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American Gastroenterological Association Institute Technical Review on the Use of Thiopurines, Methotrexate, and Anti–TNF-α Biologic Drugs for the Induction and Maintenance of Remission in Inflammatory Crohn's Disease

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that causes significant morbidity and represents a considerable burden to society and the health care system.[1–5] Based on the latest administrative data, it is estimated that 300,000 to 500,000 Americans have CD.[2,6] A recent study reported annual treatment costs of $8265 per patient, which extrapolates to yearly costs of $2.5 to $4 billion for the American population with CD.[3]

Two main principles guide the medical therapy of patients with CD. First, because this is a lifelong, relapsing disorder, therapy to induce remission (inductive therapy) is followed by therapy to maintain remission (maintenance therapy).[7] Second, the choice of inductive and maintenance therapies depends on the severity of the disease and the response to less effective strategies. In this progressive approach to therapy, mesalamine, antibiotics, and budesonide are used in patients with mild disease. Systemic corticosteroids, immunomodulators, and anti–tumor necrosis factor (TNF)-α agents are used in patients with moderately severe CD or in patients who fail to respond to therapy for mild disease. The immunomodulators include the thiopurine analogues, azathioprine (AZA) and 6-mercaptopurine (6-MP), and methotrexate (MTX). Anti–TNF-α agents approved for use in the United States include infliximab (IFX), adalimumab (ADA), and certolizumab pegol (CZP).

In this technical review, the American Gastroenterological Association addresses the relative positioning of immunomodulators and anti–TNF-α biologic agents in inducing and maintaining clinical remission in patients with inflammatory (luminal) CD. From the standpoint of patients and clinicians, selecting among immunomodulator monotherapy, anti–TNF-α monotherapy, and combination therapy is a common clinical dilemma. Providing optimal, evidence-based care to the many patients who are candidates for these potentially costly and/or toxic therapies is of critical importance to the health care system as well. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used in this technical review to assess the evidence on immunomodulators and anti–TNF-α-biologic agents in the (1) induction of remission in adult patients who have moderately severe inflammatory CD despite therapy with mesalamine, antibiotics, corticosteroids, and/or immunomodulators and (2) maintenance of medically induced remission. GRADE has been adopted by several national and international societies, including the American Gastroenterological Association,[8] and is becoming the common methodology for the streamlined development of clear, transparent, and actionable guidelines.[9]

An accompanying report[10] in this issue of GASTROENTEROLOGY integrates the results of this technical review with the other GRADE criteria to produce a set of recommendations.

Methods

Overview

This technical review (and the accompanying guideline) was based on the GRADE framework. In developing this technical review, the authors first formulated a series of specific questions that were to be answered by the guideline. The authors then identified the outcomes that were significant to answering each question and rated them as critical or important. Next, the group systematically reviewed and summarized the evidence for each outcome across studies, assessed the quality of evidence for each outcome, and finally integrated the evidence across all the outcomes to answer each specific question. The quality of the evidence was classified into 4 categories: high, moderate, low, and very low. Assessment of the quality for each outcome took into account the study design, risk of bias, inconsistency (or heterogeneity), indirectness, imprecision, and potential publication bias (see the glossary of terms in Supplementary Methods for further explanations).

Outcomes of Interest

Using the PICO format, which frames a clinical question by defining a specific population (P), intervention (I), comparator (C), and outcome (O), we outlined a total of 16 PICO questions (see Table 1). The patient population with moderate-severe active CD was defined as patients with a Crohn's Disease Activity Index (CDAI) of 220 to 450. The population with CD in remission was defined as patients with a CDAI <150 and not being treated with

Abbreviations used in this paper: ACG, American College of Gastroenterology; ADA, adalimumab; AZA, azathioprine; BSG, British Society of Gastroenterology; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CZP, certolizumab pegol; ECCO, European Crohn's and Colitis Organisation; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; IBD, inflammatory bowel disease; IFX, infliximab; 6-MP, 6-mercaptopurine; MTX, methotrexate; OR, odds ratio; PICO, population, intervention, comparator, and outcome; RCT, randomized controlled trial; RR, relative risk; SIR, standardized incidence ratio; TNF, tumor necrosis factor.

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Table 1. PICO Questions

	Population(s)	Intervention(s)	Comparator	Outcome(s)
1	a. Adults with moderate-severe CD b. Adults with CD in remission	AZA or 6-MP	Placebo	a. Induction of remission; AE: serious infections b. Disease relapse; AE: serious infections and lymphoma
2	a. Adults with moderate-severe CD b. Adults with CD in remission	MTX	Placebo	a. Induction of remission; AE: serious infections b. Disease relapse; AE: serious infections and lymphoma
3	a. Adults with moderate-severe CD b. Adults with CD in remission	Anti–TNF-α	Placebo	a. Induction of remission; AE: serious infections b. Disease relapse; AE: serious infections and lymphoma
4	a. Adults with moderate-severe CD b. Adults with CD in remission	Thiopurine or MTX + anti–TNF-α	Placebo	a. Induction of remission; AE: serious infections b. Disease relapse; AE: serious infections and lymphoma
5	a. Adults with moderate-severe CD b. Adults with CD in remission	Thiopurine	MTX	a. Induction of remission; AE: serious infections b. Disease relapse; AE: serious infections and lymphoma
6	a. Adults with moderate-severe CD b. Adults with CD in remission	Thiopurine or MTX	Anti–TNF-α	a. Induction of remission; AE: serious infections b. Disease relapse; AE: serious infections and lymphoma
7	a. Adults with moderate-severe CD b. Adults with CD in remission	Thiopurine or MTX + anti–TNF-α	Thiopurine or MTX	a. Induction of remission; AE: serious infections b. Disease relapse; AE: serious infections and lymphoma
8	a. Adults with moderate-severe CD b. Adults with CD in remission	Thiopurine or MTX + anti–TNF-α	Anti–TNF-α	a. Induction of remission; AE: serious infections b. Disease relapse; AE: serious infections and lymphoma

NOTE. The following PICOs were excluded from the technical review because of absent or insufficient data: 4a, 4b, 6b, and 7b. Moderate-severe CD was defined as a CDAI from 220 to 450. Remission was defined as a CDAI <150 and not being treated with corticosteroid therapy. Disease relapse was defined as a CDAI ≥ 150 or corticosteroid use or surgery.
AE, adverse events.

corticosteroids. The interventions were immunomodulatory monotherapy, anti-TNF monotherapy, or combination therapy. The comparators were immunomodulatory monotherapy or anti-TNF monotherapy. PICO questions for which there were either no data or insufficient data (eg, in adult patients with moderate-severe CD, should combination therapy with immunomodulators plus anti-TNF therapy versus placebo be used to induce remission?) could not be addressed in this technical review. Evidence profiles were used to display the summary estimates as well as the body of evidence for each clinical question.

For randomized controlled trials (RCTs) evaluating induction, the efficacy outcome considered critical for decision making was corticosteroid-free clinical remission, defined as a CDAI <150 or a Harvey–Bradshaw Index <4. For RCTs evaluating maintenance, the critical efficacy outcome was disease relapse, defined as a CDAI ≥ 150, corticosteroid use, or surgery.

We excluded trials without validated end points, such as trials only reporting subjective symptom improvement and trials evaluating only corticosteroid sparing. With regard to studies of induction with immunomodulators, which are agents with a delayed onset of action, we included studies with at least 12 weeks of therapy. Conversely, we excluded trials that evaluated remission after more than 26 weeks of immunomodulator therapy, because an agent cannot properly be considered inductive and clinically relevant if its onset of action occurs beyond 26 weeks. For studies evaluating maintenance, only medically induced remission was evaluated (ie, we excluded trials that evaluated maintenance of surgically induced remission). It should be noted that the thiopurine and MTX maintenance studies were conducted before the anti–TNF-α era (ie, the patients achieved remission with corticosteroids, mesalamine, and/or antibiotics). Interventions were analyzed based on their ability to reduce an undesirable outcome: failure to achieve clinical remission (in induction trials) or failure to prevent disease relapse (in maintenance trials). Based on clinical judgment, we considered a relative reduction of failure to achieve (or maintain) remission of 20% as the minimum clinically important difference for immunomodulators or anti–TNF-α agents when compared with placebo and 10% when comparing drug classes.

We selected serious infections and lymphoma as important adverse events potentially associated with serious morbidity or, rarely, mortality. Serious infection was defined as infection that led to hospitalization (the definition used by the majority of studies). These outcomes were considered important but not critical for decision making. Because lymphoma is usually associated with long-term therapy, we assessed the risk of lymphoma only during maintenance therapy.

Literature Search

Three separate literature searches were conducted: one for evidence summaries (such as meta-analyses); one for RCTs for the efficacy, infection, and lymphoma outcomes; and one for observational evidence to supplement the data on infection and lymphoma. An information specialist developed each search with input from the project team. All search results were imported using bibliographic management software for de-duplication and title and abstract screening.

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and EMBASE. Parallel searches included the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register, and HTA Database. The search strategy comprised controlled vocabulary, including the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts included and combined were "Crohn disease" and "immunomodulator therapy" and "anti-tumor necrosis factor." Methodological filters were applied to limit retrieval to RCTs, meta-analyses, systematic reviews, and health technology assessments. The results were limited to English, human, and 1995 onward. The second search consisted of the main search concepts "Crohn disease" and "immunomodulator therapy" and "anti-tumor necrosis factor" plus "lymphoma." The results were limited to English language and 2010 onward, because prior systematic reviews using appropriate search strategies had adequately covered earlier time frames. A search for observational evidence on