AGA LIVING CLINICAL PRACTICE GUIDELINE ON THE PHARMACOLOGIC MANAGEMENT OF MODERATE-TO-SEVERE CROHN'S DISEASE

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ABSTRACT

Background & Aims: This American Gastroenterological Association (AGA) living guideline is intended to support practitioners in the pharmacological management of moderate-to-severe Crohn's Disease (CD).

Methods: A multi-disciplinary panel of clinical experts and methodologists utilized 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.

Results: The Guideline Panel agreed on 16 recommendations, of which one is a strong recommendation, nine are conditional recommendations and six were identified as knowledge gaps. In adult patients with moderate-to-severely active CD, the AGA recommends the use of infliximab, adalimumab, ustekinumab, risankizumab, mirikizumab, guselkumab and upadacitinib over no treatment, and suggests the use of certolizumab pegol and vedolizumab over no treatment. In individuals who are naïve to advanced therapies, the AGA suggests using a higher efficacy medication (infliximab, adalimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, or guselkumab) rather than a lower efficacy medication (certolizumab pegol, upadacitinib). In individuals who have previously been exposed to one or more advanced therapies, the AGA suggests using a higher efficacy medication (adalimumab, risankizumab, guselkumab, upadacitinib) or intermediate efficacy medication (ustekinumab, mirikizumab) rather than a lower efficacy medication (vedolizumab, certolizumab pegol). In adult outpatients with moderate-to-severely active CD, 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 using subcutaneous methotrexate for induction and maintenance of remission but suggests against using oral methotrexate. The AGA suggests using combination therapy with infliximab and thiopurines over infliximab monotherapy, particularly in those naïve to thiopurines. The AGA also suggests using early advanced therapy over step therapy involving corticosteroids and/or immunomodulators. 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 CD.

Key words: Inflammatory bowel disease; network meta-analysis; evidence synthesis; positioning

EXECUTIVE SUMMARY

Crohn's disease (CD) affects over 1 million individuals in the United States and over 6 million individuals worldwide[1-3]. Long-term, CD-related inflammation can result in penetrating and stricturing complications, often resulting in hospitalization and surgery[4,5]. Advanced therapies, including monoclonal antibodies (also referred to as biologics) targeting tumor necrosis factor [TNF]-α (infliximab, adalimumab, and certolizumab pegol), leukocyte trafficking (vedolizumab), and interleukin 12 and 23 (ustekinumab, risankizumab, mirikizumab, and guselkumab), as well as small molecules targeting janus kinase (JAK; upadacitinib), have improved clinical outcomes in patients with CD.

The goal of these evidence-based guidelines from the American Gastroenterological Association (AGA) is to provide recommendations for the pharmacological management of moderate to severely active CD in adults, overall and in those without and those with prior exposure to an advanced therapy, the timing of using these therapies, their withdrawal, and appropriate goals of medical management.

How to Use These Guidelines

Table 1 provides an overview of each guideline recommendation, the strength of the recommendation, and the certainty of evidence used to inform it. Recommendations are accompanied by implementation considerations (based on the collective experience of the panel members) that are meant to help provide guidance regarding the recommendations. Broad overarching considerations for implementing these recommendations in clinical practice (**Table 2**). Two clinical decision support tools, which may assist clinicians in making pharmacological management decisions for patients with CD, are presented in **Figures 1** and **2**.

Additional information about the background, methods, evidence reviews, and detailed justifications for each recommendation are provided in these full guidelines. Corresponding forest plots for each pharmacological intervention and the studies used to inform it are provided both in the main document and supplemental materials. The methods, evidence reviews, and analyses related to network meta-analyses conducted for this guideline are being published alongside this guideline and are currently in revision. The term "recommend" was used to indicate strong recommendations, and the term "suggest" was used to indicate conditional recommendations. The interpretation of certainty of evidence and implications of strong and conditional recommendations for healthcare providers, patients, and policymakers are presented in **Table 3.**

Objectives and Scope of These Guidelines

The approval of advanced therapies in CD has significantly impacted the course of disease. Since the publication of the previous AGA guidelines for moderate to severe CD in 2021, two additional classes of advanced therapies and five novel agents have been approved for managing CD[6]. They have also been followed by the introduction of biosimilars for several agents over the past decade, including for infliximab, adalimumab, and ustekinumab.

The purpose of these guidelines is to provide evidence-based recommendations for the pharmacologic management of adults with moderate-to-severely active CD, defined as moderate to severe daily abdominal pain and diarrhea[7] coupled with confirmed active intestinal inflammation. These guidelines also apply to individuals with CD with mild symptoms but with predictors of future disease-related complications (such as high burden of inflammation, extensive disease, ileal/ileocolonic or upper gut involvement, etc.),[8] patients who are corticosteroid-dependent, or where the disease has a significant impact of disease on quality of life. These guidelines are intended to be used in the ambulatory setting. This guideline is not intended to inform decision making related to the management of post-operative CD, perianal CD or internal penetrating complications or stricturing CD.

Target Audience

This guideline, like all AGA guidelines, is primarily targeted towards healthcare providers in the fields of gastroenterology and primary care who depend on our expert, evidence-based recommendations to inform their clinical practice and shared decision-making with patients. Rather than represent a specific standard to adhere to, we intend these recommendations to be used by clinicians to guide their patient management decisions and to inform considerations of benefits and harms of treatments in each individual case.

1. GUIDELINE DEVELOPMENT PROCEDURES

1.1 Overview

This document represents the official recommendations of the AGA. It was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, and adheres to best practices in guideline development as outlined by the National Academy of Medicine (formerly Institute of Medicine), using a process outlined previously.[9]

1.2 Conflict of Interest

Each nominee to this Guideline Panel underwent a vetting process that required them to report all commercially funded and other relevant activities within the previous 24 months. All reported financial or intellectual conflicts were reviewed by the Chair of the AGA Institute Clinical Guidelines Committee (CGC) and adjudicated against rules and criteria in the CGC COI Policy. Only nominees whose COI status complied with this policy were appointed as Guideline Panel members.

1.3 Guideline Funding

AGA provided all financial support for the development of this guideline. No funding from industry was offered or accepted to support the writing effort.

1.4 Organization and Panel Composition

The Guideline Panel was comprised of 10 members, all selected based on their specific expertise. There were with eight clinical Content Experts with clinical and research expertise in the clinical topic, and two methodologists with specialized GRADE guideline development skills. An information specialist assisted the panel members with designing and executing the required literature searches. All Panel members participated in evidence review and the Senior Methodologist oversaw data synthesis and analysis. All members of the Guideline Panel then reviewed the results of the analysis, contributed to consensus development, and constructed the final recommendations. COIs are presented in **eTable 1** for all panel members

1.5 Document Review

The guideline underwent several levels of review including an open, 30-day Public Comment period, external Peer Review by two topic experts, and Patient Review. A network meta-analysis which informed focused questions on positioning of advanced therapies underwent separate

editorial and peer review per *Gastroenterology*'s policy. Organizational-level review was carried out by the CGC and AGA's Governing Board. At each stage, the Guideline Panel considered all reviewer comments and feedback and revised the guideline manuscript in response, as needed.

1.6 Guideline Updates

The AGA has developed these guidelines as Living Guidelines given the rapid pace of innovation and new therapies in CD.[10] 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. The evidence for focused questions in the living mode will be reviewed every 6 months.

2. METHODS

2.1 Formulation of Clinical Questions

The clinical research questions which underpin these guidelines were developed by the Guideline Panel, with methodologists and clinical content experts working together to develop specific questions which address current knowledge gaps in this area. The PICO format was used to outline the specific patient population (P), intervention (I), comparator (C), and outcome(s) for each clinical question (**Table 4**).

2.2 Outcomes of Interest

The panel selected desirable and undesirable patient-important outcomes (benefits and harms). Critical outcomes for decision-making for all the interventions included in this review are summarized in the evidence profiles. In individuals with moderate-to-severely active CD in the ambulatory setting, induction and maintenance of clinical remission were considered critical, patient-centric outcomes for decision making. Achieving endoscopic remission, corticosteroid-free remission and serious adverse events (SAEs) were considered important outcomes. While the discordance between clinical symptoms and endoscopic disease activity has been well described in patients with CD, clinical remission was deemed to be a more patient-centered outcome that was more uniformly described across clinical trials and that has been used to inform regulatory approval of all advanced therapies. Patient surveys have suggested that patients perceive improving quality of life and symptom resolution as treatment objectives; only 12.8% prioritize normalization of colonoscopy as treatment objective.[11] In clinical trials, clinical remission was most

commonly measured using the Crohn's disease activity index (CDAI), based on abdominal pain, bowel movements, general wellbeing, complications of disease, abdominal mass, anemia and weight change. CDAI scores <150 suggest clinical remission, and scores 150-220, 221-450 and >450 denoting mild, moderate and severe disease, respectively.[12] For questions on efficacy of a strategy of top-down therapy vs. gradual step-up therapy and treat-to-target of clinical vs. endoscopic remission, maintaining clinical remission and preventing disease-related complications at 1 year were deemed to be the critical outcome. The outcome of clinical remission is also consistent with prior guidelines in both CD (2021) and ulcerative colitis (2024). [6,13]

2.3 Search Strategy

The systematic review process was guided by a search protocol developed *a priori* by the Guideline Panel members in collaboration with the medical librarian. The librarian conducted a comprehensive search of the following databases Ovid MEDLINE, EMBASE, and Wiley Cochrane Library from inception to August 14, 2024, using a combination of controlled vocabulary terms supplemented with keywords. The search was limited to English language and humans. References from previous guidelines and consensus statements, as well as from conference proceedings and press releases till April 1, 2025, were also reviewed. The final strategy is available in **eTable 2**. The bibliography and included references of prior guidelines on this topic were searched to identify relevant studies that may have been missed. Additionally, content experts helped identify any ongoing studies with results expected soon.

2.5 Study Selection, Data Collection, and Analysis

These recommendations are based on evidence derived from randomized controlled trials (RCTs) that were synthesized in an updated systematic review, meta-analysis, and network meta-analysis conducted specifically for this guideline. Details regarding the network meta-analysis are published in an accompanying manuscript. Data from previously published systematic reviews were also used if no new data were identified to inform a specific PICO.

The inclusion and exclusion criteria were based on the clinical research questions developed by the Guideline Panel. Searches from all databases were combined in *Covidence* bibliographic software. The minimum trial duration for induction and maintenance therapy required was 4 weeks and 24 weeks, respectively. Adult and pediatric studies were considered where appropriate. Efficacy trials exclusively in ulcerative colitis were excluded. Given the typically inadequate sample size and follow-up time for RCTs in relation to serious but infrequent adverse events such as serious infection or neoplasm, observational studies, systematic reviews, and

meta-analyses were considered when evaluating risks of therapies. Observational studies were not included in assessments of efficacy. A consensus was reached on study inclusion. Any disagreements were resolved with adjudication by the Guideline Panel Chair and Senior Methodologist.

Data were extracted from each study, including study characteristics such as year of publication, study site, study population, intervention, comparison group, outcomes, and methods for risk-of bias assessment. Meta-analyses were conducted when more than one study contributed data for the same intervention and outcome. Dichotomous outcomes were combined to obtain a relative risk (RR) or odds ratio (OR) and 95% confidence interval (CI). These effect estimates were calculated using the Mantel-Haenszel fixed-effects model (in the absence of conceptual heterogeneity and if <5 studies) or the DerSimonian-Laird random-effects model.[14] 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 moderately-to-severely active CD. 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 rate allows for a common reference against which to estimate the predicted benefit under the assumption that relative risk and odds ratios are translatable across studies. 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. For randomized controlled trials assessing induction rates, the rate of induction of clinical remission was set at 15%, while for trials assessing maintenance of remission a pooled placebo response rate of 22% was used. Statistical heterogeneity was assessed using the I^2 statistic.[15] 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 <10.[16] 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 2025 AGA Evidence Synthesis document on comparative efficacy of different advanced therapies for management of moderate-to-severely active CD is under review at the *Journal*.

2.6 Certainty of the Evidence

The Guideline Panel used the GRADE approach to assess the certainty of evidence for the effect of the intervention on each outcome using the GradePro Guideline Development Tool software (https://gradepro.org). The GRADE approach considers factors such as study design, population studied, risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias to rate the certainty of evidence as high, moderate, low, or very low (**eTable 3**).

For questions of comparative efficacy of different pharmacological interventions, we used GRADE approach for NMA. The guideline panel set a clinically meaningful difference (CMD) threshold of 10% for comparisons with no treatment, based on consensus and in line with thresholds used in prior guidelines for moderate-to-severe UC. If the effect size was below this CMD threshold, then benefit was deemed to be trivial-to-small. These thresholds are similar to thresholds for small effect size in a Delphi consensus for guideline development and clinical decision-making by Gordon *et al.*[17] Similarly, for comparisons between two active therapies in meta-analyses, 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%). 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.

2.7 Development of Recommendations

The process of translation of evidence into guideline recommendations followed the GRADE Evidence-to-Decision framework and was achieved by means of discussion during virtual meetings of the Guideline Panel. The Evidence-to-Decision framework considers the certainty of evidence, balance of benefits and harms, patient values and preferences, feasibility, acceptability, equity, and resource use. Evidence profiles and evidence-to-decision tables are presented in **Tables 5-19**. Group consensus was reached for all the recommendations.

The interpretation of strength of recommendations is summarized in **Table 3**. The certainty of evidence and the strength of recommendation are provided for each clinical question. As per GRADE methodology, recommendations are labeled as "strong" or "conditional". The words "we recommend" indicate strong recommendations and "we suggest" indicate conditional recommendations.

3. RECOMMENDATIONS

General implementation considerations

There are several overarching considerations for implementing these recommendations in clinical practice (**Table 2**). First, as noted above, it is important to consider appropriate categorization of disease activity when considering advanced therapy initiation and that treatment decision are made based on confirmed active inflammation as concomitant functional gastrointestinal symptoms may be seen in up to one-third of patients with CD.[18] Therefore, before considering an advanced therapy, inflammation should be confirmed via objective measures of biochemical inflammation (C-reactive protein [CRP] in absence of other causes or fecal calprotectin) and/or with structural assessment via ileocolonoscopy or imaging studies (CT or MR enterography or intestinal ultrasound, dependent on center availability and expertise).

It is also advised to screen for comorbidities that may increase the risk of advanced therapies. Such screening includes screening for hepatitis B and tuberculosis given risk of reactivation with exposure to advanced therapies. Additionally, it is appropriate to review vaccination status for pneumococcus, influenza, COVID-19, herpes zoster, respiratory syncytial virus and human papilloma virus, and ensure these are accurate and up to date, consistent with general healthcare maintenance guidelines.[19] When considering JAK inhibitors, documenting lipid levels prior to therapy initiation is also recommended; these should be repeated 4-6 weeks after starting therapy. Lastly, active comorbidities that may be exacerbated by specific classes of therapies should be considered when selecting an advanced therapy. For example, TNF antagonists may be contraindicated in the setting of advanced congestive heart failure, while they and other advanced therapies may be associated with an increased risk of lymphoma, non-melanoma and melanoma skin cancer.[20-22] When prescribing JAK inhibitors, additional risks of venous thromboembolic events, cardiovascular events and stroke should be reviewed.[23]

Once an advanced therapy is initiated, disease activity monitoring should continue. International societal guidance documents such as STRIDE and STRIDE-II recommended periodic assessment of clinical response, as well as repeat biochemical assessment (CRP, fecal calprotectin) after initiating an advanced therapy.[24,25] Repeat structural assessment (i.e. ileocolonoscopy or enterography, dependent on disease location), is generally considered appropriate, although there are limited real world data to date confirming that this improves clinical outcomes over time.

3.1. USE OF ADVANCED THERAPIES

Question 1: What is the efficacy of advanced therapies for induction and maintenance of remission in moderate-to-severely active luminal Crohn's disease?

Recommendation 1: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA *recommends* the use of infliximab, adalimumab, ustekinumab, risankizumab, mirikizumab, guselkumab or upadacitinib*, over no treatment [*Strong recommendation, moderate to high certainty of evidence*]

Recommendation 2: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA *suggests* the use of certolizumab pegol or vedolizumab, over no treatment [*Conditional recommendation, moderate certainty of evidence*]

Implementation considerations:

- ***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 some patients with suboptimal response to standard dosing, particularly those with more severe disease, **extended induction regimens or dose escalation** may be beneficial for most advanced therapies.*
- *There are **two dosing options available for maintenance therapy** for risankizumab, guselkumab and upadacitinib. Higher maintenance doses may be preferred in patients with high burden of inflammation and/or more severe disease, and those who have previously failed TNF antagonists.*

* In the United States, the FDA recommends reserving use of JAK inhibitors in patients with failure or intolerance to TNF antagonist therapy.

3.1.1 Source of Evidence

The data examining the efficacy of advanced therapies in comparison to no treatment was derived from 45 placebo controlled randomized controlled trials for moderate-to-severe Crohn's disease. This included data from 15 trials of TNF antagonists (5 infliximab[26-30], 7 adalimumab[31-37], 3 certolizumab pegol[38-40]), 4 trials from anti-integrins (4 vedolizumab[41-44]), 12 trials from ustekinumab[45-50], 10 trials from IL23p19 antagonists (2 mirikizumab[50,51], 4 guselkumab[48,49,52], 4 risankizumab[53-55]), and 4 trials for upadacitinib[56,57]. All trials were conducted in patients with moderately-to-severely active CD with placebo-based controls. Patient populations were largely similar across trials in terms of patient and disease characteristics, although it is important to note that later trials had higher percentages of individuals with prior advanced therapy exposures, in comparison to early trials such as those for TNF antagonists. The majority of trials provided information regarding stratification of prior advanced therapy exposure. Biosimilar data and data

related to reformulations for alternative modes of delivery were included when appropriate. Efficacy data for the primary outcomes of induction and maintenance of clinical remission are presented by study and with summary estimates for each therapy in **eFigures 1-9**. GRADE evidence profiles for each agent are presented in **Tables 5-8**.

3.1.2 Benefits

Fully appraising the risks and benefits of a given therapy is critical to determining recommendations regarding its use. With regards to assessing a given therapy's effectiveness, the panel employed a clinically meaningful benefit (CMD) of 10% in comparison to placebo to attribute at least moderate benefit, consistent with recently published guidelines in ulcerative colitis and an international Delphi consensus on effect size thresholds for clinical guidelines in IBD.[17] On meta-analysis, infliximab, adalimumab, ustekinumab, risankizumab, guselkumab, and upadacitinib met this threshold of a CMD >10%, with magnitude of benefit in inducing remission over placebo ranging from 119 to 353 per 1000 patients treated. In contrast, the magnitude of benefit with certolizumab pegol and vedolizumab in inducing remission was 48 and 90 per 1000 patients treated, respectively, suggesting a trivial-to-small benefit. The pivotal phase 3 RCT of mirikizumab, VIVID-1, was designed as a treat-straight-through trial in which patients were randomized to mirikizumab, ustekinumab or placebo, and treated through for 52 weeks. With mirikizumab, the magnitude of benefit for inducing remission at 12 weeks, compared with placebo, was 92 per 1000 patients; however, with continued follow-up in a treat-straight-through design, the magnitude of benefit over placebo in achieving remission at week 52 was 387 per 1000 patients. Hence, the guideline panel deemed that the overall benefit with mirikizumab is moderate.

3.1.3 Harms

Adverse events considered associated with advanced therapies include serious infection and malignancies. While the overall rates of these events across clinical trials was low and often not significantly increased, it is important to note that RCTs are often underpowered with relatively short follow-up times. Observational data can be used to better inform these risks. 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 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.[58] There was no difference in the risk of serious infections between TNF antagonists and vedolizumab. There have been limited comparative safety studies of JAK inhibitors and IL23 p19 antagonists. 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 monotherapy.[59] This risk was comparable to the risk observed in patients treated with thiopurine monotherapy. The FDA has issued a black box warning on the increased risk of malignancy with TNF antagonists.[60] Currently, there is a paucity of population-representative data to inform risk estimates related to malignancy for other classes of advanced therapies.

When considering these adverse events, it is also important to balance them with the potential deleterious consequence of inadequately treating patients with moderate-to-severely active CD, and effective therapies to control disease may lower the risk of serious infections.[61-63] CD flares can reduce quality of life, impact functional status, increase the risk of corticosteroid exposure, hospitalization, or surgery, were felt to exceed these pharmacologic risks.

3.1.4 Certainty in Evidence of Effects

Overall, ustekinumab, guselkumab, and mirikizumab had high certainty of evidence for induction, while infliximab, adalimumab, risankizumab, and upadacitinib had moderate certainty of evidence, with evidence being rated down for imprecision due to low number of events (optimal information size). Infliximab and guselkumab had high certainty of evidence for maintenance of remission, whereas adalimumab, certolizumab, vedolizumab, risankizumab, mirikizumab, and upadacitinib had moderate certainty of evidence. Full evidence profiles for each therapy in comparison to placebo, as well as justifications for rating of the evidence, are presented in **Table 5-8**. The GRADE evidence-to-decision judgements for all advanced therapies are presented in **Table 9**.

3.1.5 Discussion

When considering implementing these recommendations, there are several important factors to consider. First, as noted above, therapy selection and initiation should be conducted with confirmation of active disease and after appropriate baseline laboratory evaluation is performed. Medication selection should also incorporate a patient's baseline preferences regarding risk-benefit balance as well as mode of delivery (i.e. intravenous vs. subcutaneous vs. oral therapy). Such decisions should also integrate potential interactions with competing comorbidities or extraintestinal manifestations

Infliximab, adalimumab, and ustekinumab biosimilars have been approved by the FDA for CD. Several studies have demonstrated the efficacy and safety of these biosimilars in CD, and switching from an originator to a biosimilar has not been found to be associated with an increased risk of subsequent clinical, biochemical, or endoscopic relapse[64,65]. Originator biologics and biosimilars could be used interchangeably, and that they possess similar efficacy and safety profiles. The preference of the panel was that individuals initiate the first available therapy when considering originator compounds versus biosimilars as opposed to delaying care.

Subcutaneous formulations of infliximab and vedolizumab are approved by the FDA for the use in CD. They have been shown to have comparable efficacy to their respective intravenous formulations and can be used interchangeably with intravenous formulations after induction for most patients. In the LIBERTY trial, individuals with moderate-to-severely active CD received open-label 5 mg/kg induction with CT-P13 and were then randomized to subcutaneous CT-P13 every 2 weeks or placebo, with 62.3% achieving clinical remission in the treatment arm, compared to 32.1% in the control group at 54 weeks.[66] In the VISIBLE 2 trial, participants with moderate-to-severely active CD received open-label induction with intravenous vedolizumab and were then randomized to every other week subcutaneous vedolizumab versus placebo. Those receiving vedolizumab were significantly more likely to be in remission at one year in comparison to placebo (43.2% vs 20.8%).[44]

Emerging data suggest that in some patients with suboptimal response to standard induction therapy, particularly those with severe disease, extended induction therapy may be beneficial. Observational cohorts have demonstrated the potential benefit of extended induction periods, particularly when considering JAK inhibitors or IL23 p19 antagonists, in those with more severe disease or who do not tolerate transition to maintenance dosing.[67-69] Beyond induction, some patients may also derive benefit from increased dosing during maintenance therapy as well. In the U-EXCEED trial of maintenance upadacitinib, rates of maintenance of remission were higher in those receiving 30 mg daily (47.6%) than those receiving 15 mg daily (37.3%) at 52 weeks.[56] One cannot extrapolate these findings to all therapies, however. Data on potential clinical benefit of higher maintenance dosing for guselkumab and risankizumab are evolving. Further real-world evidence assessing dose escalation strategies is needed for more recently approved agents. It is important to recognize that higher dosing of these agents may also modify their safety profile. While increased trough levels of TNF antagonists have not been associated with increased SAEs over time, clinical trials of JAK inhibitors have suggested that there may be higher rates of infectious complications at the higher dose with this class.[56]

3.1.6. Evidence gaps and future research

Several knowledge gaps and opportunities for future research currently exist. Clinical trials emphasizing potential effect modifiers on clinical and endoscopic response and remission rates will assist clinicians in appropriate medication therapies. Examples of such factors include stratification by disease location, severity, or behavior (inflammatory vs penetrating vs stricturing), race and ethnicity, and the efficacy and safety in older individuals with CD. Additionally, long term comparative safety data for recently FDA-approved therapy classes such as JAK inhibitors and IL-23p19 antagonists against older agents will better inform clinical decision making.

Additionally, there is a significant knowledge gap regarding how these therapies may be most effectively combined with each other in severe CD. Several small observational studies of various combinations of biologics and/or small molecules have demonstrated potential therapeutic benefit and limited adverse events in comparison to advanced monotherapy. For example in a recent meta-analysis of 13 observational studies comprising 266 total patients with IBD, clinical remission rates to combination advanced therapy ranged from 40.4 to 76.5%, and SAE rates ranged from 0 to 12.3%.[70] Dedicated RCTs are ongoing to better understand how to best maximize additive and/or synergistic effects of therapies across classes[71].

3.2 POSITIONING OF ADVANCED THERAPIES IN INDIVIDUALS WHO ARE NAÏVE TO ADVANCED THERAPIES

Question 2: In adult outpatients with moderate-to-severely active Crohn's disease who are naïve to advanced therapies, what is the comparative efficacy of infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, upadacitinib, risankizumab, mirikizumab and guselkumab, for induction and maintenance of remission?

Recommendation 3: In adult outpatients with moderate-to-severely active Crohn's disease who are naïve to advanced therapies, the AGA suggests using a HIGHER efficacy medication (infliximab, adalimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, guselkumab), rather than a LOWER efficacy medication (certolizumab pegol, upadacitinib). [*Conditional recommendation, low to high certainty of evidence***]**

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.*
- *There are limited data on the safety of JAK inhibitors in pregnancy. These drugs should generally be avoided in women contemplating pregnancy in the near future.*

3.2.1 Source of Evidence

With the expanding armamentarium of available therapies for the treatment of moderate-to-severely active CD, understanding how to position these agents amongst each other becomes paramount. To date, head-to-head trials have been limited in CD. In order to inform this guideline, the panel relied on phase 2 and 3 RCTs and conducted a NMA, stratified by prior exposure to advanced therapies. RCTs were used to inform these analyses, with an emphasis on induction of clinical remission as a patient-centric, uniformly reported outcome; for trials with treat-straight-through design, stratified analyses based on prior exposure to advanced therapies was also performed and informed recommendations. Separate NMAs for maintenance of remission were also conducted based on trial design (treat-straight-through versus re-randomization of responders). Pairwise comparisons were performed between active therapies, with an *a priori* threshold superiority of a CMD of 5%. The full results are of this NMA are available separately and summarized below.

The NMA included eight placebo-controlled trials of TNF antagonists (2 infliximab, 4 adalimumab, 2 certolizumab pegol), three trials of anti-integrins (3 vedolizumab), three trials of IL-12/23 antagonists (3 ustekinumab), nine trials of IL-23p19 antagonists (3 risankizumab, 2 mirikizumab, 4 guselkumab), and three trials of JAK inhibitors (3 upadacitinib). One head-to-head trials without placebo comparator were also included in these analyses. SEAVUE compared ustekinumab to adalimumab among 386 individuals.[72] Similar rates of clinical remission were appreciated with ustekinumab and adalimumab at 52 weeks (65% vs 61%).

3.2.2 Benefits

In advanced therapy naïve individuals, most therapies demonstrated clinically important benefit compared with certolizumab pegol and/or upadacitinib. Adalimumab demonstrated an important benefit when compared with certolizumab pegol with a high certainty of evidence, and probably important benefit compared with upadacitinib with moderate certainty of evidence. With regards to anti-interleukin therapies, ustekinumab demonstrated probably important benefit compared with certolizumab pegol and upadacitinib with moderate certainty of evidence. Guselkumab demonstrated probably important benefit compared with certolizumab pegol with moderate certainty of evidence, as well as possibly important benefit compared with upadacitinib with low certainty of evidence. Risankizumab demonstrated possible important benefit compared with certolizumab with low certainty of evidence, and mirikizumab demonstrated possible important benefit compared with both certolizumab pegol and upadacitinib with low certainty of evidence. Lastly, vedolizumab demonstrated possibly important benefit compared with certolizumab pegol

as well, with low certainty of evidence. Differences between other advanced therapies was either of very low certainty and/or was deemed to have trivial-to-small benefit (<5% risk difference).

When analyzing four trials with treat-straight-through designs,[48,50,72,73] guselkumab every 8 weeks demonstrated possibly trivial benefit in comparison to adalimumab (low certainty of evidence). Every 4 week therapy of guselkumab demonstrated possibly trivial benefit in comparison to every 8 week dosing (low certainty of evidence).

3.2.3 Harms

In all maintenance studies assessed in the NMA, risks of serious infection between advanced therapies and placebo were comparable, and there were no significant differences when comparing advanced therapies. When examining per-trial-defined SAEs, the risk of SAEs was lower in those treated with guselkumab 200 mg every 4 weeks in comparison to infliximab, vedolizumab, ustekinumab, and guselkumab 100 mg over 48 weeks. It is important to reiterate that RCTs are often underpowered and have inadequate follow-up time to fully capture important but uncommon adverse events, particularly adverse events that occur at a lower frequency including serious infections, neoplastic complications, thromboembolic events, or drug-induced liver injury. While not formally reviewed for the purposes of this guideline panel, observational studies and meta-analyses of clinical trials that have been published to date comparing adverse low incidence of serious adverse events,[58,74-77] though such data are still limited, particularly those recently approved by the FDA. As noted previously, when considering each therapy individually, all were felt to have only trivial risks of undesirable effects.

3.2.4 Certainty in Evidence of Effects

The certainty of evidence varied based on the comparative agents in the NMA. In general, this ranged from low to moderate certainty as described above with each pairwise comparison. The only exception to this the high level of certainty that adalimumab had an important level of benefit over certolizumab pegol.

3.2.5 Discussion

To aide clinicians in clinical decision making regarding appropriate therapy selection, and in the context of potential intra-class differences among specific therapies in IBD, the panel rated each therapy individually as opposed to grouping by class. Two groups were created: (1) higher efficacy and (2) lower efficacy. Classification criteria for higher efficacy were defined *a priori* and included an absolute difference in efficacy in comparison to lower efficacy therapies of 5% (CMD ≥5%), a

p-score in the NMA of 0.49 to 1.0 in comparison to placebo, and an absolute difference versus placebo in phase 3 clinical trials for that agent of ≥15%. Using these criteria, infliximab, adalimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, and guselkumab were classified as higher efficacy medications for the induction of remission in advanced therapy naïve individuals, while upadacitinib and certolizumab were classified as lower efficacy medications. The panel considered both the relative efficacy of therapies in induction and maintenance of clinical remission when considering categorization, though emphasis was placed on effect estimates at the end of induction for categorization. The lower efficacy of upadacitinib in biologic-naïve patients was noteworthy, especially given a significantly higher efficacy in patients with prior exposure to TNF antagonists. It is unclear what drives these differences. In pivotal trials, striking differences were observed in the efficacy of upadacitinib vs. placebo based on disease location – while upadacitinib was highly effective in patients with isolated colonic disease, there was no significant efficacy signal in patients with ileal CD

There are several factors that should be considered when implementing the recommendations of the panel with regards to positioning therapies in advanced-therapy naïve individuals. First, while the panel focused on the induction of clinical remission in advanced therapy recommendations, there are multiple other factors that both patients and providers should consider. Individual patient factors, such as age, active and prior comorbidities, frailty, and interest in future pregnancy, as well as preferred route of administration, cost considerations, and ease of access, should be incorporated into a shard decision framework. Comparative efficacy of different medications based on specific disease phenotypes, such as disease location (small bowel dominant vs. colon-dominant), behavior (inflammatory vs. fibrostenotic and penetrating), and burden of inflammation (moderate vs. severe), etc. is unclear, and may drive choice of therapies once such data is available. Such data are still sparsely reported from clinical trials limiting evidence synthesis.

While clinical trial data demonstrated minimal differences in serious infections and SAEs, it is important to recognize such studies are underpowered for measuring effect estimates for such events. When considering individual patient decision-making, there may be specific patients at higher risk for treatment related complications. These patients and their providers may place higher value on safety-related considerations when choosing a therapy.

Lastly, it is important to incorporate family planning into conversations regarding advanced therapies as well. All agents categorized as higher efficacy are currently felt to be safe in pregnancy and lactation, with robust data supporting this for TNF antagonists, vedolizumab, and ustekinumab via registries such as PIANO.[78] While not the primary focus of the data review, the

committee members felt that it was appropriate to extrapolate these recommendations to newer IL23p19 antagonists as well, while formal data supporting this are forthcoming. There are, however, concerns related to the use of JAK inhibitors in pregnancy at this time, as there are limited human data demonstrating safety and some animal models suggesting increased risk[79]. Providers and their patients should carefully consider available therapeutic agents and their risks when individualizing a therapeutic plan; panel members agreed that it would be reasonable at this time to avoid JAK inhibitors in women contemplating pregnancy in the near future.

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 remission are important treatment goals for moderate-to-severe CD. 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 largely consistent with clinical remission endpoints where available, though magnitude of benefit in achieving endoscopic outcomes was higher in trials comparing IL23p19 antagonists vs. ustekinumab. There was lack of systematic reporting of other endpoints particularly for older clinical trials that precluded using such data to inform relative positioning. Recent network meta-analyses of RCTs focusing on endoscopic remission and response outcome have also been conducted. In an analysis by Vuyyuru and colleagues, JAK inhibitors and IL23p19 antagonists were more efficacious than etrolizumab, a lymphocyte trafficking inhibitor, and JAK inhibitors were more efficacious than IL12/23p40 antagonists for inducing endoscopic response. JAK inhibitors and IL23p19 antagonists ranked highest for induction of endoscopic response. On network meta-analysis of six RCTs, all agents except vedolizumab were effective in maintaining endoscopic remission compared with placebo. TNF antagonists, IL12/23p40 antagonists, and JAK inhibitors were ranked highest for maintenance of endoscopic remission. Findings from NMA of endoscopic outcomes though should be interpreted with caution. There was paucity of RCTs of TNF antagonists reporting endoscopic outcomes with induction therapy – these agents have been well-established to induce endoscopic remission in observational studies. Moreover, these results were not consistently stratified by prior exposure to advanced therapies, which can influence magnitude of benefit.

3.2.6 Evidence Gaps and Future Research

The guideline panel employed NMA methods in order to inform advanced therapy positioning in these recommendations, comparing multiple placebo-controlled trials and four active comparator trials. It is important to reiterate that there are several evidence gaps to consider in this approach. There may be baseline heterogeneity across trials in in terms of patients such as differences in disease location, duration, behavior, and prior failure of IBD-directed therapies, that is not fully adjusted for in this approach, Additionally, inherent differences in trial design may influence the NMA's findings. While we attempted to control for one such factor through stratification (re-randomization vs treat straight through designs), it remains possible that other trial features may differ across studies that could impact our findings. Lastly, while the best prospective clinical trial data to date was used to inform this model, it will be important to continue to re-evaluate the positioning of these therapies as future active comparator data become available, and longer-term observational studies characterizing the adverse event profiles of each therapy and class become available or more recently FDA-approved treatments.

Future research priorities should target these gaps. For example, large scale, pragmatic studies comparing different therapies both in advanced therapy naïve and exposed individuals would serve to inform therapy positioning, while also incorporating more heterogenous patient populations than those routinely included in current studies, accounting for real world dose escalation strategies across multiple potential outcomes of interest (remission, response, endoscopic endpoints, and adverse events). Such studies would ideally identify ideal first-line therapies when considering specific disease characteristics, as well as address knowledge gaps such as TNF antagonist use after failure of another advanced therapy or differential efficacy of upadacitinib after failure of a first-line IL-12/23 antagonist or IL-23p19 antagonist in relation to TNF antagonist.

3.3 POSITIONING OF ADVANCED THERAPIES IN INDIVIDUALS WHO HAVE BEEN EXPOSED TO ADVANCED THERAPIES

Question 3: In adult outpatients with moderate-to-severely active Crohn's disease who have been exposed to advanced therapies, what is the comparative efficacy of infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, upadacitinib, risankizumab, mirikizumab and guselkumab for induction and maintenance of remission?
Recommendation 4: In adult outpatients with moderate-to-severely active Crohn's disease who have previously been exposed to one or more advanced therapies,

particularly TNF antagonists, the AGA suggests using a HIGHER efficacy medication (adalimumab, risankizumab, guselkumab, upadacitinib) OR an INTERMEDIATE efficacy medication (ustekinumab, mirikizumab), rather than a LOWER efficacy medication (vedolizumab, certolizumab pegol). *[Conditional recommendation, low to moderate certainty of evidence]*

Implementation considerations:

- *Second-line TNF antagonists (especially infliximab or adalimumab) are effective in patients who discontinued their first TNF antagonist either due to secondary loss of response due to immunogenicity or intolerance. They may not be effective in patients with primary non-response to TNF antagonists, and alternative mechanisms of action should be considered.*
- *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.*
- *Some patients, such as those with multiple prior biologic failures, may require longer duration of induction therapy for response.*
- *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).*
- *There is limited data on the safety of JAK inhibitors in pregnancy. These drugs should be avoided in women of childbearing age contemplating pregnancy in the near future.*

3.3.1 Source of Evidence

The evidence used to inform therapy positioning for those who have been exposed to a prior advanced therapy with moderate-to-severely active CD has been summarized in our accompanying NMA. These analyses included eight placebo-controlled trials of anti-TNFs, three trials assessing vedolizumab, three trials of ustekinumab, nine trials assessing anti-IL-23p19s, and three trials of upadacitinib, as well as two head-to-head-trials and five trials of IL-23p19 antagonists that included both placebo and an active comparator (ustekinumab). As with the analyses presented for advanced therapy naïve individuals, analyses were conducted stratified by re-randomization versus treat-straight-through design.

3.3.2 Benefits

Overall, the panel agreed that a ≥5% risk difference over an active comparator was clinically meaningful. When considering the results of the NMA, adalimumab demonstrated probably important benefit compared with vedolizumab (moderate certainty of evidence) and possibly important benefit compared with mirikizumab (low certainty of benefit) in advanced therapy exposed individuals. Risankizumab demonstrated probable important benefit compared with both vedolizumab and ustekinumab (moderate certainty of evidence), and possibly important benefit

compared with mirikizumab (low certainty of evidence). Guselkumab demonstrated probably important benefit compared with vedolizumab, ustekinumab, and mirikizumab (moderate certainty of evidence). Ustekinumab demonstrated possibly important benefit compared with vedolizumab (low certainty of evidence). Upadacitinib demonstrated possibly important benefit compared with vedolizumab and mirikizumab (low certainty of evidence). Importantly, there was no RCT data to inform positioning infliximab among advanced therapy exposed individuals.

When examining studies with a treat-straight-through design and follow-up to weeks 48 to 52, risankizumab demonstrated important benefit compared with ustekinumab (high certainty of evidence), and possibly trivial benefit compared with guselkumab 100 mg every 8 weeks (low certainty of evidence). Both guselkumab 200 mg every 4 weeks and 100 mg every 8 weeks demonstrated probable important benefit compared with ustekinumab every 8 weeks (moderate certainty of evidence). Lastly, mirikizumab demonstrated possibly important benefit compared with ustekinumab (low certainty of evidence).

3.3.3 Harms

Potential adverse events associated with advanced therapies included in this guideline have been previously discussed. The panel agreed that while there may be small differences among adverse event and infectious rates among therapies included in the NMA, that these risks were likely trivial across drug classes, and unlikely to inform choice of therapy for most patients. As noted when considering therapy selection in advanced therapy-naïve individuals, any therapeutic decision making that considers safety events must also balance these factors against the potential for immediate and longer-term consequences of incomplete disease control. This is particularly relevant in those who have already had an inadequate response or treatment-related complications and thus are more likely to experience harm with delays in appropriate therapy.

3.3.4 Certainty in Evidence of Effects

The certainty of evidence for all pairwise comparisons of advanced therapies ranged from low to moderate, as described above. The only exception to this was the high certainty of evidence noted for important benefit of risankizumab over ustekinumab when considering treat-straight-through trials.

3.3.5 Discussion

To aide clinicians in clinical decision making, and in the context of potential intra-class differences among specific therapies in IBD, the panel rated each therapy individually as opposed to grouping

by therapeutic class. As discussed related to advanced therapy-naïve individuals (see 3.2.3), the guideline felt it appropriate to consider grouping available therapies into therapeutic categories using criteria that were defined *a priori*. These criteria included an absolute difference in efficacy in comparison to lower efficacy therapies of at least 5%, a p-score in the NMA of 0.49 to 1.0 in comparison to placebo, and an absolute difference in phase 3 clinical trials for that agent of ≥10% against placebo. A smaller absolute difference was felt to be more appropriate for advanced therapy exposed individuals than in naïve individuals. Three therapeutic groups were constructed, including “higher efficacy”, “intermediate efficacy”, and “lower efficacy”. Inclusion in the higher efficacy group required meeting all three criteria noted above. Using these criteria, adalimumab, risankizumab, guselkumab, and upadacitinib were considered higher efficacy, ustekinumab and mirikizumab were considered intermediate efficacy, and vedolizumab and certolizumab pegol were considered lower efficacy therapies. Importantly, the panel recommended that, when selecting an advanced therapy, it would be appropriate to consider either a higher efficacy or intermediate efficacy medication over a lower efficacy therapy.

There are several factors to consider in the implementation of these recommendations. First, it is important to note that in the clinical trials included in this systematic review and NMA, almost all enrolled individuals had been exposed to a TNF antagonist. Therefore, there are currently limited data to inform therapy selection in those whose prior failure consisted of a non-TNF antagonist. Additionally, the results of the NMA are stratified by any prior advanced therapy. It is possible that the efficacy of given therapies decreases with the number of prior failures to advanced therapies; unfortunately, the published data regarding this potential effect are limited at this time. There are no RCT data regarding the positioning of infliximab in individuals who are advanced therapy exposed. The panel felt it would be reasonable to extrapolate recommendations from adalimumab when considering infliximab, however, and this is supported by some observational data demonstrating preserved efficacy after failure of one advanced therapy[80,81]. On the contrary, evidence for adalimumab in bio-exposed patients is largely derived from the GAIN trial which specifically included individuals who had responded to infliximab and subsequently developed intolerance or lost response, thereby a population that may be biased towards responsiveness to this class of medications.

When clinicians are considering second-line advanced therapies or beyond for moderate-to-severely active CD, they should also consider if the prior failure was secondary to immunogenicity. Second-line TNF antagonists have been shown to be effective in the setting of primary TNF antagonist failure due to anti-drug antibody formation, which can be more common with this class of therapies than other therapies. However, in those that have lost response to a

TNF antagonist without evidence of anti-drug antibodies, an alternative class of therapies should be considered.

As discussed previously with advanced therapy-naïve individuals, treatment selection for those who have failed advanced therapies should incorporate a careful consideration of individual patient factors, including but not limited to age, active or prior comorbidities, frailty, and medication access, and interest in future pregnancy. Patients' preferences with regards to preferred route of administration should be considered within this shared decision-making framework. Also, there may be variability with regards to the risks of adverse events or serious or opportunistic infections with specific medication classes. As noted above, medication selection when incorporating these factors into decision-making should also be coupled with consideration of potential risks in delays in clinical response and the possibility for short- and long-term disease related complications. With decreasing efficacy, there may be the potential for longer time periods for onset of action, which may expose individuals to prolonged periods of reduced quality of life or extended courses of corticosteroids, particularly in those with more severe disease or a higher number of prior advanced therapy failures.

Lastly, it is important to recognize that JAK inhibitors such as upadacitinib may possess a unique risk profile in comparison to other therapies. Specifically, this class may be associated with an increased risk of major adverse cardiovascular events (MACE). Prior observational research of another JAK inhibitor, tofacitinib, demonstrated a potential increased risk of MACE and venous thromboembolic events, as well as malignancy, in those using tofacitinib 10 mg bid.[82] It is important to consider the patient population in which this signal was detected to place these findings in context: the cohort consisted of individuals with rheumatoid arthritis who were 50 years of age or older, with at least one cardiovascular risk factor (i.e. prior cardiovascular or coronary artery disease, tobacco use, high density lipoprotein <40 mg/dL, a history of DM, family history of coronary heart disease, extra-articular rheumatoid arthritis). Therefore, these drugs should be used with caution in patients at high risk for atherosclerotic cardiovascular disease. Additionally, there are currently limited data regarding the safety of this class of therapies in pregnancy and lactation. Therefore, most experts agree that JAK inhibitors should generally be avoided in women contemplating pregnancy in the near future until more human data is available.

3.3.6 Evidence Gaps and Future Research

There are several knowledge gaps and opportunities for future research. There remains a lack of robust head-to-head clinical trial data comparing therapies in those with prior advanced therapy exposure. Fortunately, this is changing over time, with two recent head-to-head studies as well as

several new IL-23p19 antagonists including active comparators in their RCTs. These studies should incorporate not only clinical remission-related outcomes, but alternative outcomes including endoscopic remission, reduced rates of healthcare utilization and/or surgery, and impacts on quality of life. Second, trials assessing treatment sequencing, both for first-line therapies as well as second line therapies are needed to guide clinicians in managing moderately-to-severely active CD longitudinally. Such studies may help confirm the efficacy of JAKs such as upadacitinib as first or second line therapies and explore the biologic underpinnings of differential efficacy that appears to be dependent on such positioning. Third, while many clinical trials enroll patient populations with significant prior advanced therapy exposure, the majority of these prior exposures are to TNF antagonists. It is unclear if remission and response rates to non-TNF antagonist exposed individuals are similar. Lastly, the long-term safety profile of newer classes of therapies, in particular JAK inhibitors and IL-23p19 antagonists, is incompletely understood at the time of this guideline development. While clinical trial safety data are reassuring, these studies are also almost certainly underpowered for safety signals related to rare events, and further research is indicated.

3.4 USE OF IMMUNOMODULATORS

Question 4: In adult outpatients with moderate-to-severely active Crohn's disease, what is the efficacy of immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of remission?
Recommendation #5: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA suggests AGAINST using thiopurines monotherapy over no treatment for inducing remission. [*Conditional recommendation, very low certainty evidence*] **Recommendation #6: In adult outpatients with moderate-to-severely active Crohn's disease who have achieved remission, the AGA SUGGESTS using thiopurine monotherapy over no treatment for maintaining remission. [***Conditional recommendation, low certainty evidence***]** **Recommendation #7: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA SUGGESTS using subcutaneous or intramuscular methotrexate monotherapy over no treatment. [***Conditional recommendation, moderate certainty evidence*] **Recommendation #8: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA suggests AGAINST using oral methotrexate monotherapy over no treatment. [***Conditional recommendation, very low certainty evidence*]

Implementation considerations:

- *The typical dose of thiopurines is 2.0-2.5 mg/kg/day for azathioprine and 1.0-1.5 mg/kg/day for mercaptopurine when used as monotherapy for those with normal drug metabolism.*
- *In clinical trials of thiopurines for preventing relapse in patients who achieved remission, remission was typically induced with corticosteroids.*
- *The typical dose of methotrexate is 25 mg weekly during induction for 16-24 weeks, and 15 mg weekly for maintenance. Methotrexate should be accompanied by daily folic acid supplementation.*
- *Routine monitoring of complete blood counts and liver function tests is recommended when using thiopurines and methotrexate*
- *Use of methotrexate is contraindicated in women actively considering pregnancy.*

3.4.1 Source of Evidence

In order to inform the recommendations related to induction of remission of moderate-to-severely active CD with thiopurines, data from six clinical trials were included.[83-88] One trial of thiopurines for induction and maintenance of remission in pediatric CD was added since the last guidelines published in 2021.[88] For maintenance of remission with thiopurines, we used data from six trials.[27,83,87-90]

For induction of remission with methotrexate, we identified one RCT of subcutaneous methotrexate[91] (unchanged from previous guideline) and two RCTs of oral methotrexate[85,92] (one additional trial from previous guideline). In the two trials of oral methotrexate, the dose of methotrexate ranged from a fixed dose 12.5 mg weekly to 15 mg weekly escalated to 22.5 mg weekly in case of suboptimal response. For maintenance of remission with methotrexate, we identified one RCT of subcutaneous methotrexate and one RCT of oral methotrexate.[85,93]

3.4.2 Benefits

Thiopurines: Across the 6 trials assessing induction of remission with thiopurines, 380 individuals were enrolled. On meta-analysis of these studies, thiopurines were not more likely to induce clinical remission (RR 1.11; 95% CI, 0.96-1.30) (**eFigure 10A**). Across five trials of maintenance of remission with thiopurines, 347 individuals were enrolled. On meta-analysis, thiopurines were associated with maintenance of remission (RR 1.23; 95% CI, 1.00-1.50) (**eFigure 10B**).

Subcutaneous methotrexate: In a clinical trial of 141 individuals with CD, patients treated with subcutaneous methotrexate (25 mg per week) were more likely to achieve remission (RR 2.06; 95% CI 1.09-3.89).[91] In another trial of 76 patients, subcutaneous methotrexate (15 mg per week) was more effective compared with placebo in preventing relapse in patients who achieved clinical

remission with 16-24 weeks of open-label subcutaneous methotrexate (25 mg per week) (RR 1.67; 95% CI, 1.05-2.67).[93]

Oral methotrexate: In two clinical trials, oral methotrexate was not more effective than placebo in inducing remission (RR 0.77; 95% CI, 0.55-1.08).[85,92] In one clinical trial, oral methotrexate 12.5 mg weekly was not more effective than placebo in preventing relapse in patients with CD in remission (RR 1.35; 95% CI, 0.86-2.12).

3.4.3 Harms

The risks associated with thiopurines and methotrexate are well characterized. For thiopurines, these risks include hepatotoxicity, pancreatitis, bone marrow suppression, non-melanoma skin cancers, and lymphoproliferative disorders. Methotrexate is also associated with non-melanoma skin cancer, can cause marrow suppression or drug induced liver injury, has been associated with lymphoma, and is also associated with both pulmonary and hepatic fibrosis with long-term use.[20,21,59,94-97] Methotrexate should also be avoided in women contemplating pregnancy due to its teratogenicity. There are also risks of selecting ineffective therapies for moderate-to-severely active Crohn's disease, with the potential for increased risks of disease-related complications.

3.4.4 Certainty in Evidence of Effects

The overall benefit of thiopurines for inducing remission was uncertain with very low certainty of evidence (**Table 10**). Evidence was rated down for risk of bias due to inadequate blinding and allocation concealment, indirectness due to concomitant corticosteroid use during induction, heterogeneity in outcome definitions, and imprecision. For maintenance of remission with thiopurines, the certainty of evidence was rated as low, and was rated down for risk of bias as well as imprecision. The certainty of evidence supporting the use of subcutaneous methotrexate for inducing and maintaining remission was moderate, rated down for imprecision since the 95% CI crossed the clinically meaningful benefit of 10% compared with placebo (**Table 11**). The overall certainty of evidence supporting the use of oral methotrexate was very low, rated down for indirectness (low dose of oral methotrexate used in one trial, variability in outcome definition) and very serious imprecision (**Table 11**). The GRADE evidence-to-decision judgements are presented in **Table 12**.

3.4.5 Discussion

In weighing benefits and harms associated with thiopurines, the panel suggested against the use of thiopurines for induction of remission but suggested its use for maintenance of remission in

patients with quiescent CD. Thiopurines have a slow onset of action, potentially requiring concomitant corticosteroids for induction while also delaying the use of appropriate advanced therapies. Real-world studies and previously published systematic reviews and meta-analyses have confirmed the benefit of azathioprine when used to maintain remission in CD,[98] and the studies included in our analyses demonstrated a benefit as well.

With regards to methotrexate, there was moderate certainty evidence supporting the use of subcutaneous methotrexate for both induction and maintenance of remission. For induction, this was informed by one study utilizing 25 mg per week, whereas for maintenance of remission, the single trial evaluated used 15 mg per week. In contrast, the data supporting oral dosing of methotrexate was less robust, with the available studies showing no benefit for either inducing or maintaining remission, but with limited sample sizes for adequate assessment.

There are several implementation considerations with regards to these recommendations. First, before considering thiopurine use it is important to consider laboratory assessment to ensure their safe use. AGA guidelines recommend the routine use of thiopurine methyltransferase testing,[99] as well as baseline and close subsequent monitoring of complete blood counts and liver function tests. When using azathioprine as monotherapy, the typical dose is 2.0-2.5 mg/kg/day and for 6-mercaptopurine, 1.0-1.5 mg/kg/day.

When considering the use of methotrexate for induction and maintaining remission, baseline assessment of complete blood counts and liver function tests is also reasonable. Methotrexate use should also be coupled with daily oral folic acid supplementation to minimize the potential for folate deficiency and symptoms secondary to this. Traditional folic acid dosing is 1mg orally daily. Routine subsequent laboratory monitoring is advised while using methotrexate. Given its known teratogenicity, counselling regarding avoiding pregnancy and contraception is also advised. Lastly, it is reasonable to counsel patients regarding the potential for gastrointestinal side effects and fatigue. While these symptoms are common and may impact quality of life, patients may value the risks of some adverse events over others, including those related to inadequate control of disease.

3.4.6 Evidence Gaps and Future Research

There are several evidence gaps that should prompt future research. It is important to note that while subcutaneous methotrexate was found to be beneficial in these analyses, the trial population in which these effects were studied is likely different than the modern cohort of patients with moderate-to-severely active CD entering clinical trials. In these prior methotrexate studies, enrolled individuals were treatment naïve. It is unclear if similar benefits would be appreciated in

those with prior CS or thiopurine failures, consistent with many individuals entering clinical trials for advanced therapies. There is also likely a role for comparative effectiveness and long-term safety trials comparing subcutaneous methotrexate to biologic or small molecule therapies, as methotrexate may still have a substantive role to play in the management of moderate-to-severely active CD in resource limited settings.

3.5 COMBINATION THERAPY WITH TNF ANTAGONISTS AND IMMUNOMODULATORS

Question 5: In adult outpatients with moderate-to-severely active Crohn's disease, is combination therapy of TNF antagonists with an immunomodulator (thiopurines or methotrexate) superior to TNF monotherapy or immunomodulator monotherapy for induction and maintenance of remission?

Recommendation #9: In adult outpatients with moderate-to-severely active Crohn's disease who are naïve to thiopurines and starting infliximab, the AGA SUGGESTS using infliximab in combination with thiopurines rather than infliximab monotherapy. [*Conditional recommendation, low certainty of evidence***]**

Recommendation #10: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA makes NO RECOMMENDATION on using infliximab in combination with methotrexate over infliximab monotherapy. [*No recommendation, knowledge gap***]**

Recommendation #11: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA makes NO RECOMMENDATION on using adalimumab in combination with thiopurines or methotrexate over adalimumab monotherapy. [No recommendation, knowledge gap**]**

Implementation Considerations:

- *The benefit of routinely combining immunomodulators with TNF antagonists in patients who have previously failed immunomodulator monotherapy is uncertain.*
- *There may be benefits of adding immunomodulators when starting TNF antagonists in specific situations where patients may be at a higher risk for immunogenicity. These include patients with prior history of immunogenicity with a TNF antagonist, patients being re-exposed to TNF antagonists after a drug holiday, patients carrying HLA-DQ-A1*05 variants and patients with high drug clearance such as those with more severe disease, high burden of inflammation, low albumin, etc.*

3.5.1 Source of Evidence

Four clinical trials informed the evidence assessing the benefit of combination TNF antagonists and immunomodulators, one of which had been published since the prior guidelines. Of these studies, two focused on infliximab (one in combination with azathioprine, one in combination with methotrexate), one focused on adalimumab in combination with azathioprine, and the last

included both infliximab or adalimumab in combination with methotrexate.[100-103] Three of these studies focused on adult populations, whereas one included pediatric patients. Across these trials, follow-up times for both induction of remission (ranging from 10 to 16 weeks after treatment initiation) and maintenance of remission (ranging from 26 to 52 weeks) was variable.

3.5.2 Benefits

Two trials focused on the combination of infliximab and an immunomodulator. The SONIC trial randomized 508 biologic- and immunomodulator-naïve adults with moderate-to-severely active CD to combination infliximab plus azathioprine (n=169) vs. infliximab monotherapy (n=169) vs. azathioprine monotherapy (n=170).[101] Combination therapy with infliximab and azathioprine was associated with higher rates of remission during induction (RR 1.29; 95% CI, 1.03-1.54), and sustained remission at 26 weeks (RR, 1.28; 95%CI, 1.03-1.59). The COMMIT trial compared 63 individuals randomized to receive combination therapy with infliximab plus methotrexate (dosing ranging from 10 mg to 25 mg weekly) to 63 individuals receiving infliximab monotherapy, employing a treat-straight-through design[102]. While individuals were advanced therapy naïve, up to 25% in each arm had received prior thiopurine therapy. At week 14, there was no significant difference between each arm (RR, 0.98; 95%CI, 0.81-1.19), and this persisted through maintenance at week 50 (RR, 0.97; 95% CI, 0.71-1.32).

One RCT assessed combination therapy with adalimumab and azathioprine compared to adalimumab monotherapy. The DIAMOND trial randomized 91 individuals to combination therapy and 85 to adalimumab monotherapy in an open label trial with a treat-straight-through design.[103] Enrolled individuals were naïve to TNF antagonists and immunomodulators. There was no difference between the treatment arms for induction of clinical remission (RR, 0.85; 95% CI, 0.70-1.03) or in maintenance of clinical remission at 52 weeks (RR, 0.95; 95% CI, 0.75-1.21). Combination therapy was associated with higher rates of endoscopic remission at week 26 (84.2% vs 63.2%, p=0.02), though when analyzing the subgroup with both endoscopic evaluation at randomization and at week 52, no differences were appreciated in endoscopic remission (79.6% vs 69.8%, p=0.36). This study was open label design and had a high drop-out in the combination therapy arm: by week 26, 15 (16.5%) individuals receiving combination therapy and 1 (1.2%) receiving monotherapy had dropped out. Such high rates of treatment-related drug withdrawals have not been observed with prior trials of thiopurine or combination therapy with infliximab.

One study in pediatrics was reviewed in the panel's analyses that was not included in the prior guidelines. The COMBINE trial randomized 297 children with CD starting infliximab or

adalimumab to either adding low dose oral methotrexate vs. placebo and followed them over for 12-36 months.[100] Enrolled individuals were TNF antagonist naïve but could have previously been exposed to thiopurines or methotrexate, with prior exposure rates ranging from 12-17%. The outcome was failure to achieve or maintain steroid-free remission defined as a composite of failure to achieve remission (Short Pediatric Crohn's Disease Activity Index [SPCDAI] < 15) by week 26, failure to complete a steroid taper by week 16, SPCDAI ≥15, attributed to active Crohn's disease, at two or more consecutive visits beyond week 26, hospitalization or surgery for CD beyond week 26, use of corticosteroids for CD for ≥ 10 weeks cumulatively, beyond week 16 and/or discontinuation of TNF antagonists and/or study drug for lack of effectiveness or toxicity. A total of 40/156 participants (26%) in the combination therapy group and 48/141 participants (34%) in the monotherapy group experienced treatment failure (HR 0.69; 95% CI, 0.45-1.05). The most common component of the composite endpoint experienced by study participants was hospitalization for active IBD after week 25. On pre-specified subgroup analysis, the risk of treatment failure with combination therapy was lower in adalimumab-treated patients (combination therapy vs. adalimumab monotherapy: 11/46 vs. 20/39; HR, 0.40; 95% CI, 0.19-0.82), but not in infliximab-treated patients (combination therapy vs. infliximab monotherapy: 29/110 vs. 28/102; HR, 0.69; 95% CI, 0.45-1.05).

3.5.3 Harms

The potential risks of both TNF antagonists and immunomodulators when used as monotherapy have been described previously. While underpowered to assess rare outcomes, the data from the four clinical trials assessed for this guideline were reassuring with regards to SAE risk. In SONIC and COMMIT, there were no statistically significant differences in SAEs for combination therapy compared to TNF antagonist monotherapy.[101,102] In COMMIT, there was a numerical increase in overall adverse events with combination therapy, but the rate of SAEs remained similar between groups (11% vs 15%). Discontinuation rates in DIAMOND were high (22-24%), and adverse events associated with combination therapy were higher than with TNF antagonist monotherapy (16.5% vs 1.2%).[103]

Large observational studies with longer follow-up suggest a higher risk of serious infections and lymphoma and non-melanoma skin cancers with combination therapy in contrast to TNF antagonist monotherapy.[59,104,105]

3.5.4 Certainty in Evidence of Effects

The certainty of evidence for induction of remission with combined TNF antagonist and immunomodulator therapy in comparison to monotherapy was felt to be very low, and was rated down due heterogeneity in treatment effects, patient populations, and study design, as well as for very serious imprecision (**Table 13**). The quality of the evidence for maintenance of remission with combination TNF antagonist and immunomodulator therapy was rated as low quality of evidence, due to heterogeneity and serious imprecision. The GRADE evidence-to-decision judgements are presented in **Table 14**.

3.5.5 Discussion

When examining the totality of evidence, the magnitude of benefit with the combination of TNF antagonists with immunomodulators over TNF antagonist monotherapy was uncertain (**eFigure 11**). However, there were differences in trial design, patient population (prior exposure to immunomodulators) and interventions (concomitant treatment with corticosteroids at trial entry). Hence, the guideline panel opted to examine each trial in isolation and issue separate recommendations for specific combinations of therapy. Based on the SONIC trial, combination therapy of infliximab plus azathioprine is probably beneficial in achieving remission compared with infliximab monotherapy in infliximab- and immunomodulator-naïve patients. Based on the DIAMOND trial, the benefit of combining adalimumab with thiopurines vs. adalimumab monotherapy was uncertain for achieving remission, although rates of achieving endoscopic remission were higher with combination therapy. In contrast, based on the COMMIT and COMBINE trials, the benefit of combination of infliximab and adalimumab with methotrexate over corresponding monotherapy was uncertain.

There are several mechanisms by which combining TNF antagonists with an immunomodulator may increase the effectiveness of the TNF antagonist. First, immunomodulators have their own efficacy in treating CD, as discussed previously. This may result in an additive effect and may also in part explain why those who have previously failed immunomodulators before beginning combination therapy may not experience as robust a benefit[100,102]. This may explain differential findings appreciated across studies reviewed here: combination therapy demonstrated clinical benefit in SONIC, where individuals were treatment naïve, but no clear benefit was appreciated in COMMIT or COMBINE, where there was prior immunomodulator exposure. This has also been observed in regulatory clinical trials of TNF antagonists where no differences in treatment efficacy have been observed in subsets of patients

who were vs. were not on concomitant immunomodulators at time of trial enrollment; of note, all patients on concomitant immunomodulators in these trials were required to have moderate-to-severe activity despite immunomodulator monotherapy[106].

Second, immunomodulators decrease the risk of immunogenicity to TNF antagonists and may favorably alter pharmacokinetics leading to higher trough concentration. Recent studies have identified HLA-DQ-A1*05 as a genetic risk factor associated with increased the risk of immunogenicity, where the addition of an immunomodulator may be associated with lower risk of clinical failure and immunogenicity.[107,108] In a clinical trial of 98 patients with IBD with immune-mediated loss of response to prior TNF antagonists, addition of azathioprine at time of starting a second TNF antagonist was associated with markedly lower rates of clinical failure and unfavorable pharmacokinetics, compared with initiation of TNF antagonist monotherapy[109]. In these instances, combination therapy with immunomodulators may decrease risk of immunogenicity with TNF antagonists and may be preferred.

3.5.6 Evidence Gaps and Future Research

Several evidence gaps should be addressed through future research. While the guideline committee recommends the use of combination thiopurines with infliximab, particularly in those without prior thiopurine failure, there are limited data to guide clinicians regarding the ideal duration of combination therapy, or with optimal thiopurine dosing. There is significant practice heterogeneity regarding the use of traditional weight-based dosing for thiopurines. While retrospective data suggest that 6-thioguanine (6TGN) metabolite concentrations likely correlate with TNF-antagonist trough concentrations, the required concentration may be lower than that achieved in many individuals receiving 2.0 to 2.5 mg/kg of azathioprine (1.0 to 1.5 mg/kg 6-mercaptopurine), with one study suggesting a trough concentration greater than 125 pmol/8x10^8 red blood cells being adequate[110]. This is only further confounded by the TNF-antagonist being used, as the effects may be differential for adalimumab in comparison to infliximab[111]. Future prospective randomized controlled trials could better determine the clinical implications of these differences, as well as to identify the differences in duration of combination therapy, with significant interest among both patients and providers in future de-escalation.

While these guidelines provide specific recommendations related to the use of immunomodulators with TNF antagonists, they do not specifically address the emerging utilization of biologic and small molecule therapies in combination with each other. There is an emerging number of observational studies assessing combining these agents, which thus far have had reassuring safety and efficacy estimates. There are also future ongoing clinical trials assessing

this approach in inflammatory bowel disease. Future studies will serve to better describe in whom this approach is most advantageous, which combinations may be most effective based on mechanism of action, and in whom the risks may outweigh the benefit.

3.6 COMBINATION THERAPY WITH NON-TNF ANTAGONISTS AND IMMUNOMODULATORS

Question 6. In adult outpatients with moderate-to-severely active Crohn's disease, is combination therapy of a non-TNF-targeting biologic with an immunomodulator (thiopurines or methotrexate) superior to TNF monotherapy or immunomodulator monotherapy for induction and maintenance of remission?
Recommendation 12: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA makes NO RECOMMENDATION in favor of, or against using non-TNF-targeting biologics (vedolizumab, ustekinumab, risankizumab, mirikizumab, guselkumab) in combination with thiopurines or methotrexate or corresponding biologic monotherapy. [No recommendation, knowledge gap**]**

3.6.1 Summary of the Evidence

There are currently no RCTs comparing combination therapy with a non-TNF-targeting biologic and an immunomodulator to monotherapy with non-TNF-targeting biologic. However, several post-hoc analyses from clinical trials and observational studies have assessed the impact of concomitant immunomodulators in combination with vedolizumab or ustekinumab. These subgroup analyses were assessed for the purposes of this guideline. In GEMINI, approximately 33% (n=370) of individuals randomized to receive vedolizumab or placebo were also concurrently receiving an immunomodulator or an immunomodulator in combination with corticosteroids.[41] Similar rates of immunomodulator use were seen in clinical trials of ustekinumab (~33%, n= 304).[46] Multiple observational studies have assessed if the use of combination therapy with non-TNF-targeting biologics results in improved rates of remission as well. For example, a multi-center cohort study followed 546 individuals with IBD (CD = 286) who initiated vedolizumab or ustekinumab for one year, with 251 receiving combination therapy with either a thiopurine or methotrexate.[112] Similarly, a recently published meta-analysis included 2,053 individuals with CD across 33 studies, combining both 6 RCTs with 28 observational studies.[113]

3.6.2 Benefits

There have been heterogenous results regarding the benefits of combination therapy of a non-TNF-targeting biologics and immunomodulators in clinical trials. In subgroup analyses examining individuals receiving immunomodulators in combination with vedolizumab in GEMINI, there were similar rates of remission in those receiving immunomodulators compared to those who did not at 10 weeks (32.4% vs 26.8%).[42] Similarly, there were variable differences in response rates in those receiving an immunomodulator versus not, when stratified by concomitant steroids at week 6 for ustekinumab in UNITI[46]. Meta-analyses and observational data to date suggest that there may be no benefit of combining an immunomodulator with a non-TNF-targeting biologic. In their observational cohort of 549 individuals initiating vedolizumab or ustekinumab, Hu and colleagues observed no difference in remission rates in those receiving combination therapy compared to monotherapy for either therapy.[112] In the meta-analysis conducted by Yzet and colleagues, incorporating data from 6 clinical trials as well as 28 observational studies, there was no significant difference between combination therapy and monotherapy for vedolizumab (OR, 0.84; 95% CI, 0.68-1.05) or ustekinumab (OR, 1.10; 95% CI, 0.87-1.38).[113] Given their recent FDA approval, there remains a paucity of data regarding IL-23p19 antagonists.

3.6.3 Harms

There are limited available data regarding the rates of adverse events when receiving combination therapy with non-TNF antagonists and immunomodulators. Subgroup analyses from clinical trials as well as observational studies to date demonstrate no significant increase in serious infection or other SAEs, though long-term follow-up are lacking and it would be appropriate to consider the previously described risks of adverse events associated with immunomodulators.

3.6.4 Certainty in Evidence of Effects

The evidence reviewed was derived from *post-hoc* subgroup analyses of RCTs in patients who have previously failed immunomodulators, as well as systematic reviews and meta-analyses of observational studies, and was rated as very low.

3.6.5 Discussion

Due to uncertainty in the magnitude of benefit and harm, the panel felt this was a knowledge gap and did not issue a recommendation in favor of, or against, the use of combining non-TNF-targeting biologics and immunomodulators. One of the putative mechanisms through which addition of immunomodulators may enhance the effectiveness of biologic agents, by improving

pharmacokinetics of the biologic agent, may not apply to non-TNF-targeting biologics. As previously discussed, vedolizumab and ustekinumab appear to be less immunogenic than TNF antagonists.[114,115] In a multicenter retrospective cohort study of 369 patients with IBD, Yarur and colleagues examined the association between thiopurine exposure and pharmacokinetics of infliximab, vedolizumab and ustekinumab.[116] While concomitant thiopurines were associated with higher trough concentration of infliximab, there was no association between the use of immunomodulators and vedolizumab or ustekinumab trough concentrations, and risk of loss of response. The prevalence of anti-drug antibodies was <1% with vedolizumab and ustekinumab. However, alternatively, there may be other mechanisms by which immunomodulators may enhance the effectiveness of biologics. As seen in the SONIC trial, in immunomodulator- and biologic-naïve patients with CD, the combination of thiopurines and infliximab was more effective than infliximab monotherapy, with plausibly some benefit attributed to the independent therapeutic effect of thiopurines on CD. While such a trial does not exist for non-TNF-targeting biologics, real-world trial emulation studies comparing outcomes with combination therapy of vedolizumab and immunomodulators vs. vedolizumab monotherapy suggest lower risk of treatment failure with combination therapy in patients with CD.[117] Hence, the benefit of combination therapy of immunomodulators with non-TNF-targeting biologics is not well-defined.

There is limited role of combining immunomodulators with JAK inhibitors. Since there is no risk of immunogenicity with small molecule drugs, and there is a clearer dose-response relationship (rather than an exposure-response relationship), any purported benefit with adding immunomodulators is unlikely to be due to improving pharmacokinetics. In trials of upadacitinib in patients with CD, immunomodulators were discontinued prior to starting upadacitinib due to concern for side effects.

3.6.6 Evidence Gaps and Future Research

Clinical trials examining the efficacy and safety of combining non-TNF-targeting biologics with thiopurines and/or methotrexate vs. monotherapy with non-TNF-targeting biologics, in both immunomodulator-naïve and immunomodulators-exposed patients are warranted to inform this question.

3.7 DE-ESCALATION OF COMBINATION THERAPY

Question 7: In adult outpatients with moderate-to-severely active Crohn's disease in steroid-free remission on combination therapy of TNF antagonist + immunomodulator, is discontinuation of (a) an immunomodulator or (b) discontinuation of a TNF antagonist, inferior to continuation of combination therapy?

Recommendation 13: In adult outpatients with moderate-to-severely active Crohn's disease who are in corticosteroid-free clinical remission for at least 6 months on combination therapy of TNF antagonists and an immunomodulator, the AGA SUGGESTS withdrawing IMMUNOMODULATORS. [Conditional recommendation, low certainty of evidence**]**

> ***Comment:*** *Patients, particularly those with difficult-to-treat disease, who place a lower value on the trivial-to-small increase in risk of long-term side effects of continuing immunomodulators (such as risk of malignancy or infection), and a higher value on avoiding a trivial-to-small increase in risk of relapse with withdrawal of immunomodulators, may reasonably choose to continue combination therapy*

Implementation Considerations:

- *There may be benefit in continuing combination therapy with TNF antagonists and immunomodulators in those who are felt to be at higher risk of immunogenicity, such as those with prior immunogenic failure to a biologic therapy (i.e. anti-drug antibody formation), those with lower trough TNF antagonist concentrations despite dose escalation, or those with HLA-DQA1*05 carriage.*

Recommendation 14: In adult outpatients with moderate-to-severely active Crohn's disease 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, low certainty of evidence**]**

3.7.1 Source of Evidence

Seven RCTs were identified comparing withdrawal of either immunomodulators or TNF antagonists to continued combination therapy.[118-124] Five of these studies enrolled only individuals with CD.[118,120,121,123,124] In four of these trials, the primary intervention compared withdrawing an immunomodulator to continued combination therapy, while in two trials the primary intervention was TNF antagonist withdrawal. One trial included three arms, comparing immunomodulator withdrawal, TNF antagonist withdrawal, and continued combination therapy.[123] One trial included immunomodulator dose reduction.[119]

There was some heterogeneity regarding patients across these studies. Most patients enrolled in these studies were in corticosteroid-free remission for at least 6 months, with the average duration of remission exceeding 2 years; however, one included study of pediatric patients allowed clinical response.[120] Four of the reviewed studies required not only clinical remission but also biochemical and/or structural remission at randomization. Prior

immunomodulator use/failure was also variable, with one study including individuals who had all failed an immunomodulator, another where all were immunomodulator naïve, and two studies not reporting results stratified by this prior exposure[118-121]; one study reported no significant difference when stratifying results among those who had or had not been previously immunomodulator exposed.[123] Follow-up time was also variable across studies, ranging from 12 to 24 months.

3.7.2. Benefits

Immunomodulator Withdrawal: In total, 404 individuals from 5 studies were included in a meta-analysis of immunomodulator withdrawal (202 with withdrawal, 202 with continued combination therapy). There was no significant difference in the overall risk of relapse with immunomodulator withdrawal compared to continued combination therapy (16.8% vs 14.9%; RR, 1.15; 95% CI, 0.75-1.76) (**eFigure 12**).

TNF antagonist withdrawal: When examining outcomes related to TNF antagonist withdrawal, three trials were evaluated, with 339 individuals. The rate of clinical relapse was higher in those with TNF antagonist withdrawal than with continued combination therapy (30.6% vs 11.2%; RR, 2.23; 95% CI, 1.08-4.61) (**eFigure 12**).

3.7.3 Harms

Immunomodulator withdrawal: The risks associated with both immunomodulators and TNF antagonists, as well as of combination therapy, are discussed previously, and include increased risks of infection as well as malignancies including, but not limited to, non-melanoma skin cancer and lymphoproliferative disorders. In the included RCTs, six studies examined rates of SAE during follow-up and found no significant difference (immunomodulator withdrawal vs. continued combination therapy: (RR, 1.21; 95% CI, 0.68-2.17). However, it is important to emphasize that event rates were low, sample sizes were small, and duration of follow-up was limited to 12 to 24 months. One could hypothesize that withdrawing one of the two therapies may potentially mitigate the long-term risks of combination therapy. Several observational cohorts have demonstrated an increased risk of adverse events with combination therapy in relation to monotherapy. For example, several population-based studies have highlighted the increased risk of serious infections such as pneumonia over time with combination therapy in comparison to monotherapy.[125,126] More importantly, neoplastic risks may increase with cumulative exposure to combination therapy, such as the risk of lymphoproliferative disorders with combination TNF antagonist and thiopurine therapy.[59,97] This effect may be cumulative over time, with at least one

study demonstrating that the incidence rate of acute myeloid leukemia increased at least 2 years after thiopurine exposure in a cohort of patients with IBD.[127]

TNF-antagonist withdrawal: In the included RCTs, the risk of SAEs was similar between groups, though the number of events was relatively low (RR, 0.82; 95% CI, 0.36-1.88). As with any change in therapy in CD, the increase or decrease of adverse event risk associated with treatment modifications must be balanced against the long-term risk of disease progression. This may be of particular importance when considering TNF antagonist withdrawal during combination therapy, as the studies that assessed biologic withdrawal here demonstrated a significant increased risk of flare.

3.7.4 Certainty in Evidence of Effects

Immunomodulator withdrawal: The certainty of evidence for withdrawal of immunomodulators was judged to be low (**Table 15**). This was primarily secondary to risks of bias due to the inclusion of open-label study designs with subjective, symptom-based outcomes and serious imprecision. When considering the evidence-to-decision framework, the desirable effects of immunomodulator withdrawal (lowering risk of infectious and neoplastic complications) and undesirable anticipated effects (higher risk of CD relapse) was felt to be trivial-to-small. Based on the potential for reducing long-term risks of immunomodulator therapy, as well as the evidence demonstrating lack of inferiority for immunomodulator withdrawal in available clinical trials, the panel suggested in favor of withdrawal of immunomodulators.

TNF-antagonist withdrawal: Regarding the withdrawal of TNF antagonists, the certainty of evidence was judged to be low (**Table 15**). Besides risk of bias, evidence was rated down for imprecision as the optimal information size was not met. When considering the evidence-to-decision framework, the desirable effects were felt to be trivial, but the undesirable effects, as demonstrated by the increased risk of flare with TNF antagonist withdrawal, was felt to be moderate. Therefore, the balance of effects favor continuation of combination therapy over withdrawal of TNF antagonists.

The GRADE evidence-to-decision judgements are presented in **Table 16**.

3.7.5 Discussion

Immunomodulator withdrawal: Clinical trial evidence suggests that clinical outcomes are similar when withdrawing immunomodulators in those in corticosteroid-free remission on combination therapy. This serves as a potential opportunity to mitigate longer-term risks of combination TNF antagonist and immunomodulator therapy. However, there are several important aspects to

consider when implementing these recommendations. First, while the majority of patients included in these trials had CD, analyses for several studies reviewed also included patients with UC. Further, there was heterogeneity across assessed trials with regards to patient characteristics. This includes prior immunomodulator failure as well as follow-up time. Correlation between the impacts of immunomodulator withdrawal on both TNF antagonist trough levels as well as long-term immunogenicity were not routinely assessed, and it is possible that these effects may become more apparent with increasing time from withdrawal. In three trials, infliximab trough concentration at the end of follow-up was lower and the proportion of patients with antibodies to infliximab was higher in patients who underwent immunomodulator withdrawal compared to those who continued combination therapy. This may be an infliximab specific effect, however, as similar effects were not appreciated with adalimumab in DIAMOND2[118]. Longer time horizons may be of benefit to better understand the impact of long-term therapy withdrawal.

It is also important to individualize the recommendation of immunomodulator withdrawal, incorporating disease specific factors that may modulate the risk of relapse as well. Those with more moderate disease, such as those with limited extent, absence of concerning features such as penetrating complications, signs of systemic disease, absence of deep or serpiginous ulceration on endoscopy, and with confirmed biochemical or structural remission for a longer duration may benefit the most from de-escalation. Patient preferences regarding the risks of both continued combination therapy as well as the risks of subsequent relapse should be carefully considered in the shared decision-making process. In patients who value the potential benefit of combination therapy in decreasing risk of relapse, and place lower value on the risks of long-term combination therapy, it would be reasonable to continue combination therapy. Similarly, those at higher risk of immunogenic treatment failure with TNF antagonists, such as those with prior anti-drug antibody development or documented HLA DQA1*05 carriage status may reasonably choose to consider continuing combination therapy. It would also be reasonable to consider therapeutic drug monitoring, before and after withdrawal of immunomodulators to ensure that TNF antagonist levels remain within an acceptable range, particularly for infliximab.[128] Continued biochemical and/or structural assessment in the post-withdrawal period is appropriate to monitor for evidence of recurrence of disease as well.

TNF antagonist withdrawal: The deleterious impact of TNF-antagonist withdrawal was noted across the clinical trials reviewed for this study. However, when interpreting these data, it is important to take into account the same factors related to heterogeneity across the literature as noted above. While SAE rates were similar across studies, there was a significant association between TNF antagonist withdrawal and subsequent greater than 2-fold increased risk of relapse

of disease. There may still be a subgroup of patients who wish to pursue this strategy due to concerns about adverse events related to long-term treatment, desire to maintain drug-free remission, financial considerations, etc. While the risk of flare is likely substantial with this approach, data from the SPARE trial, as well as observational studies suggest that resumption of TNF antagonist at time of flare frequently recaptures clinical remission[123]. In the context of shared decision-making, this potential plan of reintroduction of the TNF antagonist may be informative for those contemplating withdrawal of their biologic therapy.

3.7.6 Evidence Gaps and Future Research

As highlighted above, there are several evidence gaps and potential targets for future research. Future pragmatic trials of immunomodulator withdrawal should incorporate longer time horizons, with continued focus on persistence of remission but also uniform incorporation of TNF antagonist drug level and anti-drug antibody assessment to better understand the long-term implications on trough concentrations and immunogenicity. Additionally, future trials are required to assess clinical remission rates for advanced therapy withdrawal, to not only measure persistence of remission but also rates of medication reinitiation and response rates to reintroduction after withdrawal. Such work should incorporate assessing patient preferences as well as health-related quality of life over time and can serve to identify better predictors of who may successfully hold therapy in IBD. Similar trials of withdrawal of non-TNF-targeting biologics and oral small molecule drugs are also required.

3.8 EARLY USE OF ADVANCED THERAPIES

Question #8: In adult outpatients with moderate-to-severely active Crohn's disease, is early use of advanced therapies superior to step-up therapy for decreasing the risk of disease-related complications?

Recommendation 15: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA SUGGESTS early use of advanced therapy compared with step-up therapy with initial use of corticosteroids and/or immunomodulator monotherapy. [*Conditional recommendation, very low certainty of evidence***]**

Implementation considerations:

1. *All trials that informed the evidence used combination therapy with TNF antagonists with immunomodulators.*

3.8.1 Source of Evidence

Three studies inform these recommendations. These studies primarily assessed combination therapy with a TNF antagonist and immunomodulator. In an open-label study by D'Haens and colleagues of 133 patients with recently diagnosed CD who were naïve to advanced therapies and steroids, individuals were randomized to start combination therapy with infliximab with standard induction and episodic dosing for maintenance versus corticosteroids followed by a thiopurine and then TNF-antagonist.[129] REACT-1 was a multicenter open-label cluster randomized controlled trial consisting of 1,982 participants were managed with either an algorithm incorporating early combination therapy with a TNF antagonist (adalimumab) if not improved after an initial steroid course, or treated via conventional management.[130] Lastly, in the PROFILE study, Noor and colleagues compared combination therapy with infliximab and an immunomodulator to an accelerated step-up algorithm with an initial steroid taper and examined rates of sustained steroid and surgery free remission at 48 weeks, as well as rates of disease related adverse events[131].

3.8.2. Benefits

In the study by D'Haens and colleagues, 133 individuals were enrolled; At 52 weeks of follow-up, 40/65 (61.5%) patients in the early combined immunosuppression group were in corticosteroid- and surgery-free remission, as compared with compared with 23/64 (42.2%) patients in the step therapy arm (RR, 0.67; 95% CI, 0.46-0.97)[129]. In the multi-center pragmatic REACT-1 study, there was no significant difference in the primary outcome of steroid free remission at 12 months, though there was a significantly lower rate of disease-related adverse events, which included

hospitalization, surgery or disease complications including abscess, fistula, stricture, or serious worsening of disease activity or extra-intestinal manifestations, at 24 months (HR, 0.73; 95% CI, 0.62-0.86).[130] Lastly, in PROFILE, 386 individuals were enrolled. Similar rates of symptomatic remission were observed at 1 year (RR, 1.12; 95% CI, 0.98-1.30) but significantly lower rates of disease related adverse events with early combination therapy (RR, 0.23; 95% CI, 0.09-0.59).[131]

In meta-analysis of these studies, a total of 2,497 individuals were included, across three clinical trials. With regarding to clinical remission at 12 months, the benefit of early combined immunosuppression over step therapy was uncertain (66.4% vs 60.6%; RR, 1.18; 95% CI, 0.96-1.46). However, there may be a lower risk of disease related complications at 12 months with early combination therapy compared with step therapy (17.7% vs 14.8%; RR, 0.62; 95% CI, 0.29-1.34).

3.8.3 Harms

The risk associated with immunomodulators and advanced therapies in CD have been discussed previously. It is important to consider that early advanced therapy use serves to increase the duration of exposure to these agents. However, these risks should be balanced against the potential risks of disease-related complications secondary to inadequate treatment of active disease.

3.8.4 Certainty in Evidence of Effects

The certainty of evidence quality was determined to be very low (for clinical remission) to low (for disease-related complications) (**Table 17**). While the overall population included across the three assessed studies was large, risks of bias were introduced through the inclusion of open-label studies, and there was imprecision in the derived estimates. Specifically, the quality of the evidence in relation to clinical remission was rated as very low, due to serious risk of bias due to the inclusion of open label trials, imprecision, and inconsistency in effect estimates. When considering disease related complications, the quality of evidence was determined to be low. While the trials were open-label, we opted not to rate down for risk of bias since the severe disease-related complications were objective. The evidence was rated down due to imprecision in estimates. Lastly, there were fairly significant differences in disease duration across the three included studies. Individuals enrolled in the study by D'Haens and colleagues were required to have been enrolled within 4 years of diagnosis and the median time from diagnosis to enrollment was 2 to 2.5 weeks.[129] Similarly, in PROFILE, the mean time from diagnosis to enrollment was 31.2 and 24.1 days in each treatment arm.[131] This is in contrast to REACT-1, where the mean

disease duration before enrollment was 149 and 158.1 months in the early combined immunosuppression and conventional arms, respectively.[130] The GRADE evidence-to-decision judgements are presented in **Table 18**.

3.8.5 Discussion

With the introduction of advanced therapies, the overall trajectory of disease for patients suffering from moderate-to-severely active CD has improved reducing rates of surgical intervention over time[4]. This is likely secondary to the reduced risk of structural damage such as penetrating complications like fistula or abscess formation, as well as reduced rates of fibrostenosis, that come with adequate control of the robust inflammatory response present in CD. It would therefore stand to reason that reducing overall exposure time to such inflammation would further reduce the risks of these outcomes. However, as highlighted by the data reviewed by the guideline panel here, there are limited prospective clinical trials to assess this effect. Several observational studies have appreciated an association between advanced therapy use and reduced rates of surgical intervention. For example, in a retrospective pediatric cohort of 913 patients, individuals receiving a TNF antagonist within 90 days of diagnosis were significantly less likely to experience penetrating complications over time after propensity score adjustment for multiple disease-related risk factors (HR, 0.30; 95% CI, 0.10-0.89).[132] Early TNF antagonist use has also been associated with reduced rates of perianal complications in pediatric CD in two separate cohorts.[133,134] However, observational studies remain at risk of bias, and further prospective controlled data would be beneficial to confirm these findings.

There are several caveats when interpreting both the clinical trial and observational data presented here. First, all included trials in the meta-analyses employed by the panel focused on the combination of TNF antagonist and immunomodulators therapy in those receiving “early” advanced therapy. It remains uncertain if the early initiation of other advanced therapies would provide increased or reduced benefit in reducing downstream complications when used early in the disease course. Similarly, across studies, there is variability in the definition of “early” and follow-up time is limited. It is possible that the benefits of early use may increase as disease duration increases, though long-term treatment failures could also mitigate these effects. Lastly, early use of advanced therapies inherently increases exposure time to the medications of interest and the potential risks of immunosuppression. Improved predictive markers of who might progress more rapidly may serve to further refine the identification of who might most benefit from earlier advanced therapy initiation.

3.8.6 Evidence Gaps and Future Research

Several evidence gaps remain that could be informed by future research. First, the appropriate window for "early" advanced therapy initiation remains unclear – existing trials analyzed here exhibited significant variability in disease duration. Secondly, there are limited data regarding the impact of early initiation of non-TNF antagonist advanced therapies. Future studies could consider assessing the comparative effectiveness of early use of different classes of advanced therapies with uniform enrollment and initiation time windows to address these concerns. It is also possible that there are subsets of patients that may uniquely benefit from early combination therapy in contrast to others, and unfortunately there are not yet predictive markers that have been shown to clearly identify this population. An example of such an approach would be PROFILE, where individuals were stratified by higher or lower risk for future disease related complications using a panel of 17 genetic markers. Stratified analyses by high and low risk designation demonstrated no significant difference in response to early combination therapy.[131] As future predictive markers are assessed and validated in observational research, they should be similarly incorporated into clinical trials such as those described above. Lastly, it is possible that the benefit derived from early combined immunosuppression erodes over time. Longer follow-up times in prospectively monitored cohorts would allow for closer monitoring of disease progression over time and ascertain if there is regression in benefit. Longer duration follow-up in the trial by D'Haens at 104 weeks, no differences were apparent between top down therapy vs. step therapy.

3.9 TREATING TO ENDOSCOPIC REMISSION VERSUS CLINICAL REMISSION

Question 9: In adult outpatients with moderate-to-severely active Crohn's disease, is treat-to-target of endoscopic remission (resolution of inflammation on endoscopy) superior to treat-to-target of symptomatic remission, for maintenance of remission and decreasing risk of disease-related complications?
Recommendation 16: In adult outpatients with moderate-to-severely active Crohn's disease, the AGA makes NO RECOMMENDATION in favor, or against, treating to a target of endoscopic remission, compared with treating to a target of symptomatic remission. [*No recommendation, knowledge gap***]**

3.9.1 Source of Evidence

Two RCTs were reviewed to assess whether treating to a target of endoscopic remission (systematic assessment for symptoms and endoscopic inflammation, followed by treatment

escalation in those with evidence of inflammation, regardless of presence or absence of symptoms) vs. treat-to-target of symptomatic remission (systematic assessment for symptoms, followed by treatment escalation in those with ongoing symptoms) modified likelihood of maintaining long-term remission and prevent CD-related complications. STARDUST was an open-label RCT comparing treat-to-target endoscopic monitoring to standard care in individuals with moderate-to-severely active CD who were initiating ustekinumab.[135] Individuals in the treat-to-target monitoring arm received repeated endoscopic assessments at study entry and week 16 in order to guide decision-making. Those with <25% improvement in SES-CD were assigned to receive every 8-week maintenance dosing, whereas those who met that target received every 12-week dosing. In the standard care arm, maintenance dosing was dictated by symptom response. Both arms received routine biochemical monitoring as well. The primary outcome was endoscopic response at 48 weeks; endoscopic remission rates and clinical remission and response rates were assessed as secondary outcomes.

The second trial assessed was REACT-2, a clustered RCT comparing a strategy of systematic colonoscopic (and symptom) assessment at baseline and then at 6, 12, and 24 months vs. systematic evaluation of symptoms, with stepwise algorithmic treatment escalation if target (endoscopic remission vs. symptomatic remission) was not met[136]. The measured outcomes at 24 months included clinical and endoscopic remission.

3.9.2 Benefits

Two clinical trials were included in meta-analyses to inform the recommendations for these guidelines. In STARDUST, there was no significant difference between treat-to-target of endoscopic remission vs. usual care in rates of clinical (62% vs 70%) or endoscopic remission (38% vs 30%) at 48 weeks. Adverse event rates were similar during follow-up in both arms as well (12% vs 13%)[135]. In REACT-2, outcomes of clinical and endoscopic remission were assessed at 24 months. There was a higher rate of clinical remission in the endoscopic monitoring arm than in the usual care arm (54.6% vs 45.1%), but no difference in endoscopic outcomes (33.9% vs 31.9%).[136] Based on these two studies, there were no significant differences in the outcome of clinical remission (63.2% vs. 57.3%; RR, 1.04; 95% CI, 0.78-1.39).

3.9.3 Harms

Risks associated with both immunomodulators, advanced therapy, and combination therapy have been previously discussed. When considering endoscopic remission, one could consider the risks and financial implications of endoscopic evaluation, as well as the disutility of the procedure itself.

While such risks are tangible, they are also relatively self-limited when placed in the context of improving the overall course of disease in CD. Although the studies included here specifically focused on adjusting the dosing of the index therapy for each trial, one could consider this approach in the context of switching to an alternative therapy if dose escalation has already occurred. In these instances, there would be a potential risk of future flare in those who had achieved a clinical response when striving for endoscopic remission as well.

3.9.4 Certainty in Evidence of Effects

The overall certainty of evidence was determined to be very low due to multiple factors, including serious risk of bias due to the inclusion of studies with an open label design, imprecision, and inconsistency across effect estimates (**Table 19**). Importantly, dosing of ustekinumab was also not consistent with the currently approved dosing in the United States; in STARDUST, maintenance dosing was every 12 weeks.[135] Additionally, it is important to note heterogeneity across patient populations. While individuals enrolling in STARDUST had active disease, defined via clinical and endoscopic disease activity, there was a large proportion of individuals enrolling in REACT-2 that did not have active disease.

3.9.5 Discussion

Recent position statements from an international consortium of experts have advised that longitudinal targets for the management of IBD should include not only clinical remission but also endoscopic resolution of inflammation[25]. While observational cohorts have demonstrated that patients who achieve endoscopic remission (vs. those with ongoing endoscopic activity) have favorable long-term outcomes, there are limited RCTs assessing if there is actual benefit in systematically treating towards endoscopic remission target vs. symptomatic remission targets (i.e., testing whether target has been achieved, followed by algorithmic treatment adjustment including escalating index therapy, adding an immunomodulator, followed by switching to an alternative advanced therapy and surgery) in targeting such an endpoint. There was significant heterogeneity among the studies that were included in this study, both in terms of advanced therapy, algorithms for therapy modification, and the cadence and frequency of endoscopic monitoring that challenge interpretation. Based on the significant uncertainty of evidence with regards to improving maintenance of remission or reducing the risks of adverse events, the guideline panel was not able to make a recommendation in relation to selecting endoscopic targets over clinical targets.

It is also worth emphasizing that in both of the included trials, the majority of individuals in the endoscopic healing arms were not able to meet the goal of endoscopic healing despite an algorithmic approach. For example, in STARDUST, only 11% of individuals achieved endoscopic remission[135]. This may be indicative of a particularly challenging patient population to treat. However, it is important to note that it remains conventional practice to assess for clinical, biochemical, and endoscopic response and/or remission after starting and advanced therapy. There are specific patient populations, such as those who have recently undergone intestinal resection[137], in which endoscopic evaluation may be particularly valuable in clinical decision making. The current question does not address the question related to a tight control strategy focusing on treat-to-target of biochemical remission in order to improve rates of achieving clinical and endoscopic remission. This was demonstrated in the CALM trial, and has been addressed in previous AGA guidelines on the role of biomarkers in patients with Crohn's disease.

3.9.6 Evidence Gaps and Future Research

There are several significant evidence gaps regarding this treatment approach that could be addressed by future clinical trials. Providers and investigators have begun to pursue structural outcomes given the well-described discordance between clinical symptoms, captured throughout scoring systems such as the CDAI and used to define clinical remission, and biochemical or structural outcomes such as endoscopic healing. However, there is also variation in endoscopic scoring, and histologic assessment may be more sensitive to persistent residual inflammation. There are compelling observational studies that suggest histologic resolution of inflammation may be more closely correlated with downstream clinical outcomes than endoscopic healing alone in ileal CD, for example.[138] Further, CD-related inflammation can extend deeply through the bowel wall, and there is growing recognition via technologies such as enterography or intestinal ultrasound that correcting or reducing inflammation within the epithelium of the colon or small bowel may not completely correlate with resolution of the inflammation process transmurally. Such transmural healing may also be more strongly correlated with clinical outcomes than endoscopic healing alone.[139,140] Further studies of both approved and novel advanced therapies should continue to explore these potential outcomes and their association with clinical outcomes in CD. Future efforts should also continue to refine and standardize outcome definitions for histologic and transmural healing as well.

The appropriate timing and frequency of endoscopic evaluation, as well as its relation to clinical outcomes including medication persistence, maintenance of remission, and reduction of CD-related adverse events is unclear at this time, and there is significant heterogeneity regarding

time to achieving endoscopic healing or other structural outcomes. Understanding not only these temporal associations between treatment duration and structural assessment but also the factors that might predict an expected earlier or later response is critical; Such predictive models would allow clinicians to select the appropriate assessment window and modify current therapies more accurately.

Lastly, ongoing and future clinical trials should assess to what extent treatment modifications should be considered to attain these structural goals. While dose modification of an existing therapy in an individual with clinical remission is likely of limited risk of inducing flare, considering an alternative mechanism of action to achieve mucosal, histologic, or transmural healing, particularly in asymptomatic patients, is a much different proposition given varying safety profiles of medications as well as the risk of loss of response. Similarly, with growing recognition of the potential treatment strategy of targeting multiple inflammatory pathways via combination advanced therapy, one could consider employing these approaches to achieve these structural outcomes. However, while early preliminary data are reassuring, it remains possible that these strategies also carry with them increased risks of serious adverse events related to therapy. Future clinical trials should assess these variable approaches in the context of long-term disease related complication rates to better understand the incremental value of achieving endoscopic, histologic, or transmural healing. It is imperative that such work be coupled with research exploring patient preferences for these outcomes, and that, given the personal and societal financial implications of these therapies, these findings are combined with cost-effectiveness analyses to simulate the best societal approaches as well.

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