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AGA LIVING GUIDELINES: PHARMACOLOGICAL MANAGEMENT OF MODERATE-TO-SEVERE ULCERATIVE COLITIS

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A full list of conflicts active at the time of guideline development can be accessed at AGA's National Office in Bethesda, MD.

Abstract

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 multi-disciplinary 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 (infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, guselkumab) or an intermediate efficacy medication (golimumab, ustekinumab, tofacitinib, filgotinib, mirikizumab), rather than a lower efficacy medication (adalimumab). In patients who have previously been exposed to one or more advanced therapies, particularly tumor necrosis factor- α (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). 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-ASA. The panel also proposed key implementation considerations for optimal use of these medications, 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

INTRODUCTION

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 a third requiring hospitalization for management of their disease³. 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 two decades have witnessed a significant expansion in the therapeutic armamentarium for moderate-to-severe UC. In the nearly two decades since the approval of the first biologic therapy (infliximab) for UC in 2005, there have been eleven additional advanced therapies approved for treatment of moderate-to-severe UC in the United States. Importantly, seven of these medications including two novel therapeutic classes, were approved since the publication of the most recent AGA guideline for treatment of moderate-to-severe UC in 2020⁴. Two approved treatments addressed in prior guidelines (infliximab, 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 PRO2 patient-reported disease activity scale, a stool frequency (SF) score ≥ 2 and rectal bleeding (RB) score ≥ 2 suggests moderate-to-severe UC disease activity⁵. 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 is 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 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 ulcerative colitis.

The AGA has developed these guidelines as Living Guidelines given rapid evolution in the field⁶. A living guideline is defined as one which 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 (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 Medicine⁷. 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 UC⁴, 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 (MCS), an index with scores ranging from 0–12, based on measures of stool frequency, rectal bleeding, physician global assessment, along with endoscopic disease activity⁹. Scores of 6–12 correspond to moderate-to-severe disease activity, whereas clinical remission is most consistently defined as MCS<3, with no individual subscore >1. In earlier trials, alternative cut-offs of MCS-defined remission and alternative disease activity indices such as Powell-Tuck index, Baron endoscopy score, and others were used¹⁰. In these trials, if clinical and endoscopic outcomes were reported separately, then data on clinical remission was used for analysis. While 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 randomized controlled trials (RCT) 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 which 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 two active therapies, the guideline panel set a CMD threshold of 5%, based on consensus i.e. 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 PICO) were included. If RCT-level evidence was not available for specific PICO, 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% participants had UC. Since safety outcomes are not well informed by RCTs, representative large cohort studies and high-quality systematic reviews/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 two 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% confidence intervals (CI), were calculated using the Mantel-Haenszel fixed-effects model (in the absence of conceptual heterogeneity and if <5 studies) or the DerSimonian-Liard random-effects model¹¹. First, pooled relative risk estimates were derived from pooled clinical trials for each individual therapy; these risk estimates are influenced both by efficacy of individual therapies but also the placebo rates in each of these trials. These relative risk 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 ulcerative colitis and Crohn's disease and recommendations from GRADE. Statistical heterogeneity was assessed using the I^2 statistic¹². Small study effects were examined using funnel plot symmetry and Egger's regression test, though it is important to recognize that these tests are unreliable when the number of studies is <10¹³. Direct comparisons were performed using Comprehensive Meta-Analysis, v2.0. Due to a paucity of head-to-head trials of active agents, to inform comparative efficacy of different pharmacologic 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 framework¹⁴. Briefly, using this approach, evidence from RCTs starts at high quality, and evidence from observational studies starts at low quality evidence (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

to 50 per 1000 patients treated. In utilizing 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 two interventions or if the evidence from direct comparisons was very low or low certainty evidence, then effect estimates from the NMA were used. O

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 equity¹⁵. 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 label 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. Figures 1 and 2 represent the clinical decision support tool for implementing these recommendations.

Safety of Pharmacological Therapies for Moderate-to-Severe UC

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 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 between different advanced therapies for treatment of IBD, Solitano and colleagues 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 heterogeneity¹⁶. 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.* 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 antagonists¹⁷. In contrast, in the large ORAL surveillance trial in older adults (≥ 50 years) with rheumatoid arthritis and at least one cardiovascular risk factor, tofacitinib was associated with a higher risk of serious and opportunistic infections compared with TNF antagonists¹⁸. There are limited real-world data on 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 (e.g., high disease activity, inadequate disease control, and need for corticosteroids and opioids), and individual patient-related (e.g., 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 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 monotherapy²⁵. This risk was comparable to the risk observed in patients treated with thiopurine monotherapy. Patients exposed to combination therapy had six-fold increased risk of lymphoma, as compared to unexposed patients, and 2.3–2.5 times higher risk as compared to patients exposed to monotherapy with either agent. The 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 while 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.

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

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 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* or mirikizumab over no treatment. [*Conditional recommendation, moderate certainty of evidence*]

Implementation considerations:

1. 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 EMA 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, history of cardiovascular disease (such as heart attack or stroke), and patients with 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 was 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}), three trials of anti-integrins (3 vedolizumab^{37–39}), one trial of ustekinumab⁴⁰, five trials anti-IL23 antibodies (2 mirikizumab^{41, 42}, 1 risankizumab⁴³, 2 guselkumab^{44–46}), five trials of S1P receptor modulators (2 ozanimod^{47, 48}, 3 etrasimod^{49, 50}), and eight trials of JAK inhibitors (3 upadacitinib^{51, 52}, 3 tofacitinib^{53, 54}, 2 filgotinib⁵⁵). 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 synthesis⁵⁶. 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 was available in the placebo controlled RCT comparing adalimumab and etrolizumab³⁰. 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 prior to 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 (infliximab, adalimumab) or alternate modes of delivery such as subcutaneous injections (infliximab, vedolizumab) were also included when applicable.

Data on the efficacy of each agent vs. placebo for induction and maintenance of clinical remission is shown in eFigures 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 an 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, since the magnitude of benefit was below the pre-specified 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 which could negatively impact quality of life, functional status and leads 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-to-decision judgements 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 relative risk 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 extra-intestinal manifestations or other disease-complications that may influence therapy, and patient preference for route of administration.

Three biosimilars for infliximab, ten for adalimumab, and one 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 relapse⁵⁷. In observational studies, most patients tolerated a switch to a biosimilar without an increase in loss of response or adverse events^{58, 59}. Thus, 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 drug⁶⁰.

Subcutaneous 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) 5mg/kg intravenously at weeks 0, 2, and 6⁶¹. Responders were randomized to receive either CT-P13 120mg subcutaneous (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 to placebo (20.8%). The VISIBLE 1 trial examined the efficacy of SC vedolizumab following 2 intravenous (IV) induction doses to standard IV maintenance therapy with vedolizumab or placebo⁶². 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 intravenous to subcutaneous formulations⁶³. The guideline panel felt that subcutaneous formulations of infliximab and vedolizumab are acceptable alternatives to intravenous 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 the 10mg twice daily (BID) dose of tofacitinib at week 8 in the OCTAVE trial, 52% achieved clinical response at week 16 following extended induction with 10mg BID dosing for an additional 8 weeks⁶⁴. Of these, 56.1% maintained clinical remission at 36 months. Nearly half (48%) of patients who failed to respond to the initial 8-week induction regimen with upadacitinib 45mg/day responded to an additional 8 weeks of induction therapy⁶⁵. Over half of these patients maintained clinical response at 1 year. Similarly, an additional three IV induction doses of

mirikizumab showed benefit in patients with incomplete response to the first three weeks induction dosing⁶⁶.

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 5mg BID maintenance dose, approximately 29% of patients who were de-escalated required an increase in dose back to 10mg BID with clinical response re-capturable in only 63% of patients⁶⁷. Similarly in the OCTAVE trials, 25% patients who were de-escalated were not able to remain in remission on the lower maintenance dose⁶⁸. Thus, a subset of patients may require being maintained at a higher dose. Since some of the risk of adverse effects associated with tofacitinib, particularly shingles and VTE 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.

Q2. In adult outpatients with moderate-to-severe UC who are *NAÏVE TO ADVANCED THERAPIES*, what is comparative efficacy of different advanced therapies?

Recommendations:

- 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*, risankizumab, guselkumab) OR an INTERMEDIATE efficacy medication (golimumab, ustekinumab, tofacitinib*, filgotinib*, mirikizumab), rather than a LOWER efficacy medication (adalimumab). [*Conditional recommendation, low certainty of evidence*]

Implementation considerations:

1. Individual patient factors (e.g., age, comorbidities, frailty, pregnancy, adherence) and preferences (e.g., route of administration, ease of access) should be incorporated 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 EMA 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, history of cardiovascular disease (such as heart attack or stroke), and patients with 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 (smoking, prior cardiovascular disease).
3. Vedolizumab and anti-interleukin 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 is 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 two 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 trial³⁸) 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 was difficult to compare the efficacy of treatments for maintenance of clinical remission through a NMA approach because of heterogeneity in the trial design. The only head-to-head trial was the VARSITY trial where 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 to adalimumab (22.5%). Corticosteroid-free remission rates, however, were higher with adalimumab (21.8%) compared to 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 Harm

No significant differences in the risk of infections and serious adverse events between different agents in previous network meta-analyses of clinical trials¹⁶. 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 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 non-melanoma skin cancers. Specific safety considerations regarding pregnancy and lactation are discussed in the implementation consideration 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 5–15%. 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 while 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 endpoint, 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 EMA recommends cautious use of JAK inhibitors as a first line agent in patients at risk for adverse cardiovascular outcomes including age ≥ 65 years, current or previous long-term smokers, history of cardiovascular disease (such as heart attack or stroke), and patients with a history of cancer. Restriction for use of JAK inhibitors first line is largely informed by data from the ORAL Surveillance study¹⁸. This study compared the safety of tofacitinib (5mg or 10mg BID) 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 smoking cigarette smoker [current or past], hypertension, high-density lipoprotein cholesterol level of <40 mg per deciliter, diabetes mellitus, family history of premature coronary heart disease, extraarticular 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 10mg BID dose, had a higher risk of major adverse cardiovascular events (MACE) 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 while tofacitinib and filgotinib are considered moderate-efficacy medications. In patients at high risk of MACE, 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}. While there is limited data on newer anti-IL23 inhibitors (mirikizumab, risankizumab, 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 IBD⁷³. 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 endpoints including achieving corticosteroid-free remission, maintenance of clinical remission, 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 endpoints. Where data were available, relative efficacy for maintenance endpoints was broadly consistent with induction data. Similarly, data on achievement of endoscopic improvement were also consistent with clinical remission endpoints. There was lack of systematic reporting of other endpoints particularly for older clinical trials that precluded using such data to inform relative positioning.

Q3. In adult outpatients with moderate-to-severe UC who have been EXPOSED TO ADVANCED THERAPIES, what is the comparative efficacy of different advanced therapies?

Recommendations:

- In adult outpatients with moderate-to-severe UC who have previously been exposed to one 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 (e.g., age, comorbidities, frailty, pregnancy, adherence) and preferences (e.g., route of administration, ease of access) should be incorporated within a shared decision framework in selection of advanced therapies.
2. Vedolizumab and anti-interleukin 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 is 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 (smoking, 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 UC³⁸. This trial noted no difference between the two 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. Amongst 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 clinically meaningful difference (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 5–10%. Tofacitinib, upadacitinib and ustekinumab demonstrated 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, while observational studies suggest lower risk of serious infection with vedolizumab compared with TNF antagonists, inadequate disease control is also associated with increased risk of infections²³. 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 $\geq 5\%$ or greater in direct or network head-to-head comparisons (if no direct evidence available), a p-score in the NMA of 0.49 or higher,

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 while 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% patients had exposure to TNF antagonists. Up to half 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 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 biologic exposed patients, with all differences being greater than placebo⁷⁴. 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 where 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 in 2020, we identified one new RCT comparing mercaptopurine to placebo for achieving corticosteroid-free remission at 52 weeks⁷⁷. In this trial, patients with active UC despite 5-ASA 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 endpoint of corticosteroid-free clinical remission was achieved by 14/29 patients treated with mercaptopurine compared to 3/30 patients treated with placebo. Including this trial, we identified four trials comparing thiopurines to placebo and two trials comparing thiopurines to 5-ASA for inducing corticosteroid free remission. In four out of six trials, patients were considered corticosteroid-dependent, unable to taper corticosteroids below 10–20mg/day 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 to placebo or 5-ASA (RR, 1.41; 95% CI, 0.91–2.18) (eFigure 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 26 weeks or greater, thiopurines were associated with a higher rate of corticosteroid-free clinical remission compared to 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 UC⁵⁶. For maintenance of remission, we identified four trials comparing thiopurines to placebo and three trials comparing thiopurines to 5-ASA. Maintenance of remission was defined as prevention of relapse following 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 6–18 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) (eFigure 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 UC⁵⁶. Two trials compared methotrexate to placebo and one trial compared methotrexate to 5-ASA for induction of remission. In the METEOR trial, all patients were on 10–40mg/day of corticosteroids with or without active disease. The primary outcome was corticosteroid-free remission between weeks 12–30. On meta-analysis, there was no significant difference in rates of inducing remission with methotrexate compared to placebo (RR, 1.31; 95% CI, 0.89–1.94) (eFigure 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, two trials compared methotrexate to placebo and one compared methotrexate to 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) (eFigure 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 side effects of thiopurines and methotrexate are well-recognized including risk of bone marrow suppression, hepatotoxicity (including liver fibrosis with long-term use of methotrexate), non-melanoma skin cancer and lymphoma, especially with thiopurines⁷⁸. 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 UC⁷⁹. 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 subcutaneous 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 (2007–13) and MERIT-UC recruiting 84 patients over 5 years (2012–16).

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 guideline⁵⁶. The UC-SUCCESS trial provides direct evidence for this recommendation⁸⁰. 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 endpoint of corticosteroid-free clinical remission was achieved by 39.7% of patients receiving combination therapy compared to 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 to 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 to infliximab alone (Table 13) and 159 per 1000 for combination therapy compared to 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 to 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 when compared to TNF antagonist monotherapy. In a national study from France, the risk of lymphoma was higher in patients receiving combination therapy compared to 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 Consideration

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 to those receiving infliximab or azathioprine alone⁸⁰. While 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 positivity⁸¹. 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 adalimumab treatment was associated with higher rates of endoscopic response compared with adalimumab monotherapy⁸². 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 therapy⁸³. 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 antagonists⁸⁴.

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 one randomized trial provided evidence for this recommendation. In a multi-center study of patients with IBD initiating vedolizumab or ustekinumab, there was no difference in remission rates at one year between those on combination therapy vs. monotherapy⁸⁵. 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 this data, in the VIEWS trial that 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 ($p=0.12$) but a modestly higher fecal calprotectin ($p=0.003$) and lower rates of histologic remission ($p=0.03$)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-interleukin 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 non-melanoma 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 (a) discontinuation of immunomodulator or (b) 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.* summarized the impact of withdrawal of immunomodulators in patients with IBD receiving combination therapy⁹⁰. 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 prior to attempting drug withdrawal. Compared to 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) (eFigure 16). The overall certainty of evidence was rated as very low, due to serious risk of bias, indirectness since most patients in these trials had Crohn's disease and very serious imprecision (Table 15). In contrast to immunomodulator cessation, cessation of TNF antagonists in patients on combination therapy is associated with a two-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) (eFigure 17). The overall certainty of evidence was rated as very low, due to serious risk of bias, indirectness since most patients in these trials had Crohn's disease 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 cessation⁹¹.

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 when compared to 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 less than two 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 three 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 was not different between patients who had immunomodulator withdrawal compared with those who continued combination therapy⁸². 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 IMM therapy after 12–18 months while continuing TNF antagonist use. It is important to measure TNF antagonist trough levels prior to immunomodulator withdrawal. Patients with higher trough levels are more likely to maintain clinical remission following immunomodulator withdrawal than patients with borderline or low TNF antagonist levels⁹². 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-aminosalicylates) 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-aminosalicylates. [*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 three 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 to patients treated with 5-ASAs. In the UC-SUCCESS trial, while infliximab was not more efficacious than immunomodulator monotherapy for achieving clinical remission, it was more effective for achieving endoscopic improvement⁸⁰. 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 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 damage⁹⁶. 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-aminosalicylates, 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.* 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 (0.5mg thrice daily) or azathioprine alone⁹⁷. Over the course of two 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 ten RCTs with 6,044 patients, 4,134 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 relative risk 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 non-exposure to concomitant 5-ASA, their product term, and confounders including prior biologic exposure, endoscopic severity at baseline, race, disease extent, baseline CRP, 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 complications⁹⁸. 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.

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. While large observational studies and meta-analyses have variably suggested that UC patients 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 therapy used that achieves this outcome¹⁰².

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 (for example, anti-trafficking agents). Additionally, 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 endpoint ascertained between the different clinical trials. As endpoints 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 by 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 non-immunogenic 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 six 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

Refer to Web version on PubMed Central for supplementary material.

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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

Adult outpatients with moderate to severely active ulcerative colitis	
Moderate to severely active UC defined as: • Moderate to severe symptoms with Mayo endoscopy sub-score 2 or 3 • Mild symptoms, with high burden of inflammation or poor prognostic features • Patients with corticosteroid-dependence, or refractory to oral corticosteroids	
Immunomodulator monotherapy (thiopurines, methotrexate)	
SUGGEST AGAINST using thiopurine monotherapy for inducing remission in patients with active disease <i>(Conditional recommendation, very low certainty of evidence)</i> SUGGEST using thiopurine monotherapy, rather than no treatment, for maintaining remission typically induced with corticosteroids <i>(Conditional recommendation, low certainty of evidence)</i> SUGGEST AGAINST using methotrexate monotherapy for inducing or maintaining remission <i>(Conditional recommendation, low certainty of evidence)</i>	
Combination therapy of advanced therapies with immunomodulators	
SUGGEST combining TNF antagonists with immunomodulators, rather than TNF antagonist monotherapy or immunomodulator monotherapy <i>(Conditional recommendation, low to moderate certainty of evidence)</i> NO RECOMMENDATION in favor of, or against, using non-TNF antagonist biologic in combination with immunomodulators over non-TNF antagonist monotherapy <i>(No recommendation, knowledge gap)</i>	
De-escalation of therapy	
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 <i>(Conditional recommendation, low certainty of evidence)</i> In patients with moderate-to-severe 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 <i>(Conditional recommendation, very low certainty of evidence)</i> NO RECOMMENDATION in favor of, or against, withdrawing immunomodulators or continuing combination therapy <i>(No recommendation, knowledge gap)</i>	

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

Table 1.

Focused questions and corresponding PICO's being addressed in the guidelines. 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

S#	Focused 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), SIP receptor modulators (ozanimod, etrasimod) and IL-23 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) • SIP receptor modulators (ozanimod, etrasimod) • IL-23 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
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 subcutaneous)	Placebo (or 5-aminosalicylates [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	Adult outpatients with moderate-to-severe UC	Combination therapy with a TNF antagonist and an	• TNF antagonist monotherapy	• Induction of clinical remission

S#	Focused Question	PICO Question			Critical Outcomes
		Patients	Intervention	Comparator	
	an immunomodulator (thiopurines or methotrexate) superior to TNF monotherapy or immunomodulator monotherapy for induction and maintenance of remission?		immunomodulator (thiopurines or methotrexate)	• Immunomodulator monotherapy (thiopurines or methotrexate)	• 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 (a) an immunomodulator or (b) 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 after failure of 5-ASA • 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
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

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.

Table 3. Executive summary of recommendations for the management of adult outpatients with moderate to severe ulcerative colitis

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*, upadacitinib*, ustekinumab, ozanimod, etrasimod, risankizumab and guselkumab over no treatment.<i>[(Strong recommendation, moderate to high certainty of evidence)]</i> 2. In adult outpatients with moderate-to-severe UC, the AGA suggests the use of adalimumab, filgotinib* or mirikizumab over no treatment.<i>[(Conditional recommendation, moderate certainty of evidence)]</i> 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 EMA 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, history of cardiovascular disease (such as heart attack or stroke), and patients with 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 • Subcutaneous formulations of infliximab and vedolizumab have shown comparable efficacy to the respective intravenous maintenance doses • 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	
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*, risankizumab, guselkumab) OR an INTERMEDIATE efficacy medication (golimumab, ustekinumab, tofacitinib*, filgotinib*, mirikizumab), rather than a LOWER efficacy medication (adalimumab).<i>[(Conditional recommendation, low certainty of evidence)]</i> Implementation considerations: • Individual patient factors (e.g., age, comorbidities, frailty, pregnancy, adherence) and preferences (e.g., 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 EMA 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, history of cardiovascular disease (such as heart attack or stroke), and patients with 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 (smoking, prior cardiovascular disease) • Vedolizumab and anti-interleukin 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 is limited data on the safety of JAK inhibitors and SIP 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 one 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).<i>[(Conditional recommendation, low certainty of evidence)]</i> Implementation considerations: • Individual patient factors (e.g., age, comorbidities, frailty, pregnancy, adherence) and preferences (e.g., route of administration, ease of access) should be incorporated within a shared decision framework in selection of advanced therapies. • Vedolizumab and anti-interleukin 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 is limited data on the safety of JAK inhibitors and SIP 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.<i>[(Conditional recommendation, very low certainty of evidence)]</i>	
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.<i>[(Conditional recommendation, low certainty of evidence)]</i>	

USE AND POSITIONING OF ADVANCED THERAPIES	
7. In adult outpatients with moderate-to-severe UC, the AGA suggests AGAINST using methotrexate monotherapy, for induction or maintenance of remission. <i>[Conditional recommendation, low certainty of evidence]</i>	
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. <i>[Conditional recommendation, moderate certainty of evidence]</i>	
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. <i>[Conditional recommendation, low certainty of evidence]</i>	
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. <i>[No recommendation, knowledge gap]</i>	
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. <i>[No recommendation, knowledge gap]</i>	
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. <i>[Conditional recommendation, very low certainty of evidence]</i>	
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. <i>[Conditional recommendation, low certainty of evidence]</i>	
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-aminosalicylates. <i>[Conditional recommendation, very low certainty of evidence]</i>	
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	

Table 4. Key overarching considerations in the management of adult outpatients with moderate-to-severe ulcerative colitis

1. Patients should have confirmation of active inflammation based on UC-related symptoms, biomarkers, and/or endoscopic evaluation prior to starting advanced therapies.
2. Patients should have both general and therapy-specific pre-treatment work up prior to initiation of such treatments. These include screening for hepatitis B and tuberculosis exposure prior to any biologic or advanced small molecule treatments, thiopurine methyl transferase (TPMT) testing prior to initiation of thiopurines, and a baseline electrocardiogram (EKG) prior to 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.
3. 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.
4. In order to decrease risk of serious infections with immunosuppressive therapies, vaccination against influenza, pneumococcal pneumonia, and herpes zoster (particularly prior to S1P receptor modulator or JAK inhibitor use) should be considered.
5. Initiation of advanced therapy should be followed by monitoring for symptomatic response within 3 months of initiation, symptomatic and biochemical remission within 3–6 months, and endoscopic improvement/ remission within 6–12 months.
6. 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.

Table 5. GRADE Evidence Profile comparing TNF antagonists (infliximab, adalimumab and golimumab) with placebo for induction and maintenance of remission in patients with moderate-to-severe ulcerative colitis

INFLIXIMAB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)	Risk with infliximab	Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
Induction of clinical remission (CRITICAL)	50/438 (11.4%)	142/437 (32.5%)	RR 2.70 (2.01 to 3.61)	170 more per 1,000 (from 101 more to 261 more)	875 (5 RCTs)	⊕⊕⊕○ ¹ MODERATE
Maintenance of clinical remission (CRITICAL)	78/478 (16.3%)	235/627 (37.5%)	RR 2.17 (1.73 to 2.71)	176 more per 1,000 (from 110 more to 257 more)	1105 (5 RCTs)	⊕⊕⊕⊕ HIGH
ADALIMUMAB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)	Risk with adalimumab	Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
Induction of clinical remission (CRITICAL)	59/616 (9.6%)	141/753 (18.7%)	RR 1.84 (1.37 to 2.48)	84 more per 1,000 (from 37 more to 148 more)	1369 (5 RCTs)	⊕⊕⊕○ ² MODERATE
Maintenance of clinical remission (CRITICAL)	29/342 (8.5%)	84/425 (19.8%)	RR 2.25 (1.50 to 3.37)	188 more per 1,000 (from 75 more to 356 more)	767 (2 RCTs)	⊕⊕⊕○ ^{1,3} MODERATE
GOLIMUMAB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)	Risk with golimumab	Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
Induction of clinical remission (CRITICAL)	23/320 (7.2%)	58/324 (17.9%)	RR 2.46 (1.56 to 3.90)	146 more per 1,000 (from 56 more to 290 more)	644 (2 RCTs)	⊕⊕⊕○ ^{1,3} MODERATE
Maintenance of clinical remission (CRITICAL)	36/185 (19.5%)	67/183 (36.6%)	RR 1.71 (1.19 to 2.44)	107 more per 1,000 (from 28 more to 216 more)	368 (2 RCTs)	⊕⊕⊕○ ^{1,3,4} MODERATE

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

¹Rated down for imprecision since optimal information size not met (<200 events)

²Rated down for serious imprecision since magnitude of benefit is below the 100 per 1000 absolute benefit rate of clinically meaningful difference threshold over placebo, identified by the guideline panel.

²Lower limit of 95% of absolute effect crosses the clinically meaningful difference threshold of drug over placebo

⁴Though statistical heterogeneity was noted, with use of fixed effects meta-analysis, estimate was largely driven by larger, high-quality trials

^{*}[Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%]

Table 6. GRADE Evidence Profile comparing vedolizumab with placebo for induction and maintenance of remission in patients with moderate-to-severe ulcerative colitis

VEDOLIZUMAB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Risk with placebo	Study event rates (95% CI)	Risk with vedolizumab	Relative effect (95% CI)	Absolute effect *	No of participants (studies)
Induction of clinical remission (CRITICAL)	18/231 (7.8%)		68/389 (17.5%)	RR 2.09 (1.28 to 3.43)	109 more per 1,000 (from 28 more to 243 more)	620 (2 RCTs)
Maintenance of clinical remission (CRITICAL)	41/224 (18.3%)		146/323 (45.2%)	RR 2.41 (1.78 to 3.27)	212 more per 1,000 (from 117 more to 340 more)	547 (3 RCTs)

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

¹Rated down for imprecision since optimal information size not met (<200 events)

²Lower limit of 95% of absolute effect crosses the clinically meaningful difference threshold of drug over placebo for induction of clinical remission outcome

[*Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%]

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

USTEKINUMAB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)	Risk with ustekinumab	Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
Induction of clinical remission (CRITICAL)	17/319 (5.3%)	50/322 (15.5%)	RR 2.91 (1.72 to 4.94)	191 more per 1,000 (from 72 more to 394 more)	641 (1 RCT)	⊕⊕⊕⊕ ^{1,2} MODERATE
Maintenance of clinical remission (CRITICAL)	42/175 (24.0%)	77/176 (43.8%)	RR 1.82 (1.33 to 2.49)	123 more per 1,000 (from 50 more to 224 more)	351 (1 RCT)	⊕⊕⊕⊕ ^{1,2} MODERATE
MIRIKIZUMAB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)	Risk with mirikizumab	Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
Induction of clinical remission (CRITICAL)	42/357 (11.8%)	224/930 (24.1%)	RR 1.94 (1.43 to 2.63)	94 more per 1,000 (from 43 more to 163 more)	1287 (2 RCTs)	⊕⊕⊕⊕ ³ MODERATE
Maintenance of clinical remission (CRITICAL)	49/205 (23.9%)	216/436 (49.5%)	RR 2.04 (1.57 to 2.65)	156 more per 1,000 (from 86 more to 247 more)	641 (2 RCTs)	⊕⊕⊕⊕ ² MODERATE
RISANKIZUMAB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)	Risk with risankizumab	Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
Induction of clinical remission (CRITICAL)	20/325 (6.2%)	132/650 (18.5%)	RR 3.30 (2.10 to 5.18)	230 more per 1,000 (from 110 more to 418 more)	975 (1 RCT)	⊕⊕⊕⊕ ¹ MODERATE
Maintenance of clinical remission (CRITICAL)	46/183 (25.1%)	180mg: 72/179 (40.2%) 360mg: 71/186 (38.2%)	180mg: RR 1.60 (1.18 to 2.18) 360mg: RR 1.52 (1.11 to 2.07)	180mg: 90 more per 1,000 (from 27 more to 177 more) 360mg: 78 more per 1,000 (from 17 more to 160 more)	548 (1 RCT)	180mg: ⊕⊕⊕⊕ ³ MODERATE 360mg: ⊕⊕⊕⊕ ³ MODERATE
GUSELKUMAB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)	Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)	

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USTEKINUMAB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Risk with placebo	Study event rates (95% CI)	Risk with ustekinumab	Relative effect (95% CI)	Absolute effect *	No of participants (studies)
Quality of the evidence (GRADE)						
Induction of clinical remission (CRITICAL)	32/385 (8.3%)		121/522 (23.2%)	RR 2.82 (1.95 to 4.08)	182 more per 1,000 (from 95 more to 308 more)	907 (2 RCTs)
						⊕⊕⊕⊕ ² MODERATE
Maintenance of clinical remission (CRITICAL)	36/190 (18.9%)		100mg q8w: 85/188 (45.2%)	100mg q8w: RR 2.39 (1.71 to 3.33)	100mg q8w: 209 more per 1,000 (from 107 more to 350 more)	568 (1 RCT)
			200mg q4w: 95/190 (50.0%)	200mg q4w: RR 2.64 (1.90 to 3.66)	200mg q4w: 246 more per 1,000 (from 135 more to 399 more)	⊕⊕⊕⊕ ¹ MODERATE
						180mg: ⊕⊕⊕⊕ ¹ MODERATE

¹ Rated down for imprecision since optimal information size not met (<200 events)

² Lower limit of 95% of absolute effect crosses the clinically meaningful difference threshold of drug over placebo for induction of clinical remission outcome

³ Rated down for serious imprecision since magnitude of benefit is below the 100 per 1000 absolute benefit rate of clinically meaningful difference threshold over placebo, identified by the guideline panel. [*Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%]

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

TOFACITINIB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with tofacitinib				
Induction of clinical remission (CRITICAL)	19/282 (6.7%)	177/938 (18.9%)	RR 3.23 (2.05 to 5.08)	223 more per 1,000 (from 105 more to 408 more)	1220 (3 RCTs)	⊕⊕⊕○ ¹ MODERATE
Maintenance of clinical remission (CRITICAL)		5mg BID: 68/198 (34.3%)	5mg BID: RR 3.09 (1.99 to 4.79)	5mg BID: 313 more per 1,000 (from 149 more to 569 more)	593 (1 RCT)	5mg BID: ⊕⊕⊕○ ¹ MODERATE
	22/198 (11.1%)	10mg BID: 80/197 (40.6%)	10mg BID: RR 3.65 (2.38 to 5.61)	10mg BID: 397 more per 1,000 (from 207 more to 692 more)		10mg BID: ⊕⊕⊕○ ¹ MODERATE
UPADACITINIB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with upadacitinib				
Induction of clinical remission (CRITICAL)	14/374 (3.7%)	208/716 (29.1%)	RR 7.15 (4.26 to 11.99)	615 more per 1,000 (from 326 more to 1000 more)	1090 (3 RCTs)	⊕⊕⊕⊕ HIGH
Maintenance of clinical remission (CRITICAL)	18/149 (12.1%)	15mg/d: 63/148 (42.6%)	15mg/d: RR 3.52 (2.20 to 5.65)	15mg/d: 378 more per 1,000 (from 180 more to 698 more)	451 (1 RCT)	15mg/d: ⊕⊕⊕○ ¹ MODERATE
		30mg/d: 80/154 (51.9%)	30mg/d: RR 4.30 (2.72 to 6.81)	30mg/d: 495 more per 1,000 (from 258 more to 871 more)		30mg/d: ⊕⊕⊕○ ¹ MODERATE
FILGOTINIB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with filgotinib				
Induction of clinical remission (CRITICAL)	27/279 (9.7%)	94/507 (18.5%)	RR 1.88 (1.27 to 2.80)	88 more per 1,000 (from 27 more to 180 more)	786 (2 RCTs)	⊕⊕⊕○ ² MODERATE

TOFACITINIB COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)	Risk with tofacitinib	Relative effect (95% CI)	Absolute effect *	No of participants (studies)	Quality of the evidence (GRADE)
Maintenance of clinical remission (CRITICAL)	23/188 (12.2%)	100mg/d: 41/172 (23.8%) 200mg/d: 74/198 (37.4%)	100mg/d: RR 1.77 (0.98 to 3.19)	100mg/d: 115 more per 1,000 (from 3 fewer to 328 more)	558 (1 RCT)	100mg/d: ⊕⊕⊕⊕O2 MODERATE
			200mg/d: RR 3.36 (1.87 to 6.04)	200mg/d: 354 more per 1,000 (from 131 more to 756 more)		200mg/d: ⊕⊕⊕⊕I1 MODERATE

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

¹ Rated down for imprecision since optimal information size not met (<200 events)

² Rated down for serious imprecision since magnitude of benefit is below the 100 per 1000 absolute benefit rate of clinically meaningful difference threshold over placebo, identified by the guideline panel.
[*Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%]

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-severe ulcerative colitis

OZANIMOD COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with ozanimod				
Induction of clinical remission (CRITICAL)	17/281 (6.0%)	90/496 (18.1%)	RR 2.97 (1.80 to 4.90)	197 more per 1,000 (from 80 more to 390 more)	777 (2 RCTs)	⊕⊕⊕⊕ ^{1,2} MODERATE
Maintenance of clinical remission (CRITICAL)	46/292 (15.8%)	99/297 (33.3%)	RR 2.09 (1.54 to 2.84)	163 more per 1,000 (from 81 more to 276 more)	589 (2 RCTs)	⊕⊕⊕⊕ ^{1,2} MODERATE
ETRASIMOD COMPARED TO PLACEBO FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with etrasimod				
Induction of clinical remission (CRITICAL)	38/314 (12.1%)	160/577 (27.7%)	RR 2.23 (1.61 to 3.09)	123 more per 1,000 (from 61 more to 209 more)	891 (3 RCTs)	⊕⊕⊕⊕ ^{1,2} MODERATE
Maintenance of clinical remission (CRITICAL)	11/144 (7.6%)	94/289 (32.5%)	RR 4.26 (2.36 to 7.69)	489 more per 1,000 (from 204 more to 1000 more)	433 (1 RCT)	⊕⊕⊕⊕ ¹ MODERATE

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

¹Rated down for imprecision since optimal information size not met (<200 events)

²Lower limit of 95% of absolute effect crosses the clinically meaningful difference threshold of drug over placebo

[*Absolute effects estimated based on the following placebo rates across trials: induction of clinical remission ~10%; maintenance of clinical remission ~15%]

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. Clinically meaningful difference threshold of drug over placebo was set at 10%. Judgements made by guideline panel are in **bold**. Specific decisions for each medication are in **red**.

DOMAIN	CRITERIA	JUDGEMENT					
		No	Probably No	Probably yes	YES	Varies	Don't know
Problem	Is the problem a priority?						
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	Don't 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	Don't 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/don't know
Resource use	Is the incremental cost small relative to the net benefits?	No	Probably No	Uncertain	Probably yes	Yes	Uncertain
Equity	What would be the impact on health inequities?	Increased	Probably increased	Probably no impact	Probably reduced	Reduced	Varies/Don't know
Acceptability	Is the option acceptable to key stakeholders?	No	Probably No	Probably yes	Yes	Varies	Don't know
Feasibility	Is the option feasible to implement?	No	Probably No	Probably yes	Yes	Varies	Don't know

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[Abbreviations: 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]

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

THIOPURINES COMPARED TO NO THIOPURINES FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	No of participants (studies)	Quality of the evidence (GRADE)
	Risk without Thiopurines	Risk with Thiopurines				
Achieving clinical remission (CRITICAL)	57/127 (55.7%)	86/134 (68.6%)	RR 1.41 (0.91 to 2.18)	184 more per 1,000 (from 40 fewer to 530 more)	261 (6 RCTs)	⊕○○○ ^{1,2,3} VERY LOW
Relapse after achieving remission (CRITICAL)	90/146 (61.6%)	59/157 (37.6%)	RR 0.61 (0.49 to 0.77)	240 fewer per 1,000 (from 314 fewer to 142 more)	303 (7 RCTs)	⊕⊕○○ ^{1,3} LOW

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

¹ Rated down for risk of bias (inadequate blinding)

² Rated down for indirectness (not truly induction of remission, since majority of patients received corticosteroids for inducing remission; outcomes in 1/5 trials not standardized)

³ 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

METHOTREXATE COMPARED TO NO METHOTREXATE FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Risk without methotrexate	Study event rates (95% CI)	Risk with methotrexate	Relative effect (95% CI)	Absolute effect* (from 34 fewer to 294 more)	No of participants (studies)
Achieving clinical remission (CRITICAL)	30/96 (31.3%)		40/102 (39.2%)	RR 1.31 (0.89 to 1.94)	97 more per 1,000 (from 34 fewer to 294 more)	198 (3 RCTs)
Relapse after achieving remission (CRITICAL)	39/60 (65.0%)		44/65 (67.7%)	RR 1.01 (0.79 to 1.29)	7 more per 1,000 (from 136 fewer to 189 more)	125 (3 RCTs)

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

¹ Rated down for indirectness (different modes of administering MTX, majority of patients received corticosteroids for inducing remission)

² Rated down for very serious imprecision with very wide CIs

Table 13.

GRADE Evidence Profile comparing infliximab + immunomodulators vs. infliximab monotherapy for achieving steroid-free remission in patients with moderate to severe ulcerative colitis. No trial of maintenance therapy comparing TNF- α antagonists + immunomodulators vs. TNF- α antagonist monotherapy was identified.

COMBINATION THERAPY WITH INFLIXIMAB + IMMUNOMODULATORS COMPARED TO INFLIXIMAB MONOTHERAPY FOR MODERATE- TO- SEVERE ULCERATIVE COLITIS					
Outcomes	Study event rates (95% CI)	Risk with combination therapy	Relative effect (95% CI)	Absolute effect*	No of participants (studies)
Achieving clinical remission (CRITICAL)	17/78 (21.8%)	31/80 (38.8%)	RR 1.78 (1.08 to 2.94)	170 more per 1,000 (from 17 more to 423 more)	158 (1 RCT)
Quality of the evidence (GRADE)					
MODERATE					

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

[†]Rated down for imprecision since 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. No trial of maintenance therapy comparing TNF antagonists + immunomodulators vs. immunomodulator monotherapy was identified.

COMBINATION THERAPY WITH INFLIXIMAB + IMMUNOMODULATORS COMPARED TO IMMUNOMODULATOR MONOTHERAPY FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS						
Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with Immunomodulator	Risk with Combination Therapy				
Achieving clinical remission (CRITICAL)	18/79 (22.8%)	31/80 (38.8%)	RR 1.70 (1.04 to 2.78)	159 more per 1,000 (from 9 more to 406 more)	159 (1 RCT)	⊕⊕⊕○ ¹ MODERATE

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

¹Rated down for imprecision since optimal information size not met (<200 events)

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-severe ulcerative colitis in steroid-free remission on combination therapy

WITHDRAWAL OF IMMUNOMODULATORS (WHILE CONTINUING BIOLOGIC THERAPY) COMPARED TO CONTINUING COMBINATION THERAPY IN ADULT OUTPATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS IN STEROID-FREE REMISSION						
Outcomes	Risk with continuing combination therapy	Study event rates (95% CI)	Risk with IMM withdrawal	Relative effect (95% CI)	Absolute effect*	No of participants (studies)
Risk of relapse at 12 months (CRITICAL)	30/202 (14.9%)		34/202 (16.8%)	RR 1.15 (0.75 to 1.76)	22 more per 1,000 (from 37 fewer to 113 more)	404 (5 RCTs)
Quality of the evidence (GRADE)						
⊕○○○1,2,3 VERY LOW						
WITHDRAWAL OF BIOLOGICS (WHILE CONTINUING IMMUNOMODULATOR MONOTHERAPY) COMPARED TO CONTINUING COMBINATION THERAPY IN ADULT OUTPATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS IN STEROID-FREE REMISSION						
Outcomes	Risk with continuing combination therapy	Study event rates (95% CI)	Risk with biologic withdrawal	Relative effect (95% CI)	Absolute effect*	No of participants (studies)
Risk of relapse at 12 months (CRITICAL)	22/196 (11.2%)		63/200 (31.5%)	RR 2.35 (1.38 to 4.01)	152 more per 1,000 (from 43 more to 338 more)	396 (4 RCTs)
Quality of the evidence (GRADE)						
⊕○○○1,2,4 VERY LOW						

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

¹ Rated down for serious risk of bias (open-level trials with subjective end points)

² Rated down for indirectness since most patients in these trials had Crohn’s disease

³ Rated down for very serious imprecision due to very wide confidence intervals crossing unity

⁴ Rated down for imprecision since optimal information size not met (<200 events)

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

CONTINUING 5-AMINOSALICYLATE COMPARED TO STOPPING 5-AMINOSALICYLATE IN PATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS BEING TREATED WITH ADVANCED THERAPIES WHO HAVE FAILED 5-ASA							
Outcomes	Study event rates (95% CI)		Risk with concomitant 5-ASA	Relative effect (95% CI)	Absolute effect*	No of participants (studies)	Quality of the evidence (GRADE)
Induction of clinical remission (CRITICAL)	413/1910(21.6%)		1149/4134 (27.8%)	RR 1.04 (0.78 to 1.39)	9 more per 1,000 (from 48 fewer to 84 more)	6044 (10 RCTs)	⊕⊕○○ ^{1,2} LOW

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

¹ 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)

² Rated down for serious imprecision with wide CIs