF antagonists + immunomodulators vs immunomodulator monotherapy was identified.
[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).

adalimumab treatment was associated with higher rates of endoscopic response compared with adalimumab monotherapy.[82] Given similar rates of immunogenicity across the different TNF antagonists, we extrapolated the benefit of combination therapy to all agents within this class. It has been hypothesized that achieving adequate biologic trough levels may reduce the need for combination therapy in patients receiving TNF antagonist therapy.[83] This has not been examined prospectively. Similarly, there may be greater benefit to combination therapy in patients genetically predisposed to developing anti-drug antibodies to TNF antagonists.[84]

Question 6: In adult outpatients with moderate-to-severe UC, what is the efficacy of combination therapy with immunomodulator (thiopurines, methotrexate) and non-TNF antagonist biologic agents (vedolizumab, ustekinumab, mirikizumab, risankizumab, guselkumab) in comparison to non-TNF antagonist biologic (vedolizumab, ustekinumab, mirikizumab, risankizumab) monotherapy for induction and maintenance of clinical remission?

Recommendation:

- **In adult outpatients with moderate-to-severe UC, the AGA makes no recommendation in favor of, or against. the use of non-TNF antagonist biologics in combination with an immunomodulator over non-TNF antagonist biologic alone. *[No recommendation, knowledge gap]***

Summary and Certainty of Evidence

Since the last guideline in 2020, multiple observational studies and indirect evidence from 1 randomized trial provided evidence for this recommendation. In a multicenter study of patients with IBD initiating vedolizumab or ustekinumab, there was no difference in remission rates at 1 year between those on combination therapy and on monotherapy.[85] A meta-analysis that included 33 studies (6 RCT and 28 cohort studies) identified no difference in clinical outcomes in patients with combination therapy with vedolizumab (OR, 0.84; 95% CI, 0.68–1.05) or ustekinumab (OR, 1.1; 95% CI, 0.87–1.38).[86] In contrast to these data, in the VIEWS trial, which randomized patients with UC on combination vedolizumab and thiopurine treatment to continuation of dual therapy or withdrawal, cessation of thiopurine was associated with no difference in clinical relapses ($P = .12$), but a modestly higher fecal calprotectin ($P = .003$) and lower rates of histologic remission ($P = .03$).[87]

Benefits and Harms

There are limited data on the safety of combination immunomodulator and non-TNF antagonist biologic therapy. Subgroup analyses from RCTs, as well as data from observational studies, do not suggest an increase in risk of serious infections or malignancy with combination therapy for non-TNF antagonist biologic therapy. However, these studies have mostly lacked longer-term follow-up data.

Rationale and Implementation Considerations

Mechanistically, there are several reasons why combination therapy may be less necessary with non-TNF antagonist biologic therapies. First, both vedolizumab and anti-IL agents have lower immunogenicity than TNF antagonists.[88,89] In addition, for vedolizumab, receptor saturation is already noted at low trough saturations. However, immunomodulators may have an independent benefit, especially for preventing relapse. Adding immunomodulators to non-TNF antagonist biologics, particularly in patients who are naïve to immunomodulators, may possibly be beneficial. Besides efficacy, the guideline panel also reviewed that there is an increase in risk of infections and malignancy (lymphoma and nonmelanoma skin cancers) with thiopurine use. In view of the limited and conflicting data, the guideline panel identified this area as a knowledge gap to be informed by further studies.

Question 7: In patients in steroid-free remission on combination therapy of TNF-antagonist + immunomodulator, is (1) discontinuation of immunomodulator or (2) discontinuation of TNF antagonist, superior to continuation of combination therapy?

Recommendations:

- **In patients with UC who are in corticosteroid-free clinical remission for at least 6 months on combination therapy of TNF antagonists and an immunomodulator, the AGA makes no recommendation in favor of withdrawing immunomodulators or continuing combination therapy. *[No recommendation, knowledge gap]***
- **In patients with UC who are in corticosteroid-free clinical remission for at least 6 months on combination therapy of TNF antagonists and an immunomodulator, the AGA suggests AGAINST withdrawal of TNF antagonists. *[Conditional recommendation, very low certainty of evidence]***

Summary and Certainty of Evidence

Several RCTs and observational studies have examined the impact of withdrawal of thiopurine therapy in patients on combination immunomodulator and biologic therapy. A systematic review by Katibian et al[90] summarized the impact of withdrawal of immunomodulators in patients with IBD receiving combination therapy. A total of 8 RCTs comprising 733 patients were identified; three-quarters of the patients in the studies had CD. Most studies required patients to be in sustained corticosteroid-free remission for

at least 6 months before attempting drug withdrawal. Compared with patients continuing combination therapy, there was no increase in risk of relapse among patients stopping combination therapy (16.8% vs 14.8%; RR, 1.15; 95% CI, 0.75–1.76) (Supplementary Figure 16). The overall certainty of evidence was rated as very low, due to serious risk of bias, indirectness because most patients in these trials had CD, and very serious imprecision (Table 15). In contrast to immunomodulator cessation, cessation of TNF antagonists in patients on combination therapy is associated with a 2-fold increase in risk of relapse compared with continuing combination therapy (31.5% vs 11.2%; RR, 2.35; 95% CI, 1.38–4.01) (Supplementary Figure 17). The overall certainty of evidence was rated as very low, due to serious risk of bias, indirectness because most patients in these trials had CD, and serious imprecision due to low number of events (Table 15). In the STORI trial in CD, nearly 80% of patients ceasing TNF antagonist therapy experienced a disease relapse requiring re-initiation of the biologic within 7 years after treatment cessation.[91]

Benefits and Harms

As outlined in the section above, combination therapy with an immunomodulator and TNF antagonist is associated with an increase in risk of infections and lymphoma compared with monotherapy with either agent alone. Any benefit of combination therapy should be weighed against a potential increase in risk of treatment-related adverse outcomes.

Rationale and Implementation Considerations

The guideline panel used data from both CD and UC to inform this recommendation, as it was felt that the likely expected outcomes are similar across diseases and conclusions can be extrapolated. Most clinical trials of therapy discontinuation examined outcomes with <2 years of follow-up; the panel recognized that the clinical impact of treatment discontinuation may need to be viewed over a longer time horizon. In 3 trials, infliximab trough concentrations at the end of trial were lower and proportion of patients with antibodies to infliximab was higher in patients who underwent immunomodulator withdrawal vs those who continued combination therapy. Whether the lower trough level on withdrawal would result in increased rates of clinical relapse with longer follow-up is unknown. In contrast, in the DIAMOND2 trial, mean adalimumab trough concentration and anti-adalimumab antibody positivity rate were not different between patients who had immunomodulator withdrawal compared with those who continued combination therapy.[82] Recognizing the gaps in data and the need for longer follow-up, the panel made no recommendation in favor of or against withdrawal of immunomodulators in patients on a combination of TNF antagonist and immunomodulators. In patients with moderate (as opposed to severe) disease, on their first biologic, long-duration of remission, or at higher risk for treatment-related adverse effects of infection or malignancy (such as older adults), it may be reasonable to consider discontinuation of immunomodulator therapy after 12–18 months while continuing TNF antagonist use. It is important to measure TNF antagonist trough levels before immunomodulator withdrawal. Patients with higher trough levels are more likely to maintain clinical remission after immunomodulator withdrawal than patients with borderline or low TNF antagonist levels.[92] It is also important to closely monitor for disease relapse using clinical symptoms, biomarkers, and endoscopic assessment (12–24 months after therapy withdrawal).

Question 8: In adult outpatients with moderate-to-severe UC, is upfront use of advanced therapies and/or immunomodulator therapy superior to step-up therapy (acceleration to advanced therapies and/or immunomodulator therapy only after failure of 5-ASA) for inducing and maintaining remission?

Recommendation:

- **In adult outpatients with moderate-to-severe UC, the AGA suggests early use of advanced therapies with or without immunomodulator therapy, rather than gradual step up after failure of 5-ASAs. *[Conditional recommendation, very low certainty of 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 immunosuppressive therapies, may reasonably choose gradual step therapy with 5-ASA therapy.

Summary and Certainty of Evidence

Since the last guideline published in 2020, we did not identify any new RCTs comparing a strategy of upfront use of advanced therapies and/or immunomodulator therapy vs step-up therapy in patients with moderate-to-severe UC. We also did not identify any trials comparing the efficacy of advanced therapies vs 5-ASA for patients with moderate-to-severe UC. There are 3 trials that compared thiopurines in this population.[93–95] Based on a meta-analysis of these studies, patients treated with thiopurines achieved higher rates of corticosteroid-free clinical remission compared with patients treated with 5-ASAs. In the UC-SUCCESS trial, although infliximab was not more efficacious than immunomodulator monotherapy for achieving clinical remission, it was more effective for achieving endoscopic improvement.[80] By extension, advanced therapies would be more effective than 5-ASA for induction of remission in patients with moderate-to-severe UC. It is important to note that 5-ASAs are not indicated for the treatment of moderate-to-severe UC and have been approved for mild-to-moderate UC. Based on this indirect evidence, it follows that delaying treatment of moderate-to-severe UC with advanced therapies or immunomodulators to treat with 5-ASA drugs may be detrimental, both because 5-ASAs may not work as primary therapy and because use of these drugs will introduce a treatment delay impairing quality of life and increasing risk of

Table 15. GRADE Evidence Profile Comparing Withdrawal of Immunomodulators or Withdrawal of Biologics Compared With Continuing Combination Therapy for Risk of Relapse in Patients With Moderate-to-Severe Ulcerative Colitis in Steroid-Free Remission on Combination Therapy

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with continuing combination therapy	Risk with IMM withdrawal				
Withdrawal of IMMs (while continuing biologic therapy) compared with continuing combination therapy in adult outpatients with moderate-to-severe UC in steroid-free remission						
Risk of relapse at 12 mo (CRITICAL)	30/202 (14.9%)	34/202 (16.8%)	1.15 (0.75–1.76)	22 more per 1000 (from 37 fewer to 113 more)	404 (5 RCTs)	⨁◯◯◯[c,d,e] VERY LOW

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with continuing combination therapy	Risk with biologic withdrawal				
Withdrawal of biologics (while continuing IMM monotherapy) compared with continuing combination therapy in adult outpatients with moderate-to-severe UC in steroid-free remission						
Risk of relapse at 12 mo (CRITICAL)	22/196 (11.2%)	63/200 (31.5%)	2.35 (1.38–4.01)	152 more per 1000 (from 43 more to 338 more)	396 (4 RCTs)	⨁◯◯◯[c,d,f] VERY LOW

IMM, immunomodulator.
[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for serious risk of bias (open-level trials with subjective end points).
[d]Rated down for indirectness because most patients in these trials had CD.
[e]Rated down for very serious imprecision due to very wide CIs crossing unity.
[f]Rated down for imprecision because optimal information size not met (<200 events).

complications. Based on serious indirectness of the evidence with unclear estimates of magnitude of benefit, we rated the certainty of evidence as very low.

Benefits and Harms

Risks associated with advanced therapies or immunomodulator therapy have been outlined earlier and may be greater than those associated with 5-ASA therapy. However, these risks should be interpreted in the context of risks of UC-related complications, including colectomy, hospitalization, and persistent disease activity resulting in inferior quality of life, if step-up therapy is used.

Rationale and Implementation Considerations

Inadequately controlled UC is associated with an increased risk of colectomy, hospitalization, corticosteroid use, and long-term risk of colorectal cancer. UC is a progressive disease that can result in bowel damage.[96] Hence, risk-congruent therapy is warranted to minimize risk of short- and long-term complications. Unfortunately, prediction models to identify patients at high risk of complications or disease severity indices have not been well-validated. Ideally, evidence regarding top-down vs step-up therapy would be best informed by a pragmatic RCT comparing outcomes in patients assigned to risk-congruent therapy vs conventional management. In the absence of these data, based on indirect evidence, it is likely that step-up therapy using 5-ASAs first, particularly in patients on the more severe side of the disease spectrum with more severe disease, may be detrimental.

Question 9: In adult outpatients with moderate-to-severe ulcerative colitis failing 5-ASAs, who are now to be treated with immunomodulators or advanced therapies, is continuing 5-ASAs superior to stopping the 5-ASAs for inducing and maintaining remission?

Recommendation:

- **In adult outpatients with moderate-to-severe UC, who have failed 5-ASAs, and have escalated to therapy with immunomodulators or advanced therapies, the AGA suggests stopping 5-ASAs.** ***[Conditional recommendation, low certainty of evidence]***

Implementation Considerations

1. A subset of patients who have significant but not complete response with advanced therapies or immunomodulators may benefit from ongoing 5-ASAs to achieve remission. This may be particularly important for patients with residual proctitis who may benefit from adding rectal 5-ASA.
2. The independent benefit of long-term 5-ASAs in preventing colorectal cancer in patients with IBD has not been robustly demonstrated.

Summary and Certainty of Evidence

Since the last guideline published in 2020, we did not identify any new RCTs directly addressing withdrawal of 5-ASA therapy in patients with moderate-to-severe UC being treated with immunomodulators or advanced therapies. Mantzaris et al[97] randomized patients with moderate-to-severe UC, in corticosteroid-free clinical, endoscopic, and histologic remission on azathioprine and olsalazine, to either continuing azathioprine and olsalazine (0.5 mg 3 times daily) or azathioprine alone. Over the course of 2 years, there were no observed differences in risk of relapse severe enough to merit corticosteroid use (RR, 1.02; 95% CI, 0.77–1.34).

To examine whether concomitant 5-ASA impacts treatment response with advanced therapies, we updated our prior approach, conducting a pooled analysis of individual patient-level data of RCTs of advanced therapies in patients with moderate-to-severe UC. By design, all patients in these trials had moderate-to-severely active disease, despite prior or concomitant 5-ASA exposure. The patients in these trials had to maintain their baseline medications, so they could not stop or start 5-ASA during the trial. Across 10 RCTs with 6044 patients, 4134 patients received concomitant 5-ASA at baseline and maintained stable dose throughout the induction period. Compared with patients not receiving 5-ASA, patients receiving concomitant 5-ASA were slightly older, more likely to be non-White, more likely to have moderate endoscopic activity, have shorter disease duration, slightly lower C-reactive protein, and more likely to be biologic-naïve. Subsequently, we compared the RR of active intervention vs placebo in patients who were vs not on concomitant 5-ASA during the trial, using extended modified Poisson regression model with studies being considered as clusters. The model contained main effects of drug, exposure, or nonexposure to concomitant 5-ASA, their product term, and confounders, including prior biologic exposure, endoscopic severity at baseline, race, disease extent, baseline C-reactive protein, fecal calprotectin, hemoglobin, albumin, concomitant corticosteroids, and smoking status. After adjusting for confounding variables, the ratio of RR for inducing clinical remission in those on concomitant 5-ASA vs no concomitant 5-ASA was 1.04 (95% CI, 0.78–1.39), suggesting no treatment effect modification. The overall certainty of evidence supporting lack of benefit of continuing vs stopping 5-ASAs in patients with moderate-to-severe UC being treated with advanced therapies, after prior exposure to and failure of 5-ASA, was rated as low. Evidence was rated down due to imprecision and indirectness (Table 16).

Benefits and Harms

5-ASAs are generally safe medications, with very low rates of idiosyncratic serious or life-threatening complications.[98] There are rare reports of allergic interstitial nephritis, pancreatitis, pericarditis, myocarditis, and pneumonitis. Continuing 5-ASA may add pill burden and contribute to high cost of care.

Table 16. GRADE Evidence Profile Comparing Continuing vs Stopping 5-Aminosalicylates in Patients With Moderate-to-Severe Ulcerative Colitis Being Treated With Advanced Therapies Who Have Failed 5-Aminosalicylates

Outcomes	Study event rates [n/N (%)]		Relative effect, RR (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk without concomitant 5-ASA	Risk with concomitant 5-ASA				
Continuing 5-ASA compared with stopping 5-ASA in patients with moderate-to-severe UC being treated with advanced therapies who have failed 5-ASA						
Induction of clinical remission (CRITICAL)	413/1910 (21.6%)	1149/4134 (27.8%)	1.04 (0.78–1.39)	9 more per 1000 (from 48 fewer to 84 more)	6044 (10 RCTs)	⨁⨁◯◯[c,d] LOW

[a]Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for indirectness (not trials of continuing vs stopping 5-ASA, but rather concomitant 5-ASA vs no concomitant 5-ASA at trial entry)
[d]Rated down for serious imprecision with wide CIs.

Rationale and Implementation Considerations

We relied on a combination of direct evidence in patients on thiopurines, and indirect evidence in patients treated with advanced therapies, to determine the efficacy of continuing vs stopping 5-ASA in patients who escalate therapy after failing 5-ASA. Due to the short duration of follow-up in clinical trials, we were not able to study the impact of concomitant 5-ASAs on longer-term risk of disease-related complications, including surgery and development of colorectal neoplasia. Large observational studies have suggested no difference in the risk of adverse clinical outcomes between patients who continue vs stop 5-ASA after starting advanced therapies or immunomodulators.[99–101] The guideline panel acknowledged that there may be a subset of patients with UC who have improved, but not achieved remission, with advanced therapies and who continue to experience mild to moderate symptoms due to residual proctitis—these patients may benefit from continuing or adding rectal 5-ASA. The guideline panel also acknowledged that one proposed benefit of long-term 5-ASA use is potential chemoprevention effect against colorectal cancer, but this remains unproven. Although large observational studies and meta-analyses have variably suggested that patients with UC treated with 5-ASA have lower risk of developing colorectal cancer, recent evidence suggests that chronically active disease is a strong risk factor for developing neoplasia, and sustained remission is a protective factor against colorectal cancer regardless of the therapy used that achieves this outcome.[102]

Knowledge Gaps

The guideline panel identified several knowledge gaps that need to be addressed in future studies.

- There was a paucity of head-to-head comparison trials in moderate-to-severe UC. As more treatment options become available, it is important, in addition to comparison against placebo, that these trials include a range of active comparators to accurately inform positioning of different treatments and therapeutic mechanisms.
- With the availability of multiple therapeutic options, it is likely that many treatment-exposed patients may have received treatments other than TNF antagonists. There is a gap in the literature regarding the efficacy of different therapies in the setting of failure or intolerance to non–TNF-antagonist advanced therapy. This may be particularly relevant to drugs that may have a greater overlap in their therapeutic mechanisms (eg, anti-trafficking agents). In addition, it is important that efficacy based on prior exposure from RCTs should report out separate strata of prior exposure (both single and multiple biologics, as well as type of prior advanced therapy). Observational studies are also important to address this gap in a real-world setting.
- The panel recognized the importance of treatment outcomes beyond clinical remission in the management of moderate-to-severe UC. However, there was

significant heterogeneity in the time point and end point ascertained between the different clinical trials. As end points begin to incorporate endoscopic and histologic healing, consistency in reporting outcomes across trials will be important to inform relative positioning. However, it will remain a challenge to compare older trials that may not have assessed this outcome or differed in their study design.

- The panel recognized that future selection of therapy may be based on predictive clinical and biomarker-based models. At this time, there is a paucity of data on how such models can inform treatment selection in the real-world setting. There is clearly a need for identifying biomarkers predictive of response to individual therapies, to facilitate optimal choice of therapies. Ongoing research efforts using multi-omic platforms using serum, stool, and tissue specimens have potential to inform biomarkers predictive of response to specific therapies. Once these are available, clinical trials or prospective comparative effectiveness studies using integrated clinical-, pharmacokinetic- and biomarker-based treatment positioning strategies vs usual care could provide guidance on appropriate management strategies.
- Shared decision making is an important process in selecting the management strategy for management of moderate-to-severe UC. Different therapies have distinctive risk–benefit profiles with varying balance of treatment efficacy vs risk of treatment-related side effects. In addition, different patients based on age, clinical phenotype, and disease status, have different risks of disease- vs treatment-related complications. Accurate and validated risk prediction models to accurately identify patients at high risk of disease- vs treatment-related complications, and how different treatments modify these risks, is vital to know and communicate effectively to patients. Pairing this information with patients' values and preferences would facilitate shared decision making, as the treatment landscape rapidly evolves in this field.
- The panel also recognized that there may be several novel therapeutic strategies that may be applied in the coming years, including combination advanced therapy or episodic use of nonimmunogenic advanced therapies, such as small molecules. Further primary data are required to accurately inform the positioning of such strategies.

Living Guidelines Updating Plan

Recognizing the rapid evolution of drug development and transforming treatment strategies, the AGA will update relevant recommendations from these guidelines by periodic review of evidence every 6 months. The evidence reviewed will include availability of phase 3 or phase 4 efficacy data for new treatments, treatment strategies, or existing treatments, as well as significant new safety concerns informing treatment positioning.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.10.001.

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