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CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease

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Crohn's disease (CD) is a chronic inflammatory bowel disease with substantial morbidity when not adequately controlled.[1] Historically, approximately 20% of patients with CD were hospitalized every year, and the risk of surgery within 1 year of diagnosis was 24%, 36% by 5 years, and 47% by 10 years.[2] In recent years, outcomes have improved, likely because of earlier diagnosis, increasing use of biologics, escalation or alteration of therapy based on disease severity, and endoscopic management of colorectal cancer. CD includes multiple different phenotypes. The Montreal Classification categorizes CD as stricturing, penetrating, inflammatory (nonstricturing and nonpenetrating), and perianal disease.[3–5] Each of these phenotypes can present with a range in severity from mild to severe disease.[6]

This guideline addresses the medical management of moderate to severe luminal and fistulizing CD. The International Organization for the Study of Inflammatory Bowel Diseases characterizes severe disease as having a high risk for adverse disease-related complications, including surgery, hospitalization, and disability, based on a combination of structural damage, inflammatory burden, and impact of quality of life. Contributors to severe disease include large or deep mucosal lesions on endoscopy or imaging, presence of fistula and/or perianal abscess, presence of strictures, prior intestinal resections, particularly of segments >40 cm, presence of a stoma, extensive disease (ileal involvement >40 cm, or pancolitis), anemia, elevated C-reactive protein, and low albumin. With respect to symptoms, patients with severe disease may have at least 10 loose stools per day, daily abdominal pain, presence of anorectal symptoms (eg, anorectal pain, bowel urgency, incontinence, discharge, and tenesmus), systemic corticosteroid use within the prior year, lack of symptomatic improvement despite prior exposure to biologics and/or immunosuppressive agents, or significant impact of the disease on activities of daily living.[7] Moderate to severe disease can also be defined using the Crohn's Disease Activity Index. This standardized disease assessment score categorizes severity of disease as: remission <150, mild to moderate as 150–220, moderate to severe as 220–450 and severe >450.[8] For this guideline, moderate to severe disease was considered a Crohn's Disease Activity Index score of 220 or higher.

There are a number of different drug classes available for the management of moderate to severe CD, including tumor necrosis factor (TNF)–α antagonists (ie, infliximab, adalimumab, certolizumab pegol), anti-integrin agents (natalizumab, vedolizumab), interleukin 12/23 antagonist (ustekinumab), immunomodulators (thiopurines, methotrexate), and corticosteroids (prednisone, budesonide).[1] In general, most drugs, with the exception of corticosteroids, that are initiated for induction of remission are continued as maintenance therapy. Unless otherwise specified, we do not present separate recommendations for induction and maintenance of remission. The drugs are listed, in general, in order of US Food and Drug Administration approval. This guideline does not address surgical management of moderate to severe CD. Therapeutic drug monitoring to guide the use of biologic therapy has been addressed in a separate American Gastroenterological Association (AGA) guideline and is not included in this guideline.[9]

Methods

This document presents the official recommendations of the AGA on the medical management of moderate to severe luminal and fistulizing CD in adults. This guideline addresses the outpatient medical management of moderate to severe luminal and fistulizing CD, although we anticipate that most of the recommendations would apply to inpatients as well.

Abbreviations used in this paper: **AGA, American Gastroenterological Association; CD, Crohn's disease; CI, confidence interval; GRADE, Grading of Recommendations Assessment; Development and Evaluation, MCID; minimal clinically important difference, OIS; optimal information size, OR; odds ratio, PICO; population, intervention; comparator, and outcome; PML, progressive multifocal leukoencephalopathy; RCT, randomized controlled trial; RR, relative risk; TNF, tumor necrosis factor).**

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The guideline was developed by the AGA Institute's Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that provides a detailed synthesis of the evidence from which these recommendations were formulated.[10] Development of this guideline and the accompanying technical review was fully funded by the AGA Institute without additional outside funding.

Guideline Panel Composition, Funding, and Conflict of Interest

Members of the Guideline Panel and Technical Review Panel were selected by the AGA Governing Board and Chair of the Clinical Guidelines Committee with careful consideration of conflict of interest. The Guideline Panel included the chair (J.P.T.) adult gastroenterologists with IBD expertise (E.H., E.S., H.S.), Technical Review GRADE methodology chairs (J.F., S.S.) and GRADE experts (S.S., Y.F.Y.). This guideline and its accompanying technical review[10] were developed using a process outlined previously. The AGA process for developing clinical practice guidelines follows the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and adheres to best practices in guideline development, as outlined by the National Academy of Medicine (formerly Institute of Medicine).[11]

Formulation of Clinical Questions

The Guideline Panel and Technical Review Panel identified and formulated clinical relevant questions on the medical management of moderate to severe luminal and fistulizing Crohn's disease. Each question identified the population, intervention, comparison, and patient-important outcomes (PICO). The Technical Review Panel performed a systematic search of the literature and assessed relevant evidence to address the clinical questions to inform the recommendations.[10] The evidence for each PICO question was assessed using GRADE and presented in an evidence profile in the technical review.

Development of Recommendations

The Guideline Panel and the authors of the Technical Review met virtually via a video conference call on August 14, 2020 and August 28, 2020 to discuss the findings from the technical review. During these meetings, the Guideline Panel independently formulated the guideline recommendations based on the GRADE evidence-to-decision framework. The Technical Review Panel was not involved in the formulating or finalizing of the recommendations. The certainty of available evidence and the strength of the recommendation are provided with each PICO statement (Table 1).

Evidence Review

In formulating this guideline, the predetermined critical outcomes were induction and maintenance of remission. The ability of the various drugs to achieve these outcomes are reported in the technical review with associated evidence profiles. For the questions regarding fistulizing disease, induction and maintenance of fistula remission was generally defined as complete cessation of fistula drainage. Important outcomes of interest were induction and maintenance of endoscopic remission, maintenance of corticosteroid-free remission, serious adverse events (including serious infections and malignancy), and treatment tolerability (drug discontinuation due to adverse events). These were considered in the evidence synthesis, especially if inadequate or conflicting data were observed for critical outcomes. Safety considerations with these medications have been synthesized in the accompanying technical review. In the recommendations presented in this guideline, estimates of the effect of different medications are presented as the risk for failure to induce or maintain remission, that is, a relative risk (RR) or odds ratio (OR) <1 suggests that the drug under consideration is more effective than the comparison drug or placebo for induction or maintenance of remission.

Table 1. Grading of Recommendations Assessment, Development and Evaluation Definitions for Certainty of the Evidence

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

When considering the magnitude of benefit, for trials comparing interventions vs placebo, a minimal clinically important difference (MCID) was set at 10%. Failure to meet the MCID was considered to have no clinically meaningful impact over placebo. For additional details regarding the methodology, please review the accompanying technical review.[10]

Although the certainty of evidence (Table 1) was a key factor in determining the strength of the recommendations (Table 2), the Panel also considered the balance between benefit and harm of interventions, patients' values and preferences, overall resource use (eg, cost), health equity, acceptability, and feasibility (based on the Evidence to Decision Framework). The recommendations, certainty of evidence, and strength of recommendations are summarized in Table 3.

The target audience for this guideline includes health care professionals (primary care providers, gastroenterologists, and other specialists), policy makers, and patients.

External Review

The guideline and the accompanying technical review[10] underwent independent peer review and a 30-day open public comment period. All of the comments were collected by AGA

Table 2. Grading of Recommendations Assessment, Development and Evaluation Definitions on Strength of Recommendation and Guide to Interpretation

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

staff. The comments were reviewed and addressed by the Guideline Panel and Technical Review Panel, respectively. Changes were incorporated in a revised document and if comments were not accepted, a response document was created for each comment.

Guideline Review and Anticipated Update

In accordance with the Clinical Guidelines Committee policies, all clinical guidelines are reviewed annually at the AGA Clinical Guideline Committee meeting for new information. The next update for these guidelines is anticipated in 3 years from publication (2024).

Recommendations

A summary of all the recommendations in this guideline is provided in Table 3. Optimal understanding of the guideline will be enhanced by reading the applicable portions of the technical review and its updated systematic review of the evidence.

Pharmacologic Management of Adult Patients With Moderate to Severe Luminal Crohn's Disease

Recommendation 1A. In adult outpatients with moderate to severe CD, the AGA recommends the use of anti-TNFα over no treatment for induction and maintenance of remission. *(Strong recommendation, moderate certainty evidence)*
Comment: Although the evidence supporting infliximab and adalimumab was moderate quality, the evidence for certolizumab pegol was low quality.

Recommendation 1B. In adult outpatients with moderate to severe CD, the AGA suggests the use of vedolizumab over no treatment for the induction and maintenance of remission. *(Conditional recommendation, low quality evidence for induction, moderate certainty evidence for maintenance)*
Recommendation 1C. In adult outpatients with moderate to severe CD, the AGA recommends the use of ustekinumab over no treatment for the induction and maintenance of remission. *(Strong recommendation, moderate certainty evidence)*
Recommendation 1D. In adult outpatients with moderate to severe CD, the AGA suggests against the use of natalizumab over no treatment for the induction and maintenance of remission. *(Conditional recommendation, moderate certainty evidence)*
Comment: Given evidence of harm in post-marketing data from progressive multifocal leukoencephalopathy (PML) and the availability of other drugs, the AGA suggests against the use of natalizumab. Patients who are John Cunningham virus antibody–negative who put a high value on the potential benefits and lower value on PML risk and who will adhere to ongoing monitoring for John Cunningham virus positivity, may consider using natalizumab.

The Panel recommends treating adult outpatients with moderate to severe luminal CD with infliximab, adalimumab, certolizumab pegol, vedolizumab, or ustekinumab over no treatment for the induction and maintenance of remission. In contrast, the Panel recommended against the use of natalizumab for induction or maintenance of remission due to the potential harms associated with this medication. There were 13 randomized controlled trials (RCTs) comparing the TNFα antagonists vedolizumab and

Table 3. Summary of Recommendations of the American Gastroenterological Clinical Guidelines Committee for Medical Management of Moderate to Severe Luminal and Fistulizing Crohn's Disease

Recommendation	Strength of recommendation	Certainty of evidence
1A. In adult outpatients with moderate to severe CD, the AGA recommends the use of anti-TNFα over no treatment for induction and maintenance of remission. Comment: Although the evidence supporting infliximab and adalimumab was moderate certainty, the evidence for certolizumab pegol was low certainty.	Strong	Moderate
1B. In adult outpatients with moderate to severe CD, the AGA suggests the use of vedolizumab over no treatment for the induction and maintenance of remission.	Conditional	Low for induction, moderate for maintenance
1C. In adult outpatients with moderate to severe CD, the AGA recommends the use of ustekinumab over no treatment for the induction and maintenance of remission.	Strong	Moderate
1D. In adult outpatients with moderate to severe CD, the AGA suggests against the use of natalizumab over no treatment for the induction and maintenance of remission. Comment: Given evidence of harm in post marketing data from progressive multifocal leukoencephalopathy (PML) and the availability of other drugs, the AGA suggests against the use of natalizumab. Patients who are John Cunningham virus antibody–negative who put a high value on the potential benefits and lower value on PML risk and who will adhere to ongoing monitoring for John Cunningham virus positivity, may consider using natalizumab.	Conditional	Moderate
2A. In adult outpatients with moderate to severe CD who are naïve to biologic drugs, the AGA recommends the use of infliximab, adalimumab, or ustekinumab over certolizumab pegol for the induction of remission and suggests the use of vedolizumab over certolizumab pegol for the induction of remission.	Strong Conditional	Moderate Low
2B. In adult outpatients with moderate to severe CD who never responded to anti-TNFα (primary nonresponse), the AGA recommends the use of ustekinumab and suggests the use of vedolizumab over no treatment for the induction of remission.	Strong Conditional	Moderate Low
2C. In adult outpatients with moderate to severe CD who previously responded to infliximab (secondary nonresponse), the AGA recommends the use of adalimumab or ustekinumab and suggests the use of vedolizumab over no treatment for the induction of remission. Comment: If adalimumab was the first-line drug used there is indirect evidence to suggest the option of using infliximab as a second-line agent.	Strong Conditional	Moderate Low
3A. In adult outpatients with moderate to severe CD, the AGA suggests against the use of thiopurines over no treatment for achieving remission.	Conditional	Very low
3 B. In adult outpatients with quiescent moderate to severe CD (or patients in corticosteroid-induced remission), the AGA suggests the use of thiopurines over no treatment for the maintenance of remission.	Conditional	Low
3C. In adult outpatients with moderate to severe CD, the AGA suggests the use of subcutaneous or intramuscular methotrexate monotherapy over no treatment for the induction and maintenance of remission.	Conditional	Moderate
3D. In adult outpatients with moderate to severe CD, the AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission.	Conditional	Very low
4. In adult outpatients with moderate to severe CD, the AGA recommends the use of biologic drug monotherapy over thiopurine monotherapy for the induction of remission.	Strong	Moderate

Table 3. Continued

Recommendation	Strength of recommendation	Certainty of evidence
5A. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of infliximab in combination with thiopurines for the induction and maintenance of remission over infliximab monotherapy. Comment: Based on indirect evidence, combination infliximab with methotrexate may be more effective over infliximab monotherapy.	Conditional	Moderate
5B. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of adalimumab in combination with thiopurines for the induction and maintenance of remission over adalimumab monotherapy. Comment: Based on indirect evidence, combination adalimumab with methotrexate may be more effective over adalimumab monotherapy.	Conditional	Very low
5C. In adult outpatients with moderate to severe CD, the AGA makes no recommendation regarding the use of, ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic drug monotherapy for the induction and maintenance of remission.	No recommendation	Knowledge gap
6. In adult outpatients with quiescent CD on combination therapy, the AGA makes no recommendation for withdrawal of either the immunomodulator or the biologic over ongoing combination therapy of a biologic and an immunomodulator	No recommendation	Knowledge gap
7. In adult outpatients with moderate to severe CD, the AGA suggests early introduction with a biologic with or without an immunomodulator rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids.	Conditional	Low
8A. In adult outpatients with moderate to severe CD, the AGA suggests the use of corticosteroids over no treatment for induction of remission.	Conditional	Moderate
8B. In adult outpatients with moderate to severe CD, the AGA recommends against the use of corticosteroids over no treatment for maintenance of remission.	Strong	Moderate
9. In adult outpatients with moderate to severe CD, the AGA recommends against the use of 5-aminosalicylates or sulfasalazine over no treatment for the induction or maintenance of remission.	Strong	Moderate
10A. In adult outpatients with CD and active perianal fistula, the AGA recommends the use of infliximab over no treatment for the induction and maintenance of fistula remission.	Strong	Moderate
10B. In adult outpatients with CD and active perianal fistula, the AGA suggests the use of adalimumab, ustekinumab, or vedolizumab over no treatment for the induction or maintenance of fistula remission. Comment: Evidence suggests certolizumab pegol may not be effective for induction of fistula remission.	Conditional	Low
10C. In adult outpatients with CD and active perianal fistula without perianal abscess, the AGA suggests against the use of antibiotics alone over no treatment for the induction of fistula remission.	Conditional	Low
11. In adult outpatients with CD and active perianal fistula without perianal abscess, the AGA recommends the use of biologic agents in combination with an antibiotic over a biologic drug alone for the induction of fistula remission.	Strong	Moderate

ustekinumab with placebo for induction of remission and 9 RCTs informing on maintenance of remission. Induction of remission was assessed at 4–12 weeks and maintenance of remission was evaluated at 22–54 weeks. All active interventions were superior to placebo for induction of remission (infliximab: RR, 0.54; 95% confidence interval [CI], 0.39–0.75; adalimumab: RR, 0.82; 95% CI, 0.75–0.89; certolizumab pegol: RR, 0.92 95% CI, 0.86–0.98; vedolizumab RR, 0.92; 95% CI, 0.87–0.97; ustekinumab RR, 0.90; 95% CI, 0.85–0.94). Likewise, all active interventions were superior to placebo for maintenance of remission (infliximab: RR, 0.77; 95% CI, 0.65–0.92; adalimumab: RR, 0.70; 95% CI, 0.62–0.79; certolizumab pegol RR, 0.88; 95% CI, 0.83–0.93; vedolizumab RR, 0.78; 95% CI, 0.67–0.91;

ustekinumab RR, 0.75; 95% CI, 0.64–0.89). Although natalizumab did show benefit for induction (RR, 0.88; 95% CI, 0.82–0.96) and maintenance of remission (RR, 0.58; 95% CI, 0.48–0.70) compared with placebo, given the risk of PML and the availability of other drugs not associated with this devastating adverse effect, led the Guideline Panel to recommend against its routine use in treating patients with moderate to severe luminal CD.

The overall certainty of evidence for this recommendation was moderate for infliximab, adalimumab, and ustekinumab, rating down for imprecision secondary to the low number of events (<200; low optimal information size [OIS]). For certolizumab pegol and vedolizumab, the certainty of evidence was rated down to low because of very serious imprecision because the summary risk estimates did not meet the MCID threshold of 10% over placebo. For maintenance of remission, the certainty of evidence was moderate (rated down for imprecision secondary to low OIS).

Recommendation 2A. In adult outpatients with moderate to severe CD who are naïve to biologic drugs, the AGA recommends the use of infliximab, adalimumab, or ustekinumab, over certolizumab pegol for the induction of remission *(Strong recommendation, moderate certainty evidence)* **and suggests the use of vedolizumab over certolizumab pegol for the induction of remission.** *(Conditional recommendation, low certainty evidence)*

Recommendation 2B. In adult outpatients with moderate to severe CD who never responded to anti-TNFα (primary nonresponse), the AGA recommends the use of ustekinumab *(Strong recommendation, moderate certainty evidence)* **and suggests the use of vedolizumab over no treatment for the induction of remission.** *(Conditional recommendation, low certainty evidence)*

Recommendation 2C. In adult outpatients with moderate to severe CD who previously responded to infliximab (secondary nonresponse), the AGA recommends the use of adalimumab or ustekinumab *(Strong recommendation, moderate certainty evidence)* **and suggests the use of vedolizumab over no treatment for the induction of remission.** *(Conditional recommendation, low certainty evidence)*

Comment: If adalimumab was the first-line drug used, there is indirect evidence to suggest the option of using infliximab as a second-line agent.

There were no head-to-head trials comparing the efficacy of different agents for induction and maintenance of remission. Therefore, indirect evidence was derived using network meta-analysis from drug trials with similar study designs and outcomes. Network meta-analysis can help assess comparative efficacy of several interventions and synthesize evidence across a network of RCTs, especially if there is weak (or absent) direct evidence.[12] The analysis included 8 RCTs with a total of 1458 biologic-naïve patients with moderate to severe luminal CD. On network meta-analysis, infliximab was more effective than certolizumab pegol (OR, 4.33; 95% CI, 1.83–10.27) with moderate confidence in estimates (rated down for imprecision) and low confidence in estimates supporting its use over vedolizumab (OR, 2.20; 95% CI, 0.79–6.07) or ustekinumab (OR, 2.14; 95% CI, 0.89–5.15) rated down for imprecision. There was moderate confidence in estimates for the use of ustekinumab (OR, 2.02; 95% CI, 1.09–3.75) or adalimumab (OR, 2.97; 95% CI, 1.16–6.70) over certolizumab pegol with low confidence in estimates (rated down for very serious imprecision). There was low confidence in the estimates for the use of vedolizumab over certolizumab pegol (OR 1.97; 95% CI, 0.88–4.41). There was no significant difference in the efficacy of adalimumab, ustekinumab, or vedolizumab as a first-line agent (very low certainty evidence).

The second part of the network meta-analysis compared drug efficacy after a prior failure of a TNFα antagonist. The failure of a TNFα antagonist can be categorized as primary or secondary nonresponse, as defined in the prior AGA guideline and technical review on therapeutic drug monitoring.[9]

In patients with prior TNFα antagonist exposure, 6 RCTs with 1606 patients were included in this part of the network meta-analysis. Three studies were performed exclusively in those with prior TNFα antagonist exposure (1 trial adalimumab and 2 trials of ustekinumab), 2 subgroup analyses of phase 2 trials (1 for adalimumab and 1 for vedolizumab), 1 trial of vedolizumab (GEMINI-II) in which 75% of patients had prior TNFα antagonist exposure, and 1 trial of adalimumab (GAIN) that only included patients with prior response or intolerance to infliximab. On network meta-analysis, ustekinumab was superior to placebo (OR, 2.58; 95% CI, 1.50–4.44) with moderate certainty evidence rating down for imprecision. Using adalimumab in patients with prior intolerance or secondary nonresponse to infliximab (OR, 3.57; 95% CI, 1.66–7.65) was moderate certainty evidence rating down for imprecision. Vedolizumab (OR, 1.53; 95% CI, 0.77–3.06) was supported by low certainty evidence rating down for very serious imprecision related to the very wide CIs and crossing unity). Further indirect comparisons between the drugs were performed in the technical review but were not of high enough certainty to formulate a recommendation. Of note, the studies included in the network meta-analysis did not consistently report what proportion of patients had exposure to more than 1 TNFα antagonist, exposure to multiple different classes of biologics, and reasons for failure of prior biologics (primary nonresponse vs secondary loss of response vs intolerance). In clinical practice, this information, along with information from the results of therapeutic drug monitoring (see prior AGA guideline on therapeutic drug monitoring),[9] may affect one's decision to select one biologic over another biologic.

Recommendation 3A. In adult outpatients with moderate to severe CD, the AGA suggests against the use of thiopurines monotherapy over no treatment for achieving remission. *(Conditional recommendation, very low certainty evidence)*

Recommendation 3B. In adult outpatients with quiescent moderate to severe CD (or patients in corticosteroid-induced remission), the AGA suggests the use of thiopurines monotherapy over no

treatment for the maintenance of remission. *(Conditional recommendation, low certainty evidence)*

Recommendation 3C. In adult outpatients with moderate to severe CD, the AGA suggests the use of subcutaneous or intramuscular methotrexate monotherapy over no treatment for the induction and maintenance of remission. *(Conditional recommendation, moderate certainty evidence)*

Recommendation 3D. In adult outpatients with moderate to severe CD, the AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission. *(Conditional recommendation, very low certainty evidence)*

In adult outpatients with moderate to severe luminal CD, the Guideline Panel suggests against using thiopurines over no treatment for achieving remission because 5 trials including 380 patients treated with thiopurines did not show increased efficacy compared with placebo in achieving corticosteroid-free remission in patients who were corticosteroid-dependent. The certainty of the evidence was very low due to serious bias, indirectness, and serious imprecision. However, 5 RCTs did demonstrate that thiopurines were significantly more effective than placebo or no treatment (RR, 0.62; 95% CI, 0.47–0.81) for maintaining corticosteroid-free clinical remission. The certainty of evidence was rated down for bias due to inadequate blinding and imprecision because of low OIS.

In evaluating methotrexate, the Technical Review Panel and Guideline Panel opted to evaluate oral vs intramuscular/subcutaneous methotrexate separately due to underlying differences in efficacy related to route of administration and total dose. Subcutaneous methotrexate dosed at 25 mg/wk was evaluated in 1 trial of 141 patients and was effective for induction of remission (RR, 0.75; 95% CI, 0.61–0.93). For maintenance of remission, subcutaneous methotrexate dosed at 15 mg/wk was evaluated in 1 trial of 76 patients after they had achieved remission with 16–25 weeks of 25 mg/wk subcutaneous methotrexate. Subcutaneous methotrexate was more effective than placebo for maintaining corticosteroid-free remission (RR, 0.57; 95% CI, 0.34–0.94). The certainty of evidence was moderate for induction and maintenance of remission, rating down for imprecision due to the small sample size.

In contrast to subcutaneous methotrexate, oral methotrexate was evaluated in a single RCT dosed at 12.5 mg/wk and was not effective for inducing remission (RR, 1.14; 95% CI, 0.72–1.82). In the maintenance arm of the study, 12.5 mg/wk was not more effective than placebo for maintaining remission (RR, 0.30; 95% CI, 0.04–2.27). The certainty of evidence was very low due to indirectness from the lower dose of methotrexate and very serious imprecision due to the very wide 95% CI. The Guideline Panel noted that the single RCT evaluating oral methotrexate may have used a dose that is suboptimal.[13] It is not clear if a higher dose of oral methotrexate would be more effective.

Recommendation 4. In adult outpatients with moderate to severe CD, the AGA recommends the use of biologic drug monotherapy over thiopurine monotherapy for the induction of remission. *(Strong recommendation moderate certainty of evidence)*

The Panel recommends the use of biologic drug monotherapy over thiopurine monotherapy for induction of remission. A separate recommendation for maintenance of remission was not provided because corticosteroid-sparing drugs that are started for induction of remission are typically continued for maintenance of remission. The SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease) study design was a 3-arm RCT including biologic and immunomodulator-naïve patients comparing infliximab vs azathioprine vs infliximab + azathioprine.[14] Infliximab was more effective than azathioprine for induction of clinical remission (RR, 0.79; 95% CI, 0.67–0.94) and endoscopic remission (65 of 93 vs 91 of 109; $P < .01$). The certainty of evidence was moderate, rating down for imprecision due to low OIS. Data on other biologics compared with thiopurines for induction of remission were lacking. However, given the overall efficacy of other biologics compared with placebo, and thiopurines failing to show efficacy compared with placebo for induction of remission, indirect evidence suggests that other biologics would also be more effective than thiopurines for induction of remission. Similarly, no RCTs compared biologic monotherapy with methotrexate monotherapy and data are therefore lacking.

Recommendation 5A. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of infliximab in combination with thiopurines for the induction and maintenance of remission over infliximab monotherapy. *(Conditional recommendation, moderate certainty evidence)*

Comment: Based on indirect evidence, combination infliximab with methotrexate may be more effective over infliximab monotherapy.

Recommendation 5B. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of adalimumab in combination with thiopurines for the induction and maintenance of remission over adalimumab monotherapy. *(Conditional recommendation, very low certainty evidence)*

Comment: Based on indirect evidence, combination adalimumab with methotrexate may be more effective over adalimumab monotherapy.

Recommendation 5C. In adult outpatients with moderate to severe CD, the AGA makes no recommendation regarding the use of ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic drug monotherapy for the induction and maintenance of remission. *(No recommendation, knowledge gap)*

Two trials compared infliximab with a thiopurine to infliximab monotherapy. Combination therapy was more effective for induction of remission (RR, 0.77; 95% CI, 0.64–0.92). Although there were no direct maintenance trials, both of these studies included follow-up of patients with active disease up to 50 of 52 weeks with combination therapy showing greater efficacy than infliximab monotherapy for maintenance of remission (RR, 0.74; 95% CI, 0.60–0.90). The certainty of evidence for induction of remission was moderate, rating down for imprecision, given the low OIS. Maintenance of remission certainty of evidence was low. This was rated down for indirectness (entering the maintenance with active disease and not specifically quiescent disease) and imprecision due to the low OIS.

Combination therapy using infliximab and methotrexate vs infliximab monotherapy was compared in 1 RCT with 126 patients. There was no difference in achieving corticosteroid-free remission at week 14 (RR, 1.07; 95% CI, 0.57–2.03) and at week 50 there was no difference in failure to maintain corticosteroid-free clinical remission (RR, 1.18; 95% CI, 0.68–2.03). The certainty of evidence for induction and maintenance of remission using infliximab with methotrexate was rated low due to very serious imprecision.

A single open-label RCT (DIAMOND study group) compared adalimumab and azathioprine to adalimumab monotherapy for 52 weeks. There was no difference between the 2 groups for induction of remission (RR, 1.31; 95% CI, 0.80–2.14) or maintenance of remission (RR, 1.13; 95% CI, 0.72–1.78).[15] However, combination therapy was associated with higher rates of endoscopic remission at week 26 compared with adalimumab monotherapy (48 of 57 [84.2%] vs 37 of 58 [63.2%]; $P = .02$). The certainty of evidence was very low, rating down for risk of bias (unblinded study with high rates of drug discontinuations due to treatment intolerance), indirectness of outcomes, and imprecision from the low OIS.

Importantly, use of combination therapy may be even more important in the subset of patients who have developed secondary nonresponse to TNFα antagonists. Roblin et al[16] noted that combination therapy resulted in improved outcomes without clinical failure or unfavorable pharmacokinetics at 24 months, with improvements of 77%–78% for TNFα antagonists with a thiopurine compared with 22% with TNFα antagonists monotherapy ($P < .001$).

There were no RCTs to provide data on combination therapy using vedolizumab or ustekinumab with a thiopurine or methotrexate.

The mechanism by which combination therapy provides improved induction and maintenance of remission is unclear. Adding the thiopurine or methotrexate to infliximab may result in improved drug levels and lower risk of immunogenicity by preventing anti-drug antibody formation. It is possible that the benefits of combination therapy might be achieved by therapeutic drug monitoring, using the information obtained to adjust drug dose or dosing interval. This option may provide the same benefits of combination therapy without the risk and inconvenience of adding the thiopurine or methotrexate. Importantly, if the focus is on reduction of immunogenicity, the potential benefits of combination therapy with newer biologics like vedolizumab and ustekinumab may not be beneficial because these drugs are less immunogenic compared with infliximab.

Harms that must be considered when selecting combination therapy include the increased risk of infections and 2- to 3-fold higher risk of lymphoma compared with TNFα antagonist monotherapy when adding a thiopurine.[17]

Recommendation 6. In adult outpatients with quiescent CD on combination therapy, the AGA makes no recommendation for withdrawal of either the immunomodulator or the biologic over ongoing combination therapy of a biologic and an immunomodulator.
(No recommendation, knowledge gap)

There were 3 RCTs that included 161 patients who were in maintenance of remission on combination therapy with TNFα antagonists and immunomodulators for at least 6 months (2 trials of infliximab-based combination therapy, 1 trial of adalimumab-based combination therapy). Overall, there were no significant differences in the risk of relapse over 12–24 months in patients who continued combination therapy vs withdrew immunomodulators (RR, 1.02; 95% CI, 0.71–1.46). The certainty of evidence was rated as very low due to risk of bias (unblinded trials) and very serious imprecision (wide 95% CI and the inability to exclude significant benefit or harm with continuing or combination therapy). There were no RCTs comparing continued combination therapy to withdrawal of the biologic. There was a single prospective cohort study of 115 patients with CD who were on combination therapy and discontinued infliximab.[18] The risks of relapse though was 44% at 1 year and 52% at 2 years.

Although combination therapy is associated with a higher risk of complications compared with use of a single agent, it is possible that cessation of the immunomodulator may result in some patients losing response to the biologic. This risk, however, may be mitigated with use of therapeutic drug monitoring.[19] Based on limited observational data, treatment strategies in which the biologic drug is discontinued and the immune modulator is continued might lead to a high risk of relapse. Given the limited data to support a recommendation for or against this cessation of drug when used in combination, the Panel opted to make no recommendation.

Recommendation 7. In adult outpatients with moderate to severe CD, the AGA suggests early introduction with a biologic with or without an immunomodulator rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids. *(Conditional recommendation, low certainty evidence)*

The evidence informing this recommendation was based on several RCTs. D'haens et al[20] randomized patients to early combination therapy with an immunosuppressant and infliximab compared with conventional step therapy in which patients were first given corticosteroids followed by azathioprine and infliximab. At 52 weeks, 61.5% of patients

in the early combined immunosuppression group were in corticosteroid- and surgery-free remission compared with 42.2% in the step-up therapy arm (RR for failure to achieve remission, 0.67; 95% CI, 0.46–0.97). A long-term extension arm of this trial to 8 years suggested lower rates of clinical relapse, and corticosteroid use in the patients randomized to early combination therapy. The certainty of the evidence was low due to risk of bias (open label trial) and imprecision (low OIS).

The REACT (Randomised Evaluation of an Algorithm for Crohn's Treatment) study was an open-label cluster randomized trial that compared an algorithmic approach of early combination therapy with an immunomodulator and biologic drug or conventional management of CD in 1982 patients.[21] At 12 months, there was no significant difference in rates of corticosteroid-free remission (66% early combination therapy vs 62% in usual care). However, at 24 months, patients in the early combination therapy arm had lower rates of major adverse disease-related complications compared with conventional management (hazard ratio, 0.73; 95% CI, 0.62–0.86).

Data for early use of thiopurines alone was evaluated by Cosnes et al[22] in an RCT of 122 patients in which patients were randomized to early azathioprine (within 6 months of CD diagnosis) vs conventional management in which azathioprine was only used in cases of corticosteroid dependency, in those not responding to corticosteroids, or those with perianal disease.[22] During a 3-year follow-up, no significant differences were observed in the risk of corticosteroid-requiring flare (58 of 65 [89%] vs 61 of 67 [91%]; $P = .73$), hospitalization (22 of 65 [34%] vs 26 of 67 [39%]; $P = .74$), or CD-related surgery (5 of 65 [8%] vs 4 of 67 [6%]; $P = .68$). Evidence was rated low due to risk of bias (open-label trial) and imprecision (very wide CI).

Data for 5-aminosalicylates indicate that these drugs are not effective for the management of moderate to severe CD (see question 9 below).

The Guideline Panel used these data to determine that delaying appropriate therapy by using a step-up policy may result in clinical harm from delaying appropriate disease treatment. The Panel acknowledged that the treatment paradigm of earlier therapy with a combination of a immunomodulator and a biologic drug or biologic monotherapy may result in overtreating some patients and potentially exposing them to treatment-related risks and costs with limited benefit. However, the step-up paradigm is associated with a potential risk of harm from disease progression related to inadequate disease therapy.

Recommendation 8A. In adult outpatients with moderate to severe CD, the AGA suggests the use of corticosteroids over no treatment for induction of remission. *(Conditional recommendation, moderate certainty of evidence)*

Recommendation 8B. In adult outpatients with moderate to severe CD, the AGA recommends against the use of corticosteroids over no treatment for maintenance of remission. *(Strong recommendation, moderate certainty of evidence)*

Systemic corticosteroids were evaluated in 2 RCTs with 267 patients. Corticosteroids at a prednisone dose equivalent up to 60 mg/d was more effective than placebo for induction of remission (RR, 0.57; 95% CI, 0.45–0.73). The certainty of evidence was low, rating down for bias (sequence generation and allocation concealment not reported) and imprecision given the low OIS. Three RCTs with 367 patients compared controlled-release budesonide vs placebo. Budesonide was more effective than placebo for induction of remission (RR, 0.74; 95% CI, 0.60–0.91) albeit 2 of the studies were in patients with mild to moderate CD. The certainty of evidence was rated low due to indirectness (nonmoderate to severe CD) and imprecision (low OIS).

Systemic corticosteroids as a maintenance drug were evaluated in 3 studies with 269 patients and were not more effective than placebo for maintenance of remission (RR, 1.02; 95% CI, 0.81–1.29). The certainty of evidence was low due to risk of bias (unclear randomization) and imprecision (wide 95% CI that could not exclude significant benefit or harm).

The Technical Review Panel performed an additional comparison between budesonide and systematic corticosteroids. Five RCTs compared controlled ileal release budesonide to corticosteroids, with budesonide being inferior to systematic corticosteroids for inducing remission (RR for failure to induce 1.20; 95% CI, 1.01–1.44). Nevertheless, in patients with CD involving the distal ileum and/or ascending colon who are more concerned about systemic corticosteroids and less concerned about the lower efficacy, they may reasonably choose budesonide over systematic corticosteroids.

The Panel noted that although systemic corticosteroids play an integral role in the induction of remission in patients with moderate to severe luminal CD, the adverse effects in both the short and long-term with systematic corticosteroids are substantial (see technical review). Budesonide, however, due to a first-pass metabolism in the liver is better tolerated with fewer adverse effects and no significant alterations on serum cortisol levels.[23] Nevertheless, neither systemic corticosteroids nor budesonide have a role in long-term maintenance of remission in patients with moderate to severe luminal CD.

Recommendation 9. In adult outpatients with moderate to severe CD, the AGA recommends against the use of 5-aminosalicylates or sulfasalazine over no treatment for the induction or maintenance of remission. *(Strong recommendation, moderate certainty evidence)*

Two RCTs compared 5-aminosalicylates with placebo for induction of remission but the underlying severity of CD was not clear. There was no specific subgroup with moderate to severe CD that could be extracted for our analysis. In these 2 studies, 5-aminosalicylates did not reach the MCID of 10% over placebo (RR, 0.90; 95% CI, 0.81–1.00). Sulfasalazine was evaluated in 3 RCTs, but the overall severity of CD was not clear. In these studies, sulfasalazine was more effective than placebo for induction of remission over 6–17 weeks (RR, 0.78; 95% CI, 0.65–0.93). However, it

was unclear whether these patients had moderate to severe luminal CD.

For maintenance of remission, 4 studies (415 patients) treated with sulfasalazine and 11 RCTs with 2014 patients treated with 5-aminosalicylates did not find either drug to be more effective than placebo for maintenance of remission (sulfasalazine: RR, 0.98; 95% CI, 0.82–1.17, 5-aminosalicylates: RR, 1.02; 95% CI, 0.92–1.16). The certainty of evidence was very low for sulfasalazine. This was rated down for bias (sequence generation and allocation concealment), indirectness (wide variability in characteristics and outcome measures, and imprecision (very wide 95% CI). The certainty of evidence for 5-aminosalicylates was moderate, rating down for imprecision (modest benefit and harm could not be excluded).

The Panel noted the robust safety profile of 5-aminosalicylates, but also noted that sulfasalazine is associated with many adverse events (see technical review[10]). The main concern regarding the use of 5-aminosalicylates was the lack of data on their use for induction of remission in moderate to severe luminal CD and the data showing their lack of efficacy for maintenance of remission. In general, the Panel noted that most drugs started for induction of remission should be continued for maintenance of remission and that starting a drug that is ineffective can lead to delays in appropriate therapy and worsening disease. Given the lack of induction data in patients with moderate to severe CD, and given the clear failure of 5-aminosalicylates to maintain remission, the Panel recommended against the use of 5-aminosalicylates or sulfasalazine for induction or maintenance of remission for moderate to severe luminal CD.

Pharmacologic Management of Adult Patients With Fistulizing Crohn's Disease

In CD, fistula formation can occur from one loop of bowel to another or from bowel to other structures, such as the bladder or vagina or from bowel to the skin. By far the most common form of fistula are perianal fistula.[24] Data on drug therapy for types of fistula other than perianal fistula are almost totally lacking, so the Technical Review Panel and Guideline Panel limited their focus to the medical management of perianal fistula. Surgical management of fistulizing CD was also outside the scope of the technical review and guideline.

Recommendation 10A. In adult outpatients with CD and active perianal fistula, the AGA recommends the use of infliximab over no treatment for the induction and maintenance of fistula remission. *(Strong recommendation, moderate certainty evidence)*

Recommendation 10B. In adult outpatients with CD and active perianal fistula, the AGA suggests the use of adalimumab, ustekinumab, or vedolizumab over no treatment for the induction or maintenance of fistula remission. (*Conditional recommendation, low certainty evidence)*

Comment: Evidence suggests certolizumab pegol may not be effective for induction of fistula remission.

Recommendation 10C. In adult outpatients with CD and active perianal fistula without perianal abscess, the AGA suggests against the use of antibiotics alone over no treatment for the induction of fistula remission. *(Conditional recommendation, low certainty evidence)*

Infliximab was the only medication that had a dedicated RCT to assess the efficacy of the drug to induce fistula remission. Ninety-four patients with symptomatic draining fistula were randomized to infliximab or placebo. Infliximab achieved a greater rate of induction of remission of fistula closure within 18 weeks (RR, 0.52; 95% CI, 0.34–0.78). The certainty of evidence was moderate, rating down only for imprecision due to the low OIS.

Adalimumab was evaluated in a subgroup analysis of 2 RCTs of 77 patients with symptomatic draining fistula. Adalimumab was not effective in complete fistula closure within 4 weeks compared with placebo (RR, 1.08; 95% CI, 0.93–1.27). However, indirect data indicate that adalimumab may be effective for induction of luminal CD, and in the network meta-analysis adalimumab does appear effective for induction and maintenance of remission. Unfortunately, there are no dedicated RCTs using adalimumab for induction of remission or maintenance of remission for the primary outcome of fistula remission. Similarly, certolizumab pegol was also evaluated in a subgroup analysis of 2 RCTs including 165 patients and did not show a benefit compared with placebo for inducing fistula remission (RR, 1.01; 95% CI, 0.80–1.27). The ineffectiveness of certolizumab pegol was further supported by the indirect evidence of the failure of certolizumab pegol to induce remission in moderate to severe luminal CD. The certainty of evidence was very low quality for both drugs, rating down for very serious imprecision (wide 95% CI, which could not rule out significant risk of benefit or harm) and risk of bias (randomization was not stratified based on presence/abscess of fistula).

Vedolizumab was evaluated in a subgroup analysis of a single RCT with 165 patients who had a clinical response to luminal disease, but had symptomatic draining fistula at baseline. Vedolizumab may be more effective than placebo for achieving complete fistula closure (RR, 0.81; 95% CI, 0.63–1.04) within 14 weeks. The certainty of the evidence was very low, rating down for risk of bias (randomization not stratified by presence/absence of fistula), indirectness (all patients received induction therapy with vedolizumab), and imprecision (95% CI crossing unity).

Ustekinumab was evaluated in a pooled analysis of 4 trials of induction therapy (238 patients) with active draining fistula. Ustekinumab was more effective than placebo in achieving fistula remission (RR, 0.85; 95% CI, 0.73–1.99). The certainty of evidence was rated as low quality due to risk of bias (because randomization was not stratified by presence or absence of fistula), and imprecision (OIS not met).

Antibiotics were compared with placebo in a single 3-arm RCT of 25 patients with active draining perianal fistula. The 3 arms were ciprofloxacin, metronidazole, and placebo. Antibiotics did not show more efficacy compared with placebo for induction of fistula remission (RR, 0.94; 95% CI, 0.67–1.33). The certainty of evidence was low due to very

serious imprecision (very wide 95% CI, where significant benefit or harm with antibiotic monotherapy could not be excluded).

Data on maintenance of remission for the biologics were present for some but overall quite limited. In general, a drug that is started for induction of remission is typically continued for maintenance of remission. Similarly, data on thiopurines were also quite limited and the Guideline Panel did not find sufficient evidence to formulate a recommendation.

Recommendation 11. In adult outpatients with CD and active perianal fistula without perianal abscess, the AGA recommends the use of biologic agents in combination with an antibiotic over a biologic drug alone for the induction of fistula remission. *(Strong recommendation, moderate certainty evidence)*

Two RCTs involving use of TNFα antagonists (infliximab or adalimumab) in combination with ciprofloxacin for 12 weeks was significantly more effective than using the corresponding TNFα antagonist alone in achieving fistula closure over 12–18 (RR, 0.42; 95% CI, 0.26–0.68). The certainty of evidence was moderate, rating down for imprecision due to the low OIS.

Equity

A recent review on the effects of race and ethnicity on the management of IBD patients found conflicting data on the use of medical therapies, specifically biologic agents.[25] Although some studies demonstrated that African American, Asian, and Hispanic patients with CD were less likely to receive biologics compared with White patients, other studies have shown no differences in the use of immunomodulators of TNFα antagonists among patients of different races or ethnicities. This review did highlight that African American and Hispanic populations are less likely to have commercial insurance and are more likely to have Medicaid or be uninsured, which may lead to disparities in care.

Implementation Considerations

The decision of which drug to initiate for moderate to severe CD needs to be individualized to the patient with shared decision-making. Although the data suggest that biologics as a whole are effective drugs, individual drugs may have better efficacy but need to be balanced with patient preference for mode of delivery and ability to obtain insurance approval. Although the initial phase 3 drug trials had very set inclusion and exclusion criteria, not every patient in clinical practice fits these strict criteria when deciding to use the drug. At the time of publication, there were no large randomized head-to-head studies analyzing which drug is most efficacious for moderate to severe CD. As a result, data can be obtained via a network meta-analysis to provide some guidance in this area. The limitation of a network meta-analysis needs to be considered, as these data are derived from the initial drug trials and not all patients seen in clinical practice are included in these initial drug trials. In addition, when formulating the recommendations, net benefits and harms were considered but, in general, the benefits of disease remission outweighed most concerns surrounding risks of adverse events and harms. However, when considering the use of natalizumab, the Panel noted the significant risk of harm from PML and therefore suggested against its use. However, even in this situation, the Panel still noted that some patients who put a high value on the benefits of drug therapy and lower value on PML risk may still consider the drug, with ongoing John Cunningham virus monitoring.

Discussion

These practice recommendations for the medical management of moderate to severe luminal and fistulizing CD were developed using the GRADE framework and in adherence to the standards established by the National Academy of Medicine for the development of trustworthy guidelines.[11,26] The guideline recommendations incorporated data on the benefits and risks of treatment and nontreatment, along with patient values and preferences. The goal of this guideline is to promote high-value, evidence-based care and to facilitate shared decision-making with patients in the management of moderate to severe luminal and fistulizing CD.

Current evidence supports use of multiple drug classes, including TNFα antagonists, anti-integrins, anti-interleukin 12/23 inhibitors, methotrexate (subcutaneous/intramuscular), and corticosteroid for induction of remission, and the use TNFα antagonist, anti-integrins, anti-interleukin 12/23 inhibitors, thiopurines, and methotrexate (subcutaneous/intramuscular) for the maintenance of remission. Thiopurines and methotrexate were also suggested for use as combination therapies with TNFα antagonists for induction and maintenance of remission compared with TNFα antagonist monotherapy. The Panel made no recommendation for combination therapy with other biologics, given a lack of data. Similarly, no recommendation could be made regarding withdrawal of either immunomodulators or a biologic agent over ongoing combination therapy in quiescent CD. The Panel recommended against the use of natalizumab, given the adverse effect profile and availability of other medications to manage moderate to severe CD. The Panel also recommended against the use of thiopurines for induction of remission, corticosteroids for maintenance of remission, and the use of 5-aminosalicylates for induction or maintenance of remission due to overall lack of efficacy. Finally, the Panel suggests the early introduction of a biologic with or without an immunomodulator, rather than delaying their use until after failing 5-aminosalicylates and/or corticosteroids. In patients who were initially treated with an TNFα antagonist with a primary nonresponse, the AGA recommends the use of ustekinumab and suggests the use of vedolizumab. However, in cases of those who previously responded to infliximab (secondary nonresponse), the AGA recommends the use of adalimumab or ustekinumab and suggests the use of vedolizumab. Of note, if adalimumab was the first drug failure with subsequent secondary

nonresponse, indirect evidence suggests the consideration of infliximab as a second-line agent.

In fistulizing disease, infliximab was noted to have the most robust evidence supporting its use, but other drugs did show efficacy, including adalimumab, ustekinumab, and vedolizumab. In contrast, evidence suggests certolizumab pegol may not be effective for induction of fistula remission. In cases of perianal disease with an active fistula but no abscess, combining biologics with antibiotics was most effective in inducing fistula remission.

Future Research Needs and Evidence Gaps

The Guideline Panel identified multiple knowledge gaps and areas for future research in patients with moderate to severe luminal and fistulizing CD. The last 2 decades have witnessed many important advances in CD treatment with associated improved outcomes, but there continues to be a significant fraction of patients who fail to respond sufficiently to the available treatments. In addition to the ongoing development of new drugs and drug classes, there remain unanswered questions about the optimal application of the current therapies. Importantly, direct comparisons of the benefits and harms, especially over the long-term, of the available drugs and treatment strategies are mostly lacking. There remains an urgent need for improved patient-specific predictors, clinical and biologic, of response and harm to a particular drug or drug class to improve the rational choice of initial and second-line therapeutic agents in a given patient. The need is especially great in special populations, such as those with fistulizing disease or aggressive and recurrent fibrostenosing disease. Overall, the data on risk-stratifying individual patients into low and high risk of disease complications and disability remain poor. These data would allow clinicians to better understand the optimal timing of initial therapies and the optimal duration of therapies, facilitating better shared decision-making with patients based on their values and preferences. Almost all of our data on drug efficacy and safety are based on White patients from a narrow age range. We urgently need data on treatment outcomes in diverse populations, including African American, Latinx, and elderly patients, to name just the most glaring deficiencies. We urgently need better data on benefits and risks of combining drugs, not just biologic drugs with immunomodulators, but also the combination of biologic drugs with one another, a strategy that might leverage the different mechanisms of actions of different drug classes to good effect. Fundamental questions, such as ideal target of therapy in CD, also remain unanswered. Many of the studies referenced in this guideline regarding drug efficacy focused on clinical response and remission, as defined by the Crohn's Disease Activity Index, and other mostly symptom-based indices, but newer studies now include rates of endoscopic remission and, in some cases, histologic remission. Long-term patient outcomes appear to be better when we achieve these more objective and robust targets of response and remission, but there remains uncertainty in clinical practice about when to declare a drug successful or when to change treatment strategies looking for a better outcome. For patients that do respond well, such as among those who achieve endoscopic or histologic remission, we need data to guide us in when or how to de-escalate or discontinue therapy. In summary, although our ability to treat patients with moderate to severe CD has improved markedly over the past 2 decades, there remains much left to do to ensure that every patient has the best possible outcome.

Plans for Updating This Guideline

Guidelines are living products. To remain useful, they need to be updated regularly as new information accumulates. The guidelines are reviewed annually at the AGA Clinical Practice Guideline Committee. In addition, this document will be updated when major new research is published. The need for an update will be determined no later than 2024.

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