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AGA Technical Review on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease

Siddharth Singh,[1] Deborah Proctor,[2] Frank I. Scott,[3] Yngve Falck-Ytter,[4] and Joseph D. Feuerstein[5]

[1]Division of Gastroenterology and Division of Biomedical Informatics, Department of Medicine, University of California, San Diego, La Jolla, California; [2]Division of Gastroenterology, Department of Medicine, Yale School of Medicine, New Haven, Connecticut; [3]Division of Gastroenterology and Hepatology, Department of Medicine, University of Colorado, Anschutz Medical Campus, Aurora, Colorado; [4]Division of Gastroenterology and Liver Disease, Case Western Reserve University, Cleveland, Ohio; and [5]Division of Gastroenterology and Center for Inflammatory Bowel Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts

The incidence and prevalence of Crohn's disease (CD) is rising globally. Patients with moderate to severe CD are at high risk for needing surgery and hospitalization and for developing disease-related complications, corticosteroid dependence, and serious infections. Optimal management of outpatients with moderate to severe luminal and/or fistulizing (including perianal) CD often requires the use of immunomodulator (thiopurines, methotrexate) and/or biologic therapies, including tumor necrosis factor–α antagonists, vedolizumab, or ustekinumab, either as monotherapy or in combination (with immunomodulators) to mitigate these risks. Decisions about optimal drug therapy in moderate to severe CD are complex, with limited guidance on comparative efficacy and safety of different treatments, leading to considerable practice variability. Since the last iteration of these guidelines published in 2013, significant advances have been made in the field, including the regulatory approval of 2 new biologic agents, vedolizumab and ustekinumab. Therefore, the American Gastroenterological Association prioritized updating clinical guidelines on this topic. To inform the clinical guidelines, this technical review was completed in accordance with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. The review addressed the following focused questions (in adult outpatients with moderate to severe luminal CD): overall and comparative efficacy of different medications for induction and maintenance of remission in patients with or without prior exposure to tumor necrosis factor–α antagonists, comparative efficacy and safety of biologic monotherapy vs combination therapy with immunomodulators, comparative efficacy of a top-down (upfront use of biologics and/or immunomodulator therapy) vs step-up treatment strategy (acceleration to biologic and/or immunomodulator therapy only after failure of mesalamine), and the role of corticosteroids and mesalamine for induction and/or maintenance of remission. Finally, in adult outpatients with moderate to severe fistulizing CD, this review addressed the efficacy of pharmacologic interventions for achieving fistula and the role of adjunctive antibiotics without clear evidence of active infection.

Keywords: Inflammatory Bowel Disease; Immunosuppressives; Guidelines; Evidence-based Management; Perianal Fistula; High-value Care.

Crohn's disease (CD) is a chronic inflammatory bowel disease that generally begins in young adulthood and lasts throughout life. Although the incidence and prevalence of CD has stabilized in Western Europe and North America (affecting >0.2% of the population), its incidence continues to rise in newly industrialized countries.[1] Based on population-based cohort studies, the majority of patients with CD have a relapsing–remitting course, with >50% of patients requiring corticosteroids during the course of their disease.[2] Historically, before the introduction of biologic agents, approximately 20% of patients with CD would be hospitalized every year, and 1-, 5-, and 10-year risk of requiring surgery in patients with CD was 24%, 36%, and 47%, respectively.[3] Over the last 2 decades, several therapeutic measures have improved disease outcomes, including earlier diagnosis; introduction and increasing uptake of biologic agents like tumor necrosis factor (TNF)–α antagonists; changes in approach to management of IBD with targeted use of disease-modifying immunosuppressive therapy with treatment intensification based on systematic evaluation of symptoms and disease activity; and earlier detection and endoscopic management of colorectal neoplasia.[4] Consequently, in the biologic era, 1- and 5-year risk of hospitalization is 26% and 40%, respectively; and

Abbreviations used in this paper: **AGA, American Gastroenterological Association; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CIR, controlled ileal release; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations Assessment; Development and Evaluation, JC; John Cunningham, MCID; minimal clinically important difference, OR; odds ratio, PICO; population, intervention; comparator, and outcomes; PML, progressive multifocal leukoencephalopathy; PY, person-years; RCT, randomized controlled trial; RR, relative risk; SIR, standardized incidence rate; TNF, tumor necrosis factor.**

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1-, 5-, and 10-year risk of requiring surgery in patients with CD is 12%, 18%, and 26%, respectively.[5,6]

Conventionally, clinical trials have focused on (cross-sectional) disease activity assessment, leading to regulatory approval and real-world use of immunosuppressive and/or biologic therapies for patients with moderate to severely active disease after failure of conventional therapy. However, over the last decade, there has been increasing recognition that (longitudinal) disease severity assessment, which accounts for cumulative disease-related damage and impact of disease on lifestyle, is vital to risk-stratify patients and ensure timely initiation of risk-congruent disease-modifying therapy.[7] The number of pharmacologic agents available to treat moderate to severe CD has grown over the last 7 years since the last iteration of this guideline, and now includes an anti-integrin agent (vedolizumab) and an interleukin 12/23 antagonists (ustekinumab), with several others in the pipeline. With the availability of multiple treatment options with differences in efficacy and safety profiles, there is considerable practice variability in the use of these drugs in the treatment of outpatients and inpatients with moderate to severe CD.[8,9] Variations in practice may have unintended negative consequences in patient outcomes. Therefore, the American Gastroenterological Association (AGA) prioritized updating prior clinical guidelines on the topic.[10]

Objectives of the Review

This technical review focuses on drugs and treatment strategies for the management of adult (18 years and older) outpatients with moderate to severe luminal and/or fistulizing (including perianal) CD. Patients with moderate to severe luminal CD are those with moderate to severe disease activity based on the Crohn's Disease Activity Index (CDAI), patients who are corticosteroid-dependent or have corticosteroid-refractory CD, and/or patients with severe endoscopic disease activity (large and/or deep ulcers). Although we intended to address management of fistulizing CD, most of the evidence for fistulizing disease is reported for perianal CD.

This technical review addresses the following clinical questions:

- Overall and comparative efficacy and safety of pharmacologic therapies, including thiopurines, methotrexate, TNFα antagonists (ie, infliximab, adalimumab, and certolizumab pegol), vedolizumab, natalizumab, and ustekinumab for the induction and maintenance of remission in adult outpatients with moderate to severe CD, in patients with or without prior exposure to TNFα antagonists;
- Comparative efficacy and safety of biologic monotherapy vs in combination with immunomodulator agents (ie, thiopurines or methotrexate) for the induction and maintenance of remission in adult outpatients with moderate to severe CD;
- Comparison of a top-down (upfront use of biologics and/or immunomodulator therapy) vs step-up treatment strategy (acceleration to biologic and/or immunomodulator therapy only after failure of mesalamine) in adult outpatients with moderate to severe CD; and
- Role of corticosteroids or mesalamine for the induction and maintenance of remission in adult outpatients with moderate to severe CD.
- In adult outpatients with fistulizing CD, what is the efficacy and safety of the following drugs: TNFα antagonists (ie, infliximab, adalimumab, and certolizumab pegol), vedolizumab, and ustekinumab, immunomodulator monotherapy (ie, thiopurines and methotrexate), and antibiotics?
- In adult patients with fistulizing CD (without abscess), is adding antibiotics to standard medical management superior to medical management alone?

This technical review does not address the role of therapeutic drug monitoring in management of biologic-treated patients with IBD (see separate AGA guideline and technical review),[11,12] optimal treatment targets and monitoring strategies in patients with moderate to severe CD, impact of pharmacologic interventions on the risk of colorectal neoplasia in patients with CD, role of biosimilars in the management of CD, or the surgical management of patients with moderate to severe luminal and/or perianal CD. The results of this technical review were used to inform the development of the accompanying clinical guidelines on the pharmacologic management of patients with moderate to severe luminal and fistulizing CD.

Methods

Overview

This technical review and the accompanying guideline were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The members of the Technical Review Panel were selected based on their clinical expertise and methodological training in guideline development. They went through a thorough vetting process for potential conflicts of interest in accordance with the AGA Conflict of Interest Disclosure Process. Through an iterative process, the participants developed focused clinical questions on the pharmacologic management of moderate to severe CD, updating prior questions and adding new questions of interest. After the focused questions were approved by the AGA Governing Board (on September 3, 2019), the Technical Review Panel identified relevant outcomes, systematically reviewed and summarized the evidence for each outcome across studies, and then rated the certainty of the evidence across all outcomes for each clinical question.

Formulation of Clinical Questions and Outcome Measurement

Using the PICO format, which frames a clinical question by defining a population, intervention, comparator, and outcomes (specific), the Panel finalized 11 questions to be addressed (Table 1). In outpatients with moderate to severe luminal CD, induction and maintenance of clinical remission were

Table 1. Focused Clinical Questions on the Pharmacologic Management of Moderate to Severe Crohn's Disease, and Corresponding Questions in PICO Format Addressed in This Technical Review

		PICO question			
Question	Focused question	Patients	Intervention	Comparator	Critical outcomes
Outpatients with moderate to severe luminal CD					
Question 1A	In adult outpatients with moderate to severe CD, what is the overall efficacy of TNFα antagonists (infliximab, adalimumab, certolizumab pegol), vedolizumab and ustekinumab for induction and maintenance of remission?	Adult outpatients with moderate to severe CD	TNFα antagonists (infliximab, adalimumab, certolizumab pegol) Vedolizumab Ustekinumab	Placebo	Induction of clinical remission Maintenance of clinical remission
Question 1B	In adult outpatients with moderate to severe CD, what is the efficacy and safety of natalizumab?	Adult outpatients with moderate to severe CD	Natalizumab	Placebo	Induction of clinical remission Maintenance of clinical remission Serious infection
Question 2	In adult outpatients with moderate to severe CD, what is the comparative efficacy of the different biologic agents (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab) for induction and maintenance of clinical remission in biologic-naïve patients and in patients with prior TNFα antagonist exposure?	Adult outpatients with moderate to severe CD, biologic-naïve and with prior exposure to TNFα antagonist	Infliximab Adalimumab Certolizumab pegol Vedolizumab Ustekinumab	Placebo or another active comparator	Induction of clinical remission Maintenance of clinical remission
Question 3	In adult outpatients with moderate to severe CD, what is the efficacy of immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of remission?	Adult outpatients with moderate to severe CD	Thiopurines (azathioprine, mercaptopurine) Methotrexate (oral or subcutaneous)	Placebo (or mesalamine)	Achieving remission Prevention of relapse (similar to maintenance of remission)
Question 4	In adult outpatients with moderate to severe CD, is biologic monotherapy (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab) superior to immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of remission?	Adult outpatients with moderate to severe CD	Monotherapy with TNFα antagonists (infliximab, adalimumab, certolizumab pegol) Vedolizumab Ustekinumab	Immunomodulators (thiopurines or methotrexate)	Induction of clinical remission Maintenance of clinical remission
Question 5	In adult outpatients with moderate to severe CD, is combination therapy of a biologic agent (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab) with an immunomodulator (thiopurines or methotrexate) superior to biologic	Adult outpatients with moderate to severe CD	Combination therapy with of a biologic agent (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab) + immunomodulator (thiopurines or methotrexate)	Biologic monotherapy (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekiumab)	Induction of clinical remission Maintenance of clinical remission

Table 1. Continued

Question	Focused question	PICO question			
		Patients	Intervention	Comparator	Critical outcomes
	monotherapy for induction and maintenance of remission?				
Question 6	In adult outpatients with quiescent CD on combination therapy with biologic agents and immunomodulators for more than 6 mo, is ongoing combination therapy superior to withdrawal of immunomodulators or biologic agent in decreasing the risk of relapse?	Adult outpatients who achieve remission on combination therapy with biologic and immunomodulators	Discontinuation of immunomodulators	Continuing combination therapy	Maintenance of clinical remission
Question 7	In adult outpatients with moderate to severe CD, is a top-down treatment strategy (early use of combination therapy with biologic agents with immunomodulators) superior to step therapy (escalation to biologic-based therapy only after failure of mesalamine and/or immunomodulators) for achieving remission and preventing disease complications?	Adult outpatients with moderate to severe CD	Top-down therapy Upfront use of biologic-based combination therapy	Step therapy Acceleration to biologic-based combination therapy only after failure of mesalamine or immunomodulators	Achieving remission Prevention of disease-related complications
Question 8	In adult outpatients with moderate to severe CD, what is the efficacy of corticosteroids (prednisone or budesonide) for induction and maintenance of remission?	Adult outpatients with moderate to severe CD	Prednisone (or equivalent) Budesonide	Placebo	Induction of clinical remission Maintenance of clinical remission
Question 9	In adult outpatients with moderate to severe CD, what is the efficacy of sulfasalazine and mesalamine for induction and maintenance of remission?	Adult outpatients with moderate to severe CD	Sulfasalazine Diazo-bonded mesalamine (balsalazide, olsalazine) Mesalamine	Placebo	Induction of clinical remission Maintenance of clinical remission
Outpatients with moderate to severe fistulizing CD					
Question 10	In adult outpatients with fistulizing CD, what is the efficacy and safety of the following drugs: TNFα antagonists (infliximab, adalimumab, certolizumab pegol), vedolizumab, ustekinumab, immunomodulator monotherapy (thiopurines, methotrexate), and antibiotics?	Adults with fistulizing CD	TNFα antagonists (infliximab, adalimumab, certolizumab pegol) Vedolizumab Ustekinumab Thiopurines (azathioprine, mercaptopurine) Methotrexate Antibiotics	Placebo/No treatment	Induction and maintenance of fistula closure
Question 11	In adult outpatients with fistulizing CD (without abscess), is adding antibiotics to TNFα antagonists superior to TNFα antagonists alone?	Adults with fistulizing CD (without abscess) receiving TNFα antagonists	Antibiotics	Placebo	Induction and maintenance of fistula closure

considered critical outcomes for decision-making, whereas achieving endoscopic remission, corticosteroid-free remission, and serious adverse events (serious infections and malignancy) were considered important outcomes. Although the Technical Review Panel recognized discordance between clinical symptoms and endoscopic activity in patients with CD, clinical remission was deemed to be a more patient-centered outcome that led to regulatory approval of all biologic agents. Patient surveys have suggested that patients perceive improving quality of life and complete resolution of symptoms as treatment objectives; only 12.8% prioritize normalization of colonoscopy as treatment objective.[13] Clinical remission was most commonly measured using the CDAI, based on abdominal pain, bowel movements, general wellbeing, complications of disease, abdominal mass, anemia, and weight change. In this scale, scores <150 suggest clinical remission, and scores 150–220, 221–450, and >450 denoting mild, moderate, and severe disease, respectively.[14] For the specific question on efficacy of a strategy of top-down therapy vs gradual step-up therapy, preventing disease-related complications and surgery was deemed to be the critical outcomes. In outpatients with moderate to severe fistulizing CD, induction and maintenance of fistula remission (generally defined as complete cessation of fistula drainage) was considered the critical outcome.

Table 2 summarizes the key messages for all PICOs.

Estimating Absolute Magnitude of Benefit

For trials of induction and maintenance therapy evaluating efficacy of interventions vs placebo, a minimal clinically important difference (MCID) was set at 10%. Hence, if the relative risk of medication for failure to achieve and maintain remission was >0.90, then the medication did not meet the MCID and was not deemed to have a clinically meaningful effect over placebo.

In order to provide a synthesis of the risks and benefits of different interventions to calculate absolute effect estimates, the Technical Review Panel relied on pooled placebo clinical remission rates. In trials of induction therapy with biologic agents, induction of clinical remission with placebo was set at 20%, and maintenance of clinical remission was set at 24%.[15] In trials of thiopurines and methotrexate that reported steroid-free remission as an outcome, pooled rates across placebo arms were used.

Search Strategy and Study Selection Criteria

An experienced medical librarian performed a systematic literature search of multiple electronic databases (Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, and Wiley Cochrane Library) using a combination of controlled vocabulary terms supplemented with keywords. The search was initially conducted on August 4, 2019. A focused update using PubMed for new randomized controlled trials (RCTs) on PICOs of interest was performed on July 31, 2020. For evidence synthesis, RCTs conducted in adults with moderate to severe CD, either luminal or fistulizing disease, evaluating interventions of interest (corresponding to relevant PICOs) were included. If RCT-level evidence was not available for specific PICOs, then observational studies were included to inform evidence. Minimum trial duration for induction and maintenance therapy was 2 weeks and 16 weeks, respectively. Trials in patients with ulcerative colitis were excluded; if a trial included both patients with CD and patients with ulcerative colitis, it was included only if results were stratified by disease or if >70% participants had CD. Because safety outcomes are not well informed by RCTs, representative large cohort studies and high-quality systematic reviews/meta-analyses were used to inform risk of serious infections and malignancy with different therapies. Separate systematic literature reviews were performed to identify studies informing cost-effectiveness and patients' values and preferences for different management strategies in moderate to severe CD. In addition, studies on issues of racial, ethnic, and social disparities and issues of general health equity pertinent to the topic were identified. Details of the search strategy are reported in the Supplementary Material. A total of 6238 articles were identified.

Data Extraction and Statistical Analysis

Data abstraction was conducted in duplicate, independently, by 2 investigators (J.F. and S.S.); disagreements or questions of accuracy were resolved via discussion and consensus with the Technical Review Panel.

For trials of induction and maintenance therapy, outcomes were abstracted and reported as failure to induce clinical remission (in patients with active disease) and failure to maintain remission (in patients with quiescent disease at trial entry), respectively. All analyses were conducted using true intention-to-treat analysis; patients lost to follow-up or excluded from analysis for other reasons were deemed to be treatment failures. Pooled relative risk (RR) or odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel fixed-effects model (in the absence of conceptual heterogeneity and if more than 5 studies) or the DerSimonian-Liard random-effects model.[16] Statistical heterogeneity was assessed using the I^2 statistic.[17] Small study effects were examined using funnel plot symmetry and Egger's regression test, although it is important to recognize that these tests are unreliable when the number of studies is <10.[18] Direct comparisons were performed using RevMan, version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). Due to a paucity of head-to-head trials of active agents, to inform comparative efficacy of different pharmacologic interventions, we relied on a recent network meta-analysis performed by Singh et al[19] using a multivariate consistency model, random-effects meta-regression as described by Ian White. This meta-analysis was rated as moderate quality based on AMSTAR-2 criteria.[20]

Certainty or Quality of Evidence

The certainty of evidence (also known as the quality of evidence) was judged using the GRADE framework.[21] For questions of comparative efficacy of different pharmacologic interventions for which effect estimates were derived from direct and network meta-analyses, we used the following approach: when direct evidence was available from head-to-head comparisons, this was considered the best available evidence; if there were no direct comparisons between 2 interventions (and hence, no direct meta-analysis was feasible), effect estimates from the network meta-analysis were used. In applying GRADE to network meta-analysis, first we judged the certainty of evidence for direct comparisons, then we rated the indirect estimates, starting at the lowest rating of the 2

Table 2. Summary of Key Messages From This Evidence Synthesis

Question	Key message
1A. In adult outpatients with moderate to severe CD, what is the efficacy of TNFα antagonists (infliximab, adalimumab, certolizumab pegol), vedolizumab, and ustekinumab for induction and maintenance of remission?	1. In patients with moderate to severely active CD, infliximab and adalimumab are probably more effective than placebo for inducing remission (*moderate certainty of evidence*); certolizumab pegol may be more effective than placebo for inducing remission (*low certainty of evidence*) 2. In patients with quiescent moderate to severe CD, infliximab, adalimumab, and certolizumab pegol are probably more effective than placebo for maintaining remission (*moderate certainty of evidence*) 3. In patients with moderate to severely active CD, vedolizumab may be more effective than placebo for inducing remission (*low certainty of evidence*). In patients with quiescent moderate to severe CD, vedolizumab is probably more effective than placebo for maintaining remission (*moderate certainty of evidence*). 4. In patients with moderate to severely active CD, ustekinumab is probably more effective than placebo for inducing remission (*moderate certainty of evidence*). In patients with quiescent moderate to severe CD, ustekinumab is probably more effective than placebo for maintaining remission (*moderate certainty of evidence*).
1B. In adult outpatients with moderate to severe CD, what is the efficacy and safety of natalizumab?	In patients with moderate to severely active CD, natalizumab is probably more effective than placebo for inducing and maintaining remission (*moderate certainty of evidence*). However, natalizumab is associated with a serious, potentially fatal infection, PML, which is caused by reactivation of the JC virus (*low certainty of evidence*).
2. In adult outpatients with moderate to severe CD, what is the comparative efficacy of the different biologic agents (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab) for induction and maintenance of remission in biologic-naïve patients and in patients with prior TNFα antagonist exposure?	1. In biologic-naïve patients with moderate to severely active CD, infliximab, adalimumab, and ustekinumab are probably more effective than certolizumab pegol (*moderate certainty of evidence*), and vedolizumab may be more effective than certolizumab pegol (*low certainty of evidence*) for inducing remission. 2. In biologic-naïve patients with moderate to severely active CD, infliximab may be more effective than ustekinumab or vedolizumab for inducing remission (*low certainty of evidence*). The benefit of adalimumab over ustekinumab or vedolizumab for inducing remission is uncertain (*very low certainty of evidence*). 3. In patients with moderate to severely active CD with prior TNFα antagonist exposure, ustekinumab is probably more effective than no treatment (*moderate certainty of evidence*), and vedolizumab may be more effective than no treatment (*low certainty of evidence*) in inducing remission. In a subset of patients with intolerance to or prior response to infliximab (with subsequent loss of response), adalimumab is probably more effective than no treatment in inducing remission (*moderate certainty of evidence*). 4. In patients with moderate to severely active CD with prior TNFα antagonist exposure, the benefit of adalimumab, ustekinumab, or vedolizumab over each other for inducing remission was uncertain (*very low certainty of evidence*). 5. In patients with quiescent moderate to severe CD with initial clinical response to induction therapy, adalimumab is probably more effective than certolizumab pegol (*moderate certainty of evidence*) in maintaining remission. Adalimumab may be more effective than vedolizumab and ustekinumab in maintaining clinical remission (*low certainty of evidence*). 6. In patients with quiescent moderate to severe CD with initial clinical response to induction therapy, the benefit of infliximab over certolizumab pegol, vedolizumab, or ustekinumab in maintaining remission is uncertain (*low to very low certainty of evidence*).
3. In adult outpatients with moderate to severe CD, what is the efficacy of immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of remission?	1. In adult outpatients with moderate to severely active CD, the benefit of thiopurine monotherapy for inducing remission is uncertain (*very low certainty of evidence*). In patients with moderate to severe CD in steroid-induced remission, thiopurines may be effective for maintaining remission (*low certainty of evidence*). 2. In adult outpatients with moderate to severely active CD, subcutaneous methotrexate is probably more effective than placebo for inducing remission (*moderate certainty of evidence*). In adult outpatients with quiescent moderate to severe CD, subcutaneous methotrexate is probably more effective than placebo for maintaining remission (*moderate certainty of evidence*). The benefit of oral methotrexate for inducing and maintaining remission in patients with moderate to severe CD is uncertain (*very low certainty of evidence*). 3. In adult outpatients with moderate to severe CD, the benefit of methotrexate over thiopurines for inducing or maintaining remission was uncertain (*very low certainty of evidence*).

Table 2. Continued

Question	Key message
4. In adult outpatients with moderate to severe CD, is biologic monotherapy (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab) superior to immunomodulator monotherapy (thiopurines, methotrexate) for induction and maintenance of clinical remission?	1. In adult outpatients with moderate to severely **active** CD, biologic monotherapy may be superior to thiopurine monotherapy for achieving remission (*low to moderate certainty of evidence*). In patients with **quiescent** moderate to severe CD, biologic monotherapy may be superior to thiopurine monotherapy for maintaining remission (*low certainty of evidence*). 2. In adult outpatients with moderate to severe CD, the benefit of biologic monotherapy over subcutaneous methotrexate monotherapy for achieving and maintaining remission is uncertain (*very low certainty of evidence*).
5. In adult outpatients with moderate to severe CD, is combination therapy of a biologic agent (infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab) with an immunomodulator (thiopurines or methotrexate) superior to biologic monotherapy for induction and maintenance of remission?	1. In adult outpatients with moderate to severely **active** CD, combination therapy with infliximab + thiopurines is probably superior to infliximab monotherapy for inducing remission (*moderate certainty of evidence*); combination therapy with infliximab + methotrexate may be superior to infliximab monotherapy for inducing remission (*low certainty of evidence*). In patients with **quiescent** moderate to severe CD, combination therapy with infliximab + thiopurines or methotrexate may be superior to infliximab monotherapy for maintaining remission (*low certainty of evidence*). 2. In adult outpatients with moderate to severe CD, combination therapy with adalimumab + thiopurines or methotrexate may be superior to adalimumab monotherapy for induction and maintaining remission (*very low certainty of evidence*) 3. In adult outpatients with moderate to severe CD, the benefit of combination therapy with vedolizumab or ustekinumab + thiopurines or methotrexate over corresponding biologic monotherapy for inducing and maintaining remission is uncertain (*very low certainty of evidence*)
6. In adult outpatients with quiescent CD on combination therapy with biologic agents and immunomodulators for more than 6 mo, is ongoing combination therapy superior to withdrawal of immunomodulators or biologic agent in decreasing the risk of relapse?	1. In adult patients with **quiescent** CD on combination therapy with biologic and immunomodulators for more than 6 mo, the benefit of ongoing combination therapy over withdrawal of immunomodulators is uncertain (*very low certainty of evidence*). 2. In adult patients with **quiescent** CD on combination therapy with biologic and immunomodulators for more than 6 mo, the benefit of ongoing combination therapy over withdrawal of biologics is uncertain (*very low certainty of evidence*).
7. In adult outpatients with moderate to severe CD, is top-down treatment strategy (early use of combination therapy with biologic agents with immunomodulators) superior to step therapy (escalation to biologic-based therapy only after failure of mesalamine and/or immunomodulators) for achieving remission and preventing disease complications?	In adult outpatients with moderate to severely active CD, a top-down treatment strategy (early use of combination therapy with biologic agents with immunomodulators) may be more effective than step therapy (escalation to biologic-based therapy only after failure of mesalamine and/or immunomodulators) for achieving remission and preventing disease-related complications (*low certainty of evidence*)
8. In adult outpatients with moderate to severe CD, what is the efficacy of corticosteroids (prednisone or budesonide) for induction and maintenance of remission?	1. In adult outpatients with moderate to severely active CD involving the distal ileum, CIR budesonide may be effective for inducing remission (*low certainty of evidence*). In patients with quiescent moderate to severe CD involving the distal ileum, CIR budesonide may be effective for maintaining remission (*low certainty of evidence*). However, it is important to note that budesonide has only been approved by the FDA for mild to moderate CD for short-term use. 2. In adult outpatients with moderate to severely active CD, prednisone may be effective for inducing remission (*low certainty of evidence*). In patients with quiescent moderate to severe CD, prednisone may not be effective for maintaining remission (*low certainty of evidence*). 3. In adult outpatients with moderate to severely active CD involving the distal ileum, prednisone is probably more effective than CIR budesonide for inducing remission (*moderate certainty of evidence*).

Table 2. Continued

Question	Key message
9. In adult outpatients with moderate to severe CD, what is the efficacy of sulfasalazine and mesalamine for induction and maintenance of remission?	1. In adult outpatients with moderate to severely active CD, sulfasalazine may be effective for induction of remission (*very low certainty of evidence*). In adult outpatients with quiescent moderate to severe CD, the benefit of sulfasalazine for maintenance of remission is uncertain (*very low certainty of evidence*). 2. In adult outpatients with moderate to severely active CD, the benefit of mesalamine for induction of remission is uncertain (*very low certainty of evidence*). In adult outpatients with quiescent moderate to severe CD, mesalamine is probably not effective for maintenance of remission (*moderate certainty of evidence*).
10. In adult outpatients with fistulizing CD, what is the efficacy and safety of the following drugs: TNFα antagonists (infliximab, adalimumab, certolizumab pegol), vedolizumab, ustekinumab, immunomodulator monotherapy (thiopurines, methotrexate) and antibiotics?	1. In adults with symptomatic fistulizing CD, infliximab is probably effective for achieving fistula closure (*moderate certainty of evidence*). In patients with fistulizing CD in remission, infliximab is probably effective for maintaining fistula closure (*moderate certainty of evidence*). 2. In adults with symptomatic fistulizing CD, the benefit of adalimumab and certolizumab pegol in achieving fistula closure is uncertain (*very low certainty of evidence*). In patients with fistulizing CD in remission, adalimumab and certolizumab pegol may be effective for maintaining fistula closure (*low certainty of evidence*). 3. In adults with symptomatic fistulizing CD, the benefit of vedolizumab and certolizumab pegol in achieving fistula closure is uncertain (*low certainty of evidence*). In patients with fistulizing CD in remission, vedolizumab may be effective for maintaining fistula closure (*low certainty of evidence*). 4. In adults with symptomatic fistulizing CD, ustekinumab may be effective for achieving fistula closure (*low certainty of evidence*). In patients with fistulizing CD in remission, ustekinumab may be effective for maintaining fistula closure (*low certainty of evidence*). 5. In adults with symptomatic fistulizing CD, the benefit of immunomodulator monotherapy in achieving fistula closure is uncertain (*very low certainty of evidence*). In patients with fistulizing CD in remission, immunomodulator monotherapy may be effective for maintaining fistula closure (*low certainty of evidence*). 6. In adults with symptomatic fistulizing CD, antibiotic monotherapy with ciprofloxacin may have a small benefit in achieving fistula closure (*low certainty of evidence*).
11. In adult patients with fistulizing CD (without abscess), is adding antibiotics to TNFα antagonists superior to TNFα antagonists alone?	In adults with symptomatic fistulizing CD without perianal abscess, combination of TNFα antagonists with antibiotics is probably more effective than TNFα antagonists alone for achieving fistula closure (*moderate certainty of evidence*).

pairwise estimates that contributed as first-order loops.[22] We rated down further for imprecision or intransitivity (ie, dissimilarity between studies in terms of clinical or methodologic characteristics). It is important to note that GRADE in the context of clinical guidelines may be different than GRADE in the context of systematic reviews, because the former relies on more comprehensive assessment of risks and benefits, with varying thresholds of confidence for decision-making.

Evidence-to-Decision Framework

Because this technical review was used to inform the development of clinical guidelines, besides a comprehensive risk-to-benefit analysis, information about additional factors, such as patients' values and preferences, cost-effectiveness, equity, and resource use, were also reviewed.[23] These data are summarized in the Results section.

Results

Risk Stratification of Crohn's Disease

The International Organization for the Study of Inflammatory Bowel Diseases proposed an overall index of disease severity using a modified Delphi panel. Those patients with high disease severity are at high risk of developing adverse disease-related complications, including surgery, hospitalization, and disability.[24] In this index, in patients with CD, most important factors suggestive of high disease severity (in order of relative weights) based on a combination of structural damage, inflammatory burden, and impact of quality of life are the following: large or deep mucosal lesions on endoscopy or imaging; presence of fistula and/or perianal abscess; intestinal resections, particularly of segments >40 cm; presence of stoma; extensive disease (ileal involvement >40 cm or pancolitis); at least 10 loose stools per week; presence of strictures; elevated C-reactive protein; lack of symptomatic improvement with prior exposure to biologics and/or immunosuppressive agents; significant impact of disease on activities of daily living; low albumin; presence of anorectal symptoms (eg, anorectal pain, bowel urgency, incontinence, discharge, and tenesmus); anemia; daily abdominal pain, and corticosteroid use within the last 1 year.

Such an empirical approach to risk stratification can inform treatment decisions, wherein patients at higher risk

of disease complications may benefit from more effective therapy despite treatment-related risks. Although we did not use this or other risk stratification schemes in informing absolute effect size with different interventions, we anticipate that health care providers would incorporate risk stratification in informing decisions.

Safety of Pharmacologic Therapies for Moderate to Severe Crohn's Disease

Before discussing the focused questions related to the efficacy and comparative efficacy of pharmacologic therapies for moderate to severe CD, we have briefly summarized the overall and comparative safety of different pharmacologic interventions in large cohort studies and clinical trials, focusing on serious infections and malignancy. It is important to note that clinical trials are selective in enrollment with short duration of follow-up, and data from these trials are often not able to adequately assess the safety of different therapies.

Risk of serious and opportunistic infections. Findings from key nationwide or nationally representative cohort studies on risk of serious and opportunistic infections with IBD pharmacotherapies have been summarized in Supplementary Table 1. Across studies, most consistent risk factors for serious infections are high disease activity and inadequate disease control, need for corticosteroids and opiate medication, and concomitant use of immunomodulators.[25,26]

Tumor necrosis factor–α antagonists. Safety registries have suggested that TNFα antagonists may be associated with 1.5–2 times higher risk of serious infections compared with other immunosuppressive agents. In the TREAT (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry of 6273 patients with moderate to severely active CD (3440 infliximab-treated and 2833 other treatments only) with up to 13 years of follow-up, serious infections occurred at 2.2 events per 100 person-years (PY) in infliximab-treated patients compared with 0.9/100 PY in other-treatments-only patients.[27] In the PYRAMID (Productivity) Safety and Efficacy: Long Term Results in a Dalimumab Treated Patients With Crohn's Disease) registry of 5025 adalimumab-treated patients followed for up to 6 years, treatment-emergent serious infections were reported at a rate of 4.7 events per 100 PY from 556 patients (11.1%).[28] In a retrospective French population-based cohort study using the national health insurance database of 85,850 TNFα antagonist- and/or immunomodulator-treated patients, Kirchgesner and colleagues[29] observed that the combination of TNFα antagonist and immunomodulators is associated with a higher risk of serious infections (requiring hospitalization) (2.2 per 100 PY) compared with patients treated with TNFα antagonist monotherapy (1.9 per 100 PY), which itself is associated with higher risk of infection as compared with immunomodulator monotherapy (1.1 per 100 PY). In a Danish propensity score–matched population-based cohort study, Nyboe Andersen and colleagues[30] estimated that TNFα antagonist–based therapy is associated with 2.1 times higher risk of serious infections within 1 year compared with immunomodulator-based therapy. In a meta-analysis of comparative studies, including registries and observational comparative effectiveness studies, risk of serious infections was modestly higher with combination therapy of TNFα antagonist and immunomodulators vs TNFα antagonist monotherapy (6 cohorts; RR, 1.19; 95% CI, 1.03–1.37).[31] Based on 5 cohorts, median rate of serious infections with TNFα antagonist monotherapy and immunomodulator monotherapy was 3.9 and 2.2 per 100 PY, respectively, with corresponding risk of serious infections being 64% higher with TNFα antagonist monotherapy (RR, 1.64; 95% CI, 1.19–2.27). In a retrospective cohort study using Medicare and Medicaid databases, Lewis and colleagues[32] observed that the risk of serious infections with TNFα antagonists was not significantly different than risks with prolonged corticosteroids, and the former was associated with lower mortality.

Vedolizumab. By virtue of gut specificity of its receptor, vedolizumab is presumed to be a safer biologic, although long-term safety data from registry studies are lacking. Integrated safety analysis from registration trials of vedolizumab (1349 patients with CD) showed that the risk of serious infections was low and not significantly different than rates in placebo-treated patients.[33] Among patients with CD, the incidence rate of serious infections was 3.4 per 100 PY, with perianal abscesses being the most common infection. Opportunistic infections were reported in 30 patients with CD, the most common of which were clostridial infections.

Ustekinumab. Registry studies and large real-world observational studies of ustekinumab in CD are awaited. In an integrated safety analysis of data from 6 phase 2/3 trials of ustekinumab including 2574 patients (1733 PY), incidence of serious infections was 5.02 per 100 PY (vs 5.53 in placebo-treated patients).[34] Extrapolating from other autoimmune diseases like psoriasis, the risk of serious infections with ustekinumab monotherapy may be lower compared with TNFα antagonist monotherapy. However, these findings on the relative safety of ustekinumab in patients with psoriasis should be interpreted with caution, as the dose of ustekinumab approved for use in CD is at least 50% higher than the dose used in psoriasis.

Risk of malignancy. Findings from key nationwide or nationally representative cohort studies on the risk of malignancy with IBD pharmacotherapies have been summarized in Supplementary Table 2.

Thiopurines. Thiopurines have been consistently associated with increased risk of lymphoproliferative diseases. In a meta-analysis of 18 studies, the standardized incidence rate (SIR) of lymphoma in thiopurine-treated patients was 4.9 (95% CI, 3.1–7.8), with higher rates being reported in referral-center studies (SIR, 9.2) vs population-based studies (SIR, 2.8).[35] The level of risk was statistically significant after 1 year of exposure, and risk was elevated in current (SIR, 5.7), but not former users (SIR, 1.4). On modeling, Kotlyar and colleagues[35] estimate the number of patients needed to be treated with thiopurines to cause 1 additional lymphoma ranges from 4598 in those 20–29

years to 325 in those 70–79 years. In another meta-analysis of 8 studies, Ariyaratnam and Subramanian[36] estimated a 2.3 times higher risk of nonmelanoma skin cancer in thiopurine-treated patients (95% CI, 1.5–3.5). Methotrexate has been variably associated with either no significant or a 1.5–5.0 times increased risk of lymphoproliferative disease, based on studies in patients with rheumatoid arthritis.[37]

Tumor necrosis factor–α antagonists. Several large population-based studies have identified no association between TNFα antagonist exposure and solid-organ malignancy.[38,39] TNFα antagonists have been variably associated with a 2- to 5-fold increased risk of lymphoid malignancy in population-based studies. In a French population-based study, Lemaitre and colleagues[40] estimated the annual incidence of lymphoma in patients treated with TNFα antagonist monotherapy vs unexposed patients to be 0.41 per 1000 PY vs 0.26 per 1000 PY; after adjusting for covariates, risk of lymphoma was 2.4 times higher in patients treated with TNFα antagonist monotherapy. This risk was comparable with the risk observed in patients treated with thiopurine monotherapy (OR, 0.93; 95% CI, 0.60–1.44). On meta-analysis of 4 high-quality observational studies, risk of lymphoma did not differ between TNFα antagonist monotherapy and thiopurine monotherapy, with pooled incidence rate ratio of 0.72 (95% CI, 0.48–1.07).[41] Patients exposed to combination therapy had 6.1 times higher of risk lymphoma compared with unexposed patients, and 2.3–2.5 times higher risk compared with patients exposed to monotherapy with either agent. In contrast, long-term follow-up of clinical trials or registry-based studies have not observed an increased risk of malignancy in patients treated with TNFα antagonist monotherapy. On analysis of 1594 patients with CD treated with adalimumab in clinical trials, more than 3050 PY of exposure, Osterman and colleagues observed an increased risk of malignancy in patients treated with combination therapy (SIR, 3.0; 95% CI, 1.7–5.1), but not adalimumab monotherapy (SIR, 0.6; 95% CI, 0.2–1.6).[42] Compared with patients receiving adalimumab monotherapy, those patients receiving combination therapy had an increased risk of malignancy other than nonmelanoma skin cancer (RR, 2.8; 95% CI, 1.1–7.4) and of nonmelanoma skin cancer (RR, 3.5; 95% CI, 1.1–11.1). In a large prospective registry (PYRAMID) of 5025 adalimumab-treated patients with CD over 16,680.4 PY of follow-up, observed lymphoma rate with adalimumab was lower than the estimated background rate.[28] Regardless, the US Food and Drug Administration (FDA) has issued a black box warning on the increased risk of malignancy with TNFα antagonists.[43]

Vedolizumab. Although long-term follow-up and real-world evidence are lacking, safety analyses of clinical trials and open-label extension studies have not observed any significant increase in risk of solid-organ or hematologic malignancies with vedolizumab. Loftus and colleagues[33] reported malignancy in 50 of 2243 patients with IBD (including 32 of 1349 patients with CD, with incidence rate of 0.8 per 100 PY) with vedolizumab exposure in the GEMINI long-term extension study. Indirect treatment comparison network meta-analysis of 23 RCTs suggested no difference in risk of malignancy between patients treated with TNFα antagonist vs vedolizumab (OR, 0.87; 95% CI, 0.26–2.88).[44]

Ustekinumab. In an integrated safety analyses of phase 2/3 trials of ustekinumab for psoriasis, psoriatic arthritis, and CD, the incidence of malignancy (excluding nonmelanoma skin cancer) was low and comparable among ustekinumab-treated patients (0.4 per 100 PY) and placebo-treated patients (0.2 per 100 PY).[34] Combined across indications, the SIRs (with overlapping 95% CIs) for malignancies (excluding cervical cancer in situ and nonmelanoma skin cancers, per Surveillance, Epidemiology, and End Results) in the ustekinumab and placebo groups were 0.6 (0.3–1.0) and 0.3 (0.0–1.9), respectively.

Other adverse effects associated with these medications are summarized in the Supplementary Material.

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

Question 1A. In Adult Outpatients With Moderate to Severe Crohn's Disease, What Is the Efficacy of Tumor Necrosis Factor–α Antagonists (Infliximab, Adalimumab, Certolizumab Pegol), Vedolizumab, and Ustekinumab for Induction and Maintenance of Remission?

Key messages.

1. In patients with moderate to severely active CD, infliximab and adalimumab are probably more effective than placebo for inducing remission (*moderate certainty of evidence*); certolizumab pegol may be more effective than placebo for inducing remission (*low certainty of evidence*).
2. In patients with quiescent moderate to severe CD, infliximab, adalimumab, and certolizumab pegol are probably more effective than placebo for maintaining remission (*moderate certainty of evidence*).
3. In patients with moderate to severely active CD, vedolizumab may be more effective than placebo for inducing remission (*low certainty of evidence*). In patients with quiescent moderate to severe CD, vedolizumab is probably more effective than placebo for maintaining remission (*moderate certainty of evidence*).
4. In patients with moderate to severely active CD, ustekinumab is probably more effective than placebo for inducing remission (*moderate certainty of evidence*). In patients with quiescent moderate to severe CD, ustekinumab is probably more effective than placebo for maintaining remission (*moderate certainty of evidence*).

Effect estimate. Overall, 13 RCTs informed the efficacy of different biologic agents for induction of remission in patients with moderate to severe luminal CD, and 9 trials informed their efficacy for maintenance of remission. Patients across all trials and treatment arms were generally comparable in terms of baseline prognostic variables,

inclusion/exclusion criteria, and co-interventions, although trials of non–TNF-targeting biologics had a higher proportion of patients who had been previously exposed to TNFα antagonists. Definitions of outcomes were generally similar across trials based on CDAI, and assessed between weeks 4 and 12 for induction therapy, and week 22 to 54 for maintenance therapy. Relative and absolute effect estimates are shown in Table 3.

Infliximab vs placebo. All trials evaluating the efficacy of infliximab were conducted in biologic-naïve patients. Based on 2 RCTs (106 patients), infliximab induction therapy was superior to placebo for induction of remission (Supplementary Figure 1).[45,46] In 1 trial, only a single induction dose of infliximab was administered and outcomes were assessed at week 4. In 1 RCT of 223 patients, infliximab maintenance therapy was more effective than placebo in maintaining remission (Supplementary Figure 2).[47]

Adalimumab vs placebo. Based on 3 trials (531 patients), standard induction therapy with adalimumab was superior to placebo for induction of remission (Supplementary Figure 1).[48–54] Of note, 1 trial was conducted exclusively in biologic-naïve patients, whereas another trial (GAIN) was conducted exclusively in patients with prior intolerance or secondary loss of response to infliximab; none of these patients had prior primary nonresponse to a TNFα antagonist. Based on 3 trials (422 patients) in which responders to induction therapy were re-randomized to adalimumab or placebo, adalimumab was superior to placebo for maintenance of remission (Supplementary Figure 2).[50,54,55]

Certolizumab pegol vs placebo. Based on 3 trials of induction therapy (1224 patients), certolizumab pegol was significantly more effective than placebo for induction of clinical remission in patients with moderate to severe CD (Supplementary Figure 1).[56–58] However, the relative magnitude of benefit was 0.92 (RR, 0.92; 95% CI, 0.86–0.92), which was smaller than the predefined MCID threshold of 10% over placebo. In 2 trials of maintenance therapy (1078 patients), in which responders to induction therapy were re-randomized to certolizumab pegol or placebo, certolizumab pegol was superior to placebo for maintenance of clinical remission (Supplementary Figure 2).[56,59]

Vedolizumab vs placebo. In 2 trials (784 patients), vedolizumab was significantly more effective than placebo for induction of clinical remission in patients with moderate to severe CD (Supplementary Figure 3*A*).[60,61] However, the relative magnitude of benefit was 0.92 (RR, 0.92; 95% CI, 0.87–0.97), which was smaller than the predefined MCID threshold of 10% over placebo. Importantly, in these trials, 50%–75% patients were previously exposed to TNFα antagonist(s). In a subset of biologic-naïve patients, vedolizumab was significantly and clinically more effective than placebo (RR, 0.86; 95% CI, 0.77–0.95). Among patients with clinical response to vedolizumab at week 6 or 10, one trial of maintenance therapy demonstrated that vedolizumab was superior to placebo for maintenance of remission (Supplementary Figure 3*B*).[60]

Ustekinumab vs placebo. Based on 3 trials (1177 patients), ustekinumab was superior to placebo for induction of clinical remission in patients with moderate to severe CD (Supplementary Figure 4*A*).[62,63] Two trials included only patients with prior exposure to TNFα antagonist(s). Among patients with clinical response to ustekinumab at week 6 or 8, two trials of maintenance therapy demonstrated that ustekinumab was superior to placebo for maintenance of remission (Supplementary Figure 4*B*).[62,63]

GRADE certainty of evidence. Table 3 summarizes the GRADE certainty of evidence for the studies referenced above. Most of these studies were conducted as registration trials and sponsored by industry. There was no important inconsistency or indirectness identified. For most analyses, the total number of events was <200 (except induction and maintenance of remission with certolizumab pegol and induction of remission with ustekinumab), and hence, evidence was rated down for imprecision due to failure to reach optimal information size. In addition, for comparisons of certolizumab pegol vs placebo, and vedolizumab vs placebo for induction of remission, evidence was rated down twice for very serious imprecision because the summary risk estimate was below the predefined MCID threshold of 10% over placebo.

Potential harms of intervention. Adverse effects associated with different medications have been summarized above. In addition, safety data from the pivotal clinical trials of maintenance therapies with these agents are summarized in Supplementary Table 3.

Discussion. Unlike the prior technical review on this topic, we decided to analyze each TNFα antagonist separately to better inform comparative efficacy of different agents. Although moderate certainty of evidence supported the use of infliximab or adalimumab of inducing remission, only low certainty of evidence supported the use of certolizumab pegol because it did not reach the predefined MCID over placebo. Of note, although infliximab and adalimumab (and vedolizumab and ustekinumab) have been approved by the FDA for inducing and maintaining remission, certolizumab pegol has only been approved for maintaining clinical response in patients with moderate to severely active CD who have an inadequate response to conventional therapy. Certolizumab pegol has not been approved for management of CD by the European Medicines Agency and in Canada.

Question 1B. In Adult Outpatients With Moderate to Severe Crohn's Disease, What Is the Efficacy and Safety of Natalizumab?

Key message. In patients with moderate to severely active CD, natalizumab is probably more effective than placebo for inducing and maintaining remission (*moderate certainty of evidence*). However, natalizumab is associated with a serious potentially fatal infection, progressive multifocal leukoencephalopathy (PML), which is caused by reactivation of the John Cunningham (JC) virus (*low certainty of evidence*).

Table 3. GRADE Evidence Profile Comparing Infliximab, Adalimumab, Certolizumab Pegol, Vedolizumab, and Ustekinumab With Placebo for Induction and Maintenance of Remission in Patients With Moderate to Severe Luminal Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with infliximab				
Infliximab compared with placebo for moderate to severe luminal CD						
Induction of clinical remission (CRITICAL)	43/54 (79.6)	23/52 (44.2)	RR 0.54 (0.39–0.75)	92 fewer per 1000 (from 122 fewer to 50 fewer)	106 (2 RCTs)	⊕⊕⊕◯[c] MODERATE
Maintenance of clinical remission (CRITICAL)	87/110 (79.1)	69/113 (61.1)	RR 0.77 (0.65–0.92)	55 fewer per 1000 (from 84 fewer to 19 fewer)	223 (1 RCT)	⊕⊕⊕◯[c] MODERATE

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with adalimumab				
Adalimumab compared with placebo for moderate to severe luminal CD						
Induction of clinical remission (CRITICAL)	239/263 (90.9)	196/268 (73.1)	RR 0.82 (0.75–0.89)	36 fewer per 1000 (from 50 fewer to 22 fewer)	531 (3 RCTs)	⊕⊕⊕◯[c] MODERATE
Maintenance of clinical remission (CRITICAL)	180/210 (85.7)	127/212 (59.9)	RR 0.70 (0.62–0.79)	72 fewer per 1000 (from 91 fewer to 50 fewer)	422 (3 RCTs)	⊕⊕⊕◯[c] MODERATE

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with certolizumab pegol				
Certolizumab pegol compared with placebo for moderate to severe luminal CD						
Induction of clinical remission (CRITICAL)	489/608 (80.4)	455/616 (73.9)	RR 0.92 (0.86–0.98)	16 fewer per 1000 (from 28 fewer to 4 fewer)	1224 (3 RCTs)	⊕⊕◯◯[d] LOW
Maintenance of clinical remission (CRITICAL)	443/536 (82.6)	393/542 (72.5)	RR 0.88 (0.83–0.93)	29 fewer per 1000 (from 41 fewer to 17 fewer)	1078 (2 RCTs)	⊕⊕⊕◯[e] MODERATE

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Vedolizumab				
Vedolizumab compared with placebo for moderate to severe luminal CD						
Induction of clinical remission (CRITICAL)	320/355 (90.1)	357/429 (83.2)	RR 0.92 (0.87–0.97)	16 fewer per 1000 (from 26 fewer to 6 fewer)	784 (2 RCTs)	⊕⊕◯◯[d] LOW

Table 3. Continued

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Vedolizumab				
Maintenance of clinical remission (CRITICAL)	120/153 (78.4)	94/154 (61.0)	RR 0.78 (0.67–0.91)	53 fewer per 1000 (from 79 fewer to 22 fewer)	307 (1 RCT)	⊕⊕⊕◯[c] MODERATE

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with ustekinumab				
Ustekinumab compared with placebo for moderate to severe luminal CD						
Induction of clinical remission (CRITICAL)	515/588 (87.6)	460/589 (78.1)	RR 0.90 (0.85–0.94)	96 fewer per 1000 (from 131 fewer to 53 fewer)	1177 (3 RCTs)	⊕⊕⊕◯[e] MODERATE
Maintenance of clinical remission (CRITICAL)	137/204 (67.2)	101/200 (50.5)	RR 0.75 (0.64–0.89)	168 fewer per 1000 (from 242 fewer to 74 fewer)	404 (2 RCT)	⊕⊕⊕◯[c] MODERATE

[a]To calculate absolute effect estimate, we used pooled placebo rate of 20% for induction of remission, and 24% for maintenance of remission.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).
[d]Rated down for very serious imprecision because effect estimate was smaller than the minimal clinically important difference of at least 10% over placebo.
[e]Rated down for serious imprecision because 95% CI of effect estimate was smaller than the minimal clinically important difference of at least 10% over placebo.

Effect estimate. In 2 trials of biologic-naïve patients (1424 patients), natalizumab was more effective than placebo for inducing remission, although the 95% CI of the effect estimate crossed the 10% MCID threshold (RR, 0.88; 95% CI, 0.82–0.96) (Supplementary Figure 5*A*).[64,65] In 1 trial of 338 patients with initial response to induction therapy, natalizumab was more effective than placebo in maintaining remission (Supplementary Figure 5*B*).[64]

Potential harms of intervention. Most common adverse events observed in clinical trials of natalizumab in CD were headache and upper respiratory infections. Importantly, during post-marketing surveillance, cases of PML were identified. This is a demyelinating disease of the brain caused by reactivation of the JC virus, without specific treatment beyond reconstitution of the immune system; 3-month mortality with PML is 20%–50%, and survivors frequently experience long-term neurologic deficits.[66] In a comprehensive review of post-marketing sources, clinical studies, and an independent Swedish registry, Bloomgren and colleagues[67] identified 212 confirmed cases of PML among 99,571 patients with multiple sclerosis treated with natalizumab (2.1 cases per 1000 patients). All 54 patients with PML for whom samples were available before the diagnosis were positive for anti-JC virus antibodies. When the risk of PML was stratified according to 3 risk factors (anti-JC virus antibodies, prior use of immunosuppressants, and increased duration of natalizumab treatment), the risk of PML was lowest among the patients who were negative for anti-JC virus antibodies, with the incidence estimated to be 0.09 cases or less per 1000 patients (95% CI, 0–0.48). Patients who were positive for anti-JC virus antibodies, had taken immunosuppressants before the initiation of natalizumab therapy, and had received 25–48 months of natalizumab treatment, had the highest estimated risk (incidence, 11.1 cases per 1000 patients [95% CI, 8.3–14.5]). After these observations, natalizumab is available only through a special restricted distribution

Table 4. GRADE Evidence Profile Comparing Natalizumab With Placebo for Induction and Maintenance of Remission, and Risk of Progressive Multifocal Leukoencephalopathy in Patients With Moderate to Severe Luminal Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with natalizumab				
Induction of clinical remission (CRITICAL)	323/431 (74.9)	633/983 (64.4)	RR 0.88 (0.82–0.96)	24 fewer per 1000 (from 36 fewer to 8 fewer)	1414 (2 RCTs)	⊕⊕⊕◯[b] MODERATE
Maintenance of clinical remission (CRITICAL)	133/170 (78.2)	76/168 (45.2)	RR 0.58 (0.48–0.70)	101 fewer per 1000 (from 125 fewer to 72 fewer)	338 (1 RCT)	⊕⊕⊕◯[c] MODERATE
Risk of PML (CRITICAL)	Positive for JC virus antibody: 0	~1%	RR >20	≤ 0.09 per 1000 patients (95% CI, 0–0.48)	99,571 (registry)	⊕⊕◯◯[d] LOW
	Negative for JC virus antibody: 0	~0.01		11.1 per 1000 patients (95% CI, 8.3–14.5)		⊕⊕◯◯[d] LOW

[a]To calculate absolute effect estimate, we used pooled placebo rate of 20% for induction of remission, and 24% for maintenance of remission.
[b]Rated down for imprecision because 95% CI of effect estimate was smaller than the minimal clinically important difference of at least 10% over placebo.
[c]Rated down for imprecision because optimal information size not met (<200 events).
[d]Rated down for risk of bias (derived from observational studies).

program called the TOUCH Prescribing Program, and should be used as monotherapy. Natalizumab should not be administered to patients who are positive for JC-virus antibodies at baseline (approximately 57% of patients with multiple sclerosis); patients who are started on this agent require frequent monitoring for JC virus seroconversion.[68]

GRADE certainty of evidence. The overall body of evidence supporting the efficacy of natalizumab over placebo was rated as moderate certainty, being rated down for imprecision (Table 4). Low certainty evidence from observational studies suggested natalizumab is probably associated with risk of PML, particularly in patients who are positive for anti-JC virus antibody.

Discussion. The efficacy and safety of natalizumab was not examined in the prior technical review. Natalizumab was the first non–TNFα-targeting biologic for the management of CD in 2008. Although it was effective for inducing and maintaining remission, extensive postmarketing surveillance evaluation confirmed a causative association with PML. CD is not a fatal condition and only affords a modestly higher excess lifetime mortality compared with the general population; in contrast, PML carries a very poor prognosis.[69] Considering PML is very unlikely to occur in the general population with CD, any excess risk of this condition observed with CD is highly unacceptable.

Question 2. In Adult Outpatients With Moderate to Severe Crohn's Disease, What Is the Comparative Efficacy of the Different Biologic Agents (Infliximab, Adalimumab, Certolizumab pegol, Vedolizumab, Ustekinumab) for Induction and Maintenance of Clinical Remission in Biologic-Naïve Patients and in Patients With Prior Tumor Necrosis Factor–α Antagonist Exposure?

Key messages.

1. In biologic-naïve patients with moderate to severely active CD, infliximab, adalimumab, and ustekinumab are probably more effective than certolizumab pegol (*moderate certainty of evidence*), and vedolizumab may be more effective than certolizumab pegol (*low certainty of evidence*) in inducing remission.

2. In biologic-naïve patients with moderate to severely active CD, infliximab may be more effective than ustekinumab or vedolizumab for inducing remission (*low certainty of evidence*). The benefit of adalimumab over ustekinumab or vedolizumab for inducing remission is uncertain (*very low certainty of evidence*).

3. In patients with moderate to severely active CD with prior TNFα antagonist exposure, ustekinumab is probably more effective than no treatment (*moderate certainty of evidence*), and vedolizumab may be more

effective than no treatment (*low certainty of evidence*) in inducing remission. In a subset of patients with intolerance to or prior response to infliximab (with subsequent loss of response), adalimumab is probably more effective than no treatment in inducing remission (*moderate certainty of evidence*).

4. In patients with moderate to severely active CD with prior TNFα antagonist exposure, the benefit of adalimumab, ustekinumab, or vedolizumab over each other for inducing remission was uncertain (*very low certainty of evidence*).
5. In patients with quiescent moderate to severe CD with initial clinical response to induction therapy, adalimumab is probably more effective than certolizumab pegol (*moderate certainty of evidence*) in maintaining remission. Adalimumab may be more effective than vedolizumab and ustekinumab in maintaining clinical remission (*low certainty of evidence*).
6. In patients with quiescent moderate to severe CD with initial clinical response to induction therapy, the benefit of infliximab over certolizumab pegol, vedolizumab, or ustekinumab in maintaining remission is uncertain (*low to very low certainty of evidence*).

Effect estimates and certainty of evidence.

Induction of remission, biologic-naïve patients. No head-to-head trials were identified and all evidence on comparative efficacy was derived from a previously published network meta-analysis.[19] Overall, 8 RCTs including 1458 biologic-naïve patients with moderate to severe CD treated with infliximab (2 trials), adalimumab (2 trials), certolizumab pegol (1 trial), vedolizumab (2 trials), and ustekinumab (1 trial) were included. Results of network meta-analysis are summarized in Table 5. There was moderate confidence in estimates supporting the use of infliximab over certolizumab pegol (OR, 4.33; 95% CI, 1.83–10.27) (evidence rated down for imprecision) and low confidence in estimates supporting its use over vedolizumab (OR, 2.20; 95% CI, 0.79–6.07) and ustekinumab (OR, 2.14; 95% CI, 0.89–5.15) (evidence rated down for very serious imprecision); there was moderate confidence in estimates supporting the use of ustekinumab (OR, 2.02; 95% CI, 1.09–3.75) and adalimumab (OR, 2.97; 95% CI, 1.16–6.70) over certolizumab pegol (evidence rated down for imprecision). There was no significant difference in the efficacy of ustekinumab and vedolizumab as a first-line agent (*very low certainty evidence*).

Induction of remission in patients with prior tumor necrosis factor–α antagonist exposure. No head-to-head trials were identified and all evidence on comparative efficacy was derived from a previously published network meta-analysis.[19] Overall, 6 RCTs including 1606 patients with moderate to severe CD with prior exposure to TNFα antagonists were identified. These included 3 trials conducted exclusively in patients with prior exposure to TNFα antagonists (1 trial of adalimumab and 2 trials of ustekinumab), and 2 subgroup analyses of phase 3 trials (1 each of adalimumab and vedolizumab); 1 trial of vedolizumab (GEMINI-III) included 75% patients with prior exposure to TNFα antagonists. One trial of adalimumab (GAIN) selectively included only patients with prior response or intolerance to infliximab, and excluded patients with nonresponse to infliximab. There were no trials of infliximab or certolizumab pegol in patients with prior exposure to TNFα antagonists that met inclusion criteria. On network meta-analysis, compared with placebo, moderate certainty evidence supported the use of ustekinumab (OR, 2.58; 95% CI, 1.50–4.44) for induction of clinical remission (evidence rated down due to imprecision) (Table 6). In a subset of patients with intolerance to or prior response to infliximab (with subsequent loss of response), moderate certainty

Table 5. GRADE Summary of Findings Reporting the Comparative Efficacy of Different Pharmacologic Agents for Inducing Clinical Remission in Biologic-Naïve Patients With Moderate to Severe Luminal Crohn's Disease Based on Network Meta-Analysis

Medications	Relative effect, OR (95% CI)	Overall quality of evidence
Selected agents vs infliximab		
Adalimumab	0.64 (0.22–1.88)	Low (very serious imprecision)
Certolizumab pegol	0.23 (0.10–0.55)	Moderate (imprecision)
Vedolizumab	0.46 (0.16–1.26)	Low (very serious imprecision)
Ustekinumab	0.47 (0.19–1.12)	Low (very serious imprecision)
Selected agents vs adalimumab		
Certolizumab pegol	0.36 (0.15–0.86)	Moderate (imprecision)
Vedolizumab	0.71 (0.25–1.98)	Low (very serious imprecision)
Ustekinumab	0.73 (0.30–1.76)	Low (very serious imprecision)
Selected agents vs certolizumab pegol		
Vedolizumab	1.97 (0.88–4.41)	Low (very serious imprecision)
Ustekinumab	2.02 (1.09–3.75)	Moderate (imprecision)
Selected agents vs vedolizumab		
Ustekinumab	1.02 (0.45–2.32)	Low (very serious imprecision)

Table 6. GRADE Summary of Findings Reporting the Comparative Efficacy of Different Pharmacologic Agents for Inducing Clinical Remission in Patients With Prior Exposure to Tumor Necrosis Factor–α Antagonists With Moderate to Severe Luminal Crohn's Disease Based on Network Meta-Analysis

Medications	Relative effect, OR (95% CI)	Overall quality of evidence
Selected agents vs placebo		
Adalimumab	3.57 (1.66–7.65)	Moderate (imprecision, indirectness[a])
Vedolizumab	1.53 (0.77–3.06)	Low (very serious imprecision)
Ustekinumab	2.58 (1.50–4.44)	Moderate (imprecision)
Selected agents vs adalimumab		
Vedolizumab	0.43 (0.15–1.20)	Very low (very serious imprecision, intransitivity[b])
Ustekinumab	0.72 (0.28–1.85)	Very low (very serious imprecision, intransitivity[b])
Selected agents vs vedolizumab		
Ustekinumab	1.68 (0.68–4.15)	Very low (very serious imprecision, intransitivity[b])

[a]Adalimumab comparison vs placebo was rated down for indirectness (because adalimumab trials excluded patients with primary nonresponse to infliximab (ie, only included patients who had secondary loss of response or intolerance). When focusing on a subset of patients with patients with intolerance to or prior response to infliximab (with subsequent loss of response), evidence was rated as moderate quality
[b]All comparisons of vedolizumab vs ustekinumab vs TNFα antagonists were rated down for intransitivity due to differences in patient characteristics. Study-level estimates did not 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).

evidence supported the use of adalimumab (OR, 3.57; 95% CI, 1.66–7.65) (evidence rated down due to imprecision). Low certainty evidence supported the use of vedolizumab (OR, 1.53; 95% CI, 0.77–3.06) for induction of clinical remission over placebo, due to very serious imprecision (very wide CIs, crossing unity). On indirect comparison of active interventions, although the effect estimate favored adalimumab and ustekinumab over vedolizumab, the certainty of evidence was rated as very low due to very serious imprecision and intransitivity due to differences in patients included in trials of adalimumab and ustekinumab or vedolizumab. Prior treatment exposure and response is an important effect modifier. Study-level estimates did not 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).

Maintenance of remission in patients with clinical response to induction therapy. No head-to-head trials of maintenance therapy were identified and all evidence on comparative efficacy was derived from a previously published network meta-analysis.[19] Overall, 9 RCTs including 1854 patients with moderate to severe CD treated with infliximab (2 trials), adalimumab (3 trials), certolizumab pegol (1 trial), vedolizumab (1 trial), and ustekinumab (2 trials) were included. All trials re-randomized patients who responded to induction therapy, regardless of prior TNFα antagonist exposure status. On comparison of active interventions, moderate certainty evidence supported the use of adalimumab over certolizumab pegol (OR, 1.97; 95% CI, 1.04–3.73) (evidence rated down for imprecision) (Table 7). Low certainty evidence supported the use of adalimumab over ustekinumab (OR, 2.19; 95% CI, 1.15–4.16) and vedolizumab (OR, 1.96; 95% CI, 0.93–3.85) for maintenance of remission (evidence rated down for imprecision and intransitivity due to difference in characteristics of patients included in trials, particularly with regard to prior exposure to TNFα antagonists). The benefit of other interventions over one another was uncertain.

Potential harms of intervention. There has been very limited direct assessment of comparative safety of different biologic interventions. In the network meta-analysis of clinical trials of maintenance therapy, the rate of serious infections was low and was not deemed amenable to network meta-analysis. Large real-world comparative safety data on TNFα antagonists vs vedolizumab vs ustekinumab were not identified.

Discussion. The previous technical review did not examine the comparative efficacy of different biologic agents. In the absence of head-to-head trials, evidence derived from indirect comparisons has been used to inform clinical practice and guidelines. All of the trials included in the analysis reported on biologic-naïve patients and patients with prior TNFα antagonist exposure separately had comparable inclusion criteria, trial design, prevalence of risk factors that likely influence treatment response, and used similar outcome measures. Therefore, in the opinion of the Technical Review Panel, a comparison across trials could be undertaken without the introduction of significant intransitivity at least for biologic-naïve patients. Although all TNFα antagonists have similar mechanism of action, the differences in efficacy among infliximab, adalimumab, and certolizumab pegol may be related to differences in the pharmacokinetics and bioavailability of the drugs, given their different dosing schema and route of administration. Limited real-world observational studies have suggested comparable risk of hospitalization and surgery with

Table 7. GRADE Summary of Findings Reporting the Comparative Efficacy of Different Pharmacologic Agents for Maintaining Clinical Remission in All Patients With Moderate to Severe Crohn's Disease, Who Have Responded to Induction Therapy, Regardless of Prior Biologic Exposure, Based on Network Meta-Analysis

Medications	Relative effect, OR (95% CI)	Overall quality of evidence
Selected agents vs infliximab		
Adalimumab	1.54 (0.75–3.17)	Low (very serious imprecision)
Certolizumab pegol	0.78 (0.41–1.51)	Low (very serious imprecision)
Vedolizumab	0.81 (0.39–1.67)	Very low (very serious imprecision, intransitivity[a])
Ustekinumab	0.71 (0.37–1.36)	Very low (very serious imprecision, intransitivity[a])
Selected agents vs adalimumab		
Certolizumab pegol	0.51 (0.27–0.96)	Moderate (imprecision)
Vedolizumab	0.51 (0.26–1.07)	Low (imprecision, intransitivity[a])
Ustekinumab	0.46 (0.24–0.87)	Low (imprecision, intransitivity[a])
Selected agents vs certolizumab pegol		
Vedolizumab	1.03 (0.54–1.97)	Very low (very serious imprecision, intransitivity[a])
Ustekinumab	0.90 (0.51–1.59)	Very low (very serious imprecision, intransitivity[a])
Selected agents vs vedolizumab		
Ustekinumab	0.87 (0.46–1.66)	Low (very serious imprecision)

[a]All comparisons of vedolizumab and ustekinumab vs TNFα antagonists were rated down for intransitivity because a significant proportion of patients in trials of vedolizumab and ustekinumab had previously been exposed to TNFα antagonists.

infliximab vs adalimumab,[70] and a lower risk of unplanned health care use with infliximab vs certolizumab pegol.[71] Ongoing head-to-head trials would further enhance clinical decision-making and our confidence in comparative efficacy of different medications.

In contrast to biologic-naïve patients, the Technical Review Panel was concerned about significant intransitivity in trials comparing patients with prior TNFα antagonist exposure. Patients treated with adalimumab in clinical trials generally had exposure to only a single TNFα antagonist. In contrast, in trials of vedolizumab or ustekinumab, a significant proportion of patients may have been exposed to 2 or more biologic agents before clinical trial intervention and may be inherently difficult to treat. Similarly, there may be potential differences in efficacy of second-line interventions, depending on underlying reason for discontinuation of prior TNFα antagonist (primary nonresponse vs secondary loss of response vs intolerance).[72] In trials of adalimumab, only patients with loss of response or intolerance to a prior TNFα antagonist were included; patients with primary nonresponse to TNFα antagonist were excluded. In contrast, in trials of vedolizumab and ustekinumab, a substantial proportion of patients had inadequate response to a TNFα antagonist (primary nonresponse). Because of these important uncertainties and differences between study populations, we opted to rate down evidence for intransitivity the evidence regarding prior TNFα antagonist–exposed patients. Recent registry studies have compared real-world effectiveness and safety of ustekinumab vs vedolizumab in patients with CD with prior failure of TNFα antagonists. In a French observational study of 239 patients with TNFα antagonist-refractory CD, Alric and colleagues[73] observed that treatment with ustekinumab was associated with a higher rate of clinical remission (vs vedolizumab: 54.4% vs 38.3%; OR, 1.92; 95% CI, 1.09–3.39), but not steroid-free clinical remission (44.7% vs 34.0%; OR, 1.57; 95% CI, 0.88–2.79) compared with vedolizumab at week 48. Townsend and colleagues[74] observed a higher rate of steroid-free clinical remission in ustekinumab-treated patients compared with vedolizumab-treated patients in their cohort of 130 patients with TNFα antagonist-refractory CD (at 2 months: OR, 2.79; 95% CI, 1.06–7.39; at 12 months: OR, 2.01; 95% CI, 0.89–4.56). In a Dutch registry-based study, Biemans and colleagues[75] observed higher rates of corticosteroid-free clinical remission (ustekinumab vs vedolizumab: OR, 2.58; 95% CI, 1.36–4.90) and biochemical remission (OR, 2.34; 95% CI, 1.10–4.96) with ustekinumab; safety outcomes were comparable between the 2 groups (infections: OR, 1.26; 95% CI, 0.63–2.54; hospitalizations: OR, 0.67; 95% CI, 0.32–1.39).

Safety is a key factor in clinical decision-making. However, there was limited evidence to inform comparative safety of different interventions. There are 2 key factors that determine the safety of biologic therapy in patients with CD. First, the intrinsic immunosuppressive effect of the agent, and second, its effectiveness in controlling disease; achieving corticosteroid-free remission; and avoiding disease-related complications.[76] Biologically, vedolizumab may cause less systemic immune suppression compared with TNFα antagonists and ustekinumab. However, the most consistent risk factors for serious infections have been underlying disease severity and concomitant use of corticosteroids and immunosuppressive therapies. By adequately controlling disease activity and minimizing corticosteroid use, a strategy using effective medications to induce and maintain corticosteroid-free remission may be associated with a lower risk of serious infections compared with using an ineffective but potentially "safer" medication.

Question 3. In Adult Outpatients With Moderate to Severe Crohn's Disease, What Is the Efficacy of Immunomodulator Monotherapy (Thiopurines, Methotrexate) for Induction and Maintenance of Clinical Remission?

Key messages.

1. In adult outpatients with moderate to severely active CD, the benefit of thiopurine monotherapy for inducing remission is uncertain (*very low certainty of evidence*). In patients with moderate to severe CD in steroid-induced remission, thiopurines may be effective for maintaining remission (*low certainty of evidence*).
2. In adult outpatients with moderate to severely active CD, subcutaneous methotrexate is probably more effective than placebo for inducing remission (*moderate certainty of evidence*). In adult outpatients with quiescent moderate to severe CD, subcutaneous methotrexate is probably more effective than placebo for maintaining remission (*moderate certainty of evidence*). The benefit of oral methotrexate for inducing and maintaining remission in patients with moderate to severe CD is uncertain (*very low certainty of evidence*).
3. In adult outpatients with moderate to severe CD, the benefit of methotrexate over thiopurines for inducing or maintaining remission was uncertain (*very low certainty of evidence*).

Effect estimates and certainty of evidence. *Thiopurines for moderate to severe CD, induction and maintenance of remission.* Compared with the previous technical review in 2013, no new trials evaluating the efficacy of thiopurines for inducing remission were identified.[10,77] In 5 trials (380 patients), thiopurines were not significantly more effective than placebo in achieving corticosteroid-free clinical remission in corticosteroid-dependent patients with CD (Supplementary Figure 6*A*). The overall body of evidence supporting the use of thiopurines for induction of remission was rated as very low certainty due to serious risk of bias (due to inadequate blinding and allocation concealment), indirectness (because these trials did not truly assess induction of remission, but rather the ability to achieve corticosteroid-free clinical remission, over a wide range of times, using a variety of disease activity indices with definitions inconsistent with modern definitions of remission) and serious imprecision (due to wide 95% CI) (Table 8). Since the last technical review, 2 more RCTs (beyond 3 RCTs in the original review) evaluating the efficacy of thiopurines for maintaining corticosteroid-free clinical remission were identified.[78,79] On meta-analysis, 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 (Supplementary Figure 6*B*). The overall body of evidence was rated down for serious risk of bias (inadequate blinding) and imprecision (due to low event rate not meeting optimal information size) (Table 8).

Methotrexate (subcutaneous and oral) for moderate to severe CD, induction and maintenance of remission. In contrast to the previous technical review, we opted to examine different routes and dosing of methotrexate separately, due to differences in efficacy. In 1 trial (141 patients) evaluating subcutaneous methotrexate (25 mg/wk) for induction of remission, methotrexate was significantly more effective than placebo for inducing remission (RR, 0.75; 95% CI, 0.61–0.93) (Supplementary Figure 7*A*).[80] Similarly, in 1 trial (76 patients) evaluating subcutaneous methotrexate (15 mg/wk) vs placebo for maintenance of remission in patients who achieved remission with 16–24 weeks of open-label subcutaneous methotrexate (25 mg/wk), Feagan and colleagues[81] observed subcutaneous methotrexate was more effective than placebo for maintaining corticosteroid-free remission (RR, 0.57; 95% CI, 0.34–0.94) (Supplementary Figure 7*B*). The overall body of evidence supporting subcutaneous methotrexate for inducing and maintaining remission in patients with moderate to severe CD was moderate certainty, with evidence being rated down for imprecision due to small sample size (Table 8). In contrast, a single RCT examining oral methotrexate 12.5 mg/wk demonstrated this dose and route of administration was not effective for inducing remission in patients with corticosteroid-dependent active CD (RR, 1.14; 95% CI, 0.72–1.82) (Supplementary Figure 8*A*).[82] In the same trial, risk of relapse in 22 patients achieving remission was not different between those continuing on oral methotrexate 12.5 mg/wk vs those receiving placebo (RR, 0.30; 95% CI, 0.04–2.27) (Supplementary Figure 8*B*). The overall body of evidence was rated as very low certainty due to indirectness (use of low-dose methotrexate) and very serious imprecision (very wide 95% CI) (Table 8).

Thiopurine vs methotrexate for moderate to severe Crohn's disease, induction and maintenance of remission. The evidence profile for this comparison was similar to the previous technical review. No additional studies were identified. In 3 RCTs, with variables doses and routes of administration, methotrexate failed to show or exclude a beneficial or detrimental effect over thiopurines on failure of remission at 24–36 weeks (RR, 1.17; 95% CI, 0.82–1.67). The overall body of evidence was rated as very low certainty due to indirectness and very serious imprecision due to very wide CIs. In 2 small RCTs (50 patients) in which patients who achieved remission with initial therapy were followed up to 38–76 weeks for risk of disease relapse, the results failed to show or exclude a beneficial effect of methotrexate over thiopurines (RR, 0.53; 95% CI 0.22–1.27). Evidence was rated as very low certainty due to indirectness (lack of randomization at start of maintenance therapy) and very serious imprecision due to very wide CIs.

Potential harms of intervention. Risks of adverse effects with thiopurines and methotrexate have been summarized above. Besides the direct risks associated with these therapies, risks associated with use of ineffective therapies and delay in initiation of more effective therapies

Table 8. GRADE Evidence Profile Comparing Thiopurines, Subcutaneous and Oral Methotrexate With Placebo for Induction and Maintenance of Remission in Patients With Moderate to Severe Luminal Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with thiopurines				
Thiopurines compared with placebo for moderate to severe luminal CD						
Achieving clinical remission (CRITICAL)	115/183 (62.8)	102/197 (51.8)	RR 0.87 (0.71–1.06)	82 fewer per 1000 (from 182 fewer to 38 more)	380 (5 RCTs)	⊕◯◯◯[c,d,e] VERY LOW
Relapse after achieving clinical remission (CRITICAL)	75/172 (43.6)	49/175 (28.0)	RR 0.62 (0.47–0.81)	166 fewer per 1000 (from 231 fewer to 83 fewer)	347 (5 RCT)	⊕⊕◯◯[c,f] LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with subcutaneous methotrexate				
Subcutaneous methotrexate compared with placebo for moderate to severe luminal CD						
Achieving clinical remission (CRITICAL)	38/47 (80.9)	57/94 (60.6)	RR 0.75 (0.61–0.93)	202 fewer per 1000 (from 315 fewer to 57 fewer)	141 (1 RCT)	⊕⊕⊕◯[f] MODERATE
Relapse after achieving clinical remission (CRITICAL)	22/36 (61.)	14/40 (35.0)	RR 0.57 (0.35–0.94)	263 fewer per 1000 (from 397 fewer to 37 fewer)	76 (1 RCT)	⊕⊕⊕◯[f] MODERATE

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with oral methotrexate				
Oral methotrexate compared with placebo for moderate to severe luminal CD						
Achieving clinical remission (CRITICAL)	14/26 (53.8)	16/26 (61.5)	RR 1.14 (0.72–1.82)	75 more per 1000 (from 151 fewer to 442 more)	52 (1 RCT)	⊕◯◯◯[g,h] VERY LOW
Relapse after achieving clinical remission (CRITICAL)	4/12 (33.3)	1/10 (10.0)	RR 0.30 (0.04–2.27)	233 fewer per 1000 (from 320 fewer to 423 more)	22 (1 RCT)	⊕◯◯◯[g,h] VERY LOW

[a]To calculate absolute effect estimate, we used pooled placebo rate of 20% for achieving remission, and 24% for preventing relapse after achieving clinical remission.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for risk of bias (due to inadequate blinding and allocation concealment).
[d]Rated down for indirectness (because these trials did not truly assess induction of remission, but rather the ability to achieve corticosteroid-free clinical remission, over a wide range of time, using a variety of disease activity indices with definitions inconsistent with modern definitions of remission).
[e]Rated down for imprecision because 95% CI crosses unity
[f]Rated down for imprecision because optimal information size not met (<200 events).
[g]Rated down for indirectness (used low dose oral methotrexate <15 mg/wk).
[h]Rated down for very serious imprecision due to very wide 95% CI (unable to rule out significant risk of harm with intervention).

also need to be considered when evaluating potential harms of these interventions.

Discussion. Based on evidence presented above, thiopurine monotherapy may be effective for maintaining corticosteroid-free remission in patients with CD; however, the benefit of thiopurines for induction of remission is unclear. Thiopurines have a slow onset of action, and so they have been used conventionally as maintenance agents rather than induction agents. In a double-blind clinical trial (AZTEC), Panés and colleagues randomly assigned patients with newly diagnosed CD (fewer than 8 weeks) to azathioprine vs placebo.[78] At 76 weeks, no significant differences were observed in rates of corticosteroid-free clinical remission, CD-related hospitalization or surgery between the 2 groups. On post-hoc analyses, in a subset of patients requiring corticosteroids at trial entry, no significant difference was observed between azathioprine vs placebo for maintaining sustained corticosteroid-free clinical remission (17 of 37 [36.2%] vs 13 of 45 [28.9%]; $P = .51$). In another post-hoc analysis, azathioprine-treated patients experienced lower risk of moderate to severe clinical relapse compared with placebo-treated patients (8 of 68 [11.8%] vs 19 of 63 [30.2%]; $P = .01$). Real-world cohort studies and meta-analyses have confirmed effectiveness of thiopurines in reducing the risk of surgery in patients with CD.[83] Differences in the efficacy of methotrexate in CD were observed based on route of administration and dose; only subcutaneous methotrexate at doses of 15 mg/wk or higher was effective in achieving remission, whereas oral methotrexate at doses <15 mg/wk was not effective. It is unclear whether this is a function of the route of methotrexate administration, dose administered, or both.

Question 4. In Adult Outpatients With Moderate to Severe Crohn's Disease, Is Biologic Monotherapy (Infliximab, Adalimumab, Certolizumab Pegol, Vedolizumab, Ustekinumab) Superior to Immunomodulator Monotherapy (Thiopurines, Methotrexate) for Induction and Maintenance of Clinical Remission?

Key messages.

1. In adult outpatients with moderate to severely active CD, biologic monotherapy may be superior to thiopurine monotherapy for achieving remission (*low to moderate certainty of evidence*). In patients with quiescent moderate to severe CD, biologic monotherapy may be superior to thiopurine monotherapy for maintaining remission (*low certainty of evidence*).

2. In adult outpatients with moderate to severe CD, the benefit of biologic monotherapy over subcutaneous methotrexate monotherapy for achieving and maintaining remission is uncertain (*very low certainty of evidence*).

Effect estimates and certainty of evidence. *Biologic monotherapy vs thiopurine monotherapy for moderate to severe Crohn's disease, induction and maintenance of remission.* Only a single, 3-arm RCT (SONIC), in biologic- and immunomodulator-naïve patients with moderate to severe CD, comparing infliximab vs azathioprine vs infliximab + azathioprine was identified that directly informed this evidence.[84] Although this trial was not powered to examine differences in efficacy of infliximab vs azathioprine, a significantly higher proportion of infliximab-treated patients achieved corticosteroid-free clinical remission at all time points, including week 6 (failure to achieve corticosteroid-free clinical remission, infliximab vs azathioprine: 119 of 169 vs 146 of 170; $P < .01$) and 10 (106 of 169 vs 129 of 170; $P < .01$). At the 26-week primary efficacy end point of the trial, infliximab was more effective than azathioprine in achieving corticosteroid-free clinical remission (RR, 0.79; 95% CI, 0.67–0.94) and endoscopic remission (defined as resolution of ulcers) (65 of 93 vs 91 of 109; $P < .01$). Overall quality of evidence supporting the use of infliximab monotherapy over thiopurine monotherapy for induction of remission was rated as moderate certainty, being rated down for imprecision due to low event rate (Table 9).

No trials of maintenance therapy in patients with quiescent moderate to severe CD comparing biologic monotherapy vs thiopurine monotherapy were identified. The SONIC trial provided indirect evidence on efficacy of these agents for maintaining remission, with a subset of patients entering a blinded extension to 50 weeks. Baseline characteristics of patients who opted to enter the blinded extension is not available, so their remission status at the time of entering the blinded extension is unclear; it is conceivable that patients in remission or responding to index therapy may preferably choose to enroll in blinded extension. Of 97 infliximab monotherapy-treated and 75 azathioprine-treated patients who opted to participate in blinded extension to week 50, 33 and 34 patients failed to achieve corticosteroid-free clinical remission, respectively (RR, 0.75; 95% CI, 0.52–1.09). Overall quality of evidence supporting the use of infliximab monotherapy over thiopurine monotherapy for maintenance of remission was rated as low certainty, being rated down for indirectness (because characteristics of patients entering blinded extension were unclear and did not necessarily include patients with quiescent disease; responding patients were not re-randomized) and serious imprecision due to wide CIs.

No trials comparing other biologic agents vs thiopurines for induction or maintenance of remission were identified; evidence for this question was informed indirectly from evidence presented in focused questions 1 and 3. Low to moderate certainty evidence supported the use of biologic agents over placebo in inducing remission in patients moderate to severely active CD with failure of conventional therapy (frequently including patients who had failed thiopurine therapy), whereas very low certainty suggested uncertain benefit of thiopurines for induction of remission, in biologic-naïve patients. Hence, based on indirectness of evidence, the overall body of evidence supporting the use of non–infliximab biologic monotherapy over thiopurine monotherapy for induction of remission was rated as low certainty; no single summary estimate could be drawn. For maintenance of remission, in the absence of head-to-head

Table 9. GRADE Evidence Profile Comparing Biologic Monotherapy vs Thiopurine Monotherapy for Achieving Remission in Patients With Moderate to Severe Luminal Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with immunomodulator monotherapy	Risk with biologic monotherapy				
Biologic monotherapy compared with immunomodulator monotherapy for moderate to severe luminal CD						
Induction of clinical remission (CRITICAL)	129/170 (75.9)	90/169 (53.3)	RR 0.70 (0.60–0.83)	228 fewer per 1000 (from 304 fewer to 129 fewer)	339 (1 RCT)	⊕⊕⊕◯[c] MODERATE
Maintenance of clinical remission (CRITICAL)	34/75 (45.3)	33/97 (34.0)	RR 0.75 (0.52–1.09)	113 fewer per 1000 (from 281 fewer to 41 more)	172 (blinded extension of 1 RCT)	⊕⊕◯◯[d,e] LOW

NOTE. No trials of non-TNF biologic therapy vs thiopurines were identified.
[a]To calculate absolute effect estimate, we used observed rate on IMM monotherapy for induction and maintenance of remission.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).
[d]Rated down for indirectness (because characteristics of patients entering blinded extension was unclear and did not necessarily include patients with quiescent disease; responding patients were not re-randomized).
[e]Rated down for imprecision because 95% CI crosses unity.

comparison for non–infliximab biologic monotherapy vs thiopurine monotherapy, and evidence in focused questions 1 and 3 providing low to moderate certainty evidence supporting the use of biologics and thiopurines for maintaining remission, the benefit of biologic monotherapy vs thiopurine monotherapy for maintaining remission in patients with quiescent CD was uncertain (very low certainty of evidence, being rated down for very serious indirectness and imprecision).

Biologic monotherapy vs methotrexate monotherapy for moderate to severe CD, induction and maintenance of remission. No RCTs comparing biologic monotherapy vs methotrexate monotherapy for induction and maintenance of remission were identified. Evidence for this question was informed indirectly from evidence presented in focused questions 1 and 3. With low to moderate certainty evidence supporting the use of biologics and methotrexate for inducing and maintaining remission, the benefit of biologic monotherapy vs methotrexate monotherapy for inducing and maintaining remission in patients with moderate to severe CD was uncertain (very low certainty of evidence, being rated down for very serious indirectness and imprecision).

Potential harms of intervention. As noted above, there may be a slightly higher risk of serious and opportunistic infections with biologic agents vs immunomodulators. Both TNFα antagonists and thiopurine monotherapy have been associated with a comparable increase in risk of lymphoma.

Discussion. The pivotal SONIC trial confirmed the efficacy of infliximab monotherapy vs thiopurine monotherapy for inducing remission. In a subset of likely responding patients who opted to enroll in a blinded extension of SONIC to 50 weeks, infliximab monotherapy was not significantly more effective than azathioprine monotherapy for achieving clinical remission to 50 weeks. In contrast, in a network meta-analysis published in 2014, adalimumab and infliximab had a >98% probability of being superior to thiopurines for maintenance of remission, although it is important to note that there is considerable heterogeneity in the design and conduct of trial comparing biologics and immunomodulators.[85] Similarly, in viewing surgically induced remission as a more robust form of disease quiescence, network meta-analyses have confirmed a higher efficacy of TNFα antagonists over thiopurine monotherapy for preventing endoscopic relapse and clinical relapse.[86] Hence, indirect evidence may suggest that biologic agents, particularly infliximab and adalimumab, may be more effective than thiopurine monotherapy for maintaining remission.

Whether there is any difference between biologic monotherapy and methotrexate in inducing and maintaining of remission is unclear, given the lack of head-to-head trials. No significant differences were identified in the previously mentioned network meta-analysis for individual biologic agents vs methotrexate, although adalimumab monotherapy had >90% probability of being superior to methotrexate for both induction or maintenance of remission.[85]

Question 5. In Adult Outpatients With Moderate to Severe CD, Is Combination Therapy of a Biologic Agent (Infliximab, Adalimumab, Certolizumab Pegol, Vedolizumab, Ustekinumab) With an Immunomodulator (Thiopurines or Methotrexate) Superior to Biologic Monotherapy for Induction and Maintenance of Remission?

Key messages.

1. In adult outpatients with moderate to severely active CD, combination therapy with infliximab + thiopurines is probably superior to infliximab monotherapy for inducing remission (*moderate certainty of evidence*); combination therapy with infliximab + methotrexate may be superior to infliximab monotherapy for inducing remission (*low certainty of evidence*). In patients with quiescent moderate to severe CD, combination therapy with infliximab + thiopurines or methotrexate may be superior to infliximab monotherapy for maintaining remission (*low certainty of evidence*).

2. In adult outpatients with moderate to severe CD, combination therapy with adalimumab + thiopurines or methotrexate may be superior to adalimumab monotherapy for inducing and maintaining remission (*very low certainty of evidence*)

3. In adult outpatients with moderate to severe CD, the benefit of combination therapy with vedolizumab or ustekinumab + thiopurines or methotrexate over corresponding biologic monotherapy for inducing and maintaining remission is uncertain (*very low certainty of evidence*)

Effect estimates and certainty of evidence. *Combination therapy with infliximab + thiopurines vs infliximab monotherapy for moderate to severe Crohn's disease, induction and maintenance of remission.* Two trials provided data on the efficacy of infliximab + thiopurines vs infliximab monotherapy in patients with moderate to severe CD.[46,84] Based on meta-analysis, combination therapy was more effective than infliximab monotherapy for induction of remission in patients with moderate to severely active CD (RR, 0.77; 95% CI, 0.64–0.92) (Supplementary Figure 9*A*). Overall quality of evidence supporting the use of combination therapy with infliximab + thiopurines over infliximab monotherapy for induction of remission was rated as moderate certainty, being rated down for imprecision due to low event rate (Table 10). Although statistical heterogeneity was observed, both studies suggested superior efficacy, with variability being observed in the magnitude of effect. Hence, evidence was not rated down for heterogeneity.

No true trials of maintenance therapy in patients with quiescent moderate to severe CD comparing infliximab + thiopurines vs infliximab monotherapy were identified. Both the SONIC trial and RCT by Lemann et al included patients with active disease at baseline who were treated through week 50/52.[46,84] On meta-analysis, combination therapy was

Table 10. GRADE Evidence Profile Comparing the Combination of Biologics + Immunomodulators (Thiopurines, Methotrexate) With Biologic Monotherapy for Induction and Maintenance of Remission in Patients With Moderate to Severe Luminal Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with infliximab monotherapy	Risk with infliximab + thiopurines				
Infliximab + thiopurines compared with infliximab monotherapy for moderate to severe luminal CD						
Achieving clinical remission (CRITICAL)	122/196 (62.2)	92/200 (47.5)	RR 0.77 (0.64–0.92)	143 fewer per 1000 (from 224 fewer to 50 fewer)	396 (2 RCTs)	⊕⊕⊕◯[c] MODERATE
Maintenance of clinical remission (CRITICAL)	112/196 (57.1)	84/200 (42.0)	RR 0.74 (0.60–0.90)	149 fewer per 1000 (from 229 fewer to 57 fewer)	396 (2 RCTs)	⊕⊕◯◯[c,d] LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with infliximab monotherapy	Risk with infliximab + methotrexate				
Infliximab + methotrexate compared with infliximab monotherapy for moderate to severe luminal CD						
Achieving clinical remission (CRITICAL)	14/63 (22.2)	15/63 (23.8)	RR 1.07 (0.57–2.03)	16 more per 1000 (from 96 fewer to 229 more)	126 (1 RCT)	⊕⊕◯◯[e] LOW
Maintenance of clinical remission (CRITICAL)	17/63 (27.0)	20/63 (31.7)	RR 1.18 (0.68–2.03)	49 more per 1000 (from 86 fewer to 278 more)	126 (1 RCT)	⊕⊕◯◯[e] LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with adalimumab monotherapy	Risk with adalimumab + thiopurines				
Adalimumab + thiopurines compared with adalimumab monotherapy for moderate to severe luminal CD						
Achieving clinical remission (CRITICAL)	20/85 (30.8)	28/91 (30.8)	RR 1.31 (0.80–2.14)	73 more per 1000 (from 47 fewer to 268 more)	176 (1 RCT)	⊕◯◯◯[e,f,g] VERY LOW
Maintenance of clinical remission (CRITICAL)	24/85 (28.2)	29/91 (31.9)	RR 1.13 (0.72–1.78)	37 more per 1000 (from 79 fewer to 220 more)	176 (1 RCT)	⊕◯◯◯[e,f,g] VERY LOW

[a]To calculate absolute effect estimate, we used observed rates with infliximab monotherapy for induction and maintenance of remission.
[b]GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different . Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).
[d]Rated down for indirectness (because patients had active disease at baseline, rather than quiescent disease).
[e]Rated down for very serious imprecision due to very wide 95% CI (unable to rule out significant risk of harm with intervention).
[f]Rated down for risk of bias (unblinded study, very high rates of discontinuation due to treatment intolerance as compared with other studies).
[g]Rated down for indirectness (used endoscopic remission as surrogate because primary outcome of clinical remission could be biased due to open-label design).

more effective than infliximab monotherapy for maintenance of remission (RR, 0.74; 95% CI, 0.60–0.90) (Supplementary Figure 9*B*). As above, the SONIC trial also provided indirect evidence on efficacy of these agents for maintaining remission, with a subset of patients entering blinded extension to 50 weeks. Baseline characteristics of patients who opted to enter blinded extension are not available, so their remission status at time of blinded extension is unclear; it is conceivable that patients in remission or responding to index therapy may preferably choose to enroll in blinded extension. Of 108 patients treated with infliximab + azathioprine and 97 infliximab monotherapy–treated patients who opted to participate in blinded extension to week 50, 28 and 33 patients failed to achieve corticosteroid-free clinical remission, respectively (RR, 0.76; 95% CI, 0.50–1.16). Overall quality of evidence supporting the use of combination therapy with infliximab + thiopurines over infliximab monotherapy for maintenance of remission was rated as low certainty, being rated down for indirectness (because patients had active disease at baseline rather than quiescent disease) and imprecision due to low event rate (Table 10).

Combination therapy with infliximab + methotrexate vs infliximab monotherapy for moderate to severe Crohn's disease, induction and maintenance of remission. In a single, double-blind, 50-week RCT, Feagan and colleagues[87] compared infliximab + methotrexate vs infliximab monotherapy in 126 patients with CD who had initiated prednisone induction therapy within the preceding 6 weeks. No significant differences were observed in failure to achieve corticosteroid-free clinical remission at week 14 between combination therapy and infliximab monotherapy (15/63 vs 14/63; RR, 1.07; 95% CI, 0.57–2.03). Extending to 50 weeks, no significant differences were observed in failure to maintain corticosteroid-free clinical remission between combination therapy and infliximab monotherapy (20 of 63 vs 17 of 63; RR, 1.18; 95% CI, 0.68–2.03). Indirect evidence suggested higher infliximab trough concentrations and lower risk of immunogenicity in patients receiving combination therapy compared with patients receiving infliximab monotherapy, which has been associated with higher effectiveness and treatment persistence in infliximab-treated patients. In addition, several large well-designed observational studies have confirmed higher effectiveness of combination therapy over biologic monotherapy, particularly for TNFα antagonists.[88,89] Hence, the overall body of evidence supporting the use of combination therapy with infliximab + methotrexate over infliximab monotherapy for induction and maintenance of remission was rated as low certainty, being rated down for very serious imprecision (Table 10).

Combination therapy with adalimumab + thiopurines vs adalimumab monotherapy for moderate to severe CD, induction and maintenance of remission. In a single, open-label, RCT from the DIAMOND study group in Japan, biologic- and immunomodulator-naïve patients with moderate to severely active CD were randomized to adalimumab + azathioprine vs adalimumab monotherapy for 52 weeks.[90] At 26 weeks (primary study end point), no significant differences were observed in failure to achieve clinical remission (28 of 91 vs 20 of 85; RR, 1.31; 95% CI, 0.80–2.14). Importantly, in this trial, 15 patients (16.5%) in the combination group and 1 patient (1.2%) in the adalimumab monotherapy group withdrew due to adverse effects of the medications, and primary analyses were performed using nonresponder imputation. Such high rates of treatment-related drug withdrawals have not been observed with prior trials of thiopurine or combination therapy with infliximab. On objective evaluation of endoscopy at week 26, combination therapy was associated with significantly higher rates of endoscopic remission vs adalimumab monotherapy (48 of 57 [84.2%] vs 37 of 58 [63.2%]; $P = .02$). On extension to 52 weeks, no significant differences were observed for maintenance of clinical remission between combination therapy vs adalimumab monotherapy (failure to maintain remission: 29 of 91 vs 24 of 85; RR, 1.13; 95% CI, 0.72–1.78); data specifically for subset of patients in remission at week 26 were not available. On analysis of patients with endoscopy at both randomization and week 52 follow-up, no significant differences were observed in proportion of patients with endoscopic remission with combination therapy vs adalimumab monotherapy (39 of 49 [79.6%] vs 37 of 53 [69.8%]; $P = .36$). Overall, the quality of evidence supporting the use of combination therapy with adalimumab + thiopurines over adalimumab monotherapy for induction and maintenance of remission was rated as very low certainty, being rated down for risk of bias (unblinded study, very high rates of discontinuation due to treatment intolerance compared with other studies), indirectness (use of endoscopic remission as surrogate, besides clinical remission), and imprecision (due to low event rate) (Table 10).

Combination therapy with vedolizumab or ustekinumab + thiopurines (or methotrexate) vs vedolizumab or ustekinumab monotherapy for moderate to severe Crohn's disease, induction and maintenance of remission. No randomized trials were identified comparing combination therapy of newer non–TNF-targeting biologics with immunomodulators vs monotherapy with the corresponding biologic. In a systematic review and meta-analysis of 9 studies of vedolizumab in CD (post-hoc analyses of RCTs and observational studies), combination therapy was not superior to vedolizumab monotherapy for achieving clinical outcomes during induction or maintenance (odds of favorable clinical outcomes: OR, 0.84; 95% CI, 0.53–1.33).[91] Similarly, in 15 studies of ustekinumab, no benefit was observed with combination therapy vs ustekinumab monotherapy (15 studies; OR, 1.1; 95% CI, 0.87–1.38). In this meta-analysis, clinical benefit was variably defined as clinical remission, clinical response, or physician global assessment, and studies evaluated both induction and maintenance of remission/response. Importantly, in both RCTs and observational studies, the majority of patients had previously failed immunomodulators. The overall body of evidence supporting the use of combination therapy of newer non–TNF-targeting biologics with immunomodulators vs monotherapy with the corresponding biologic derived primarily from observational studies was rated as very low certainty due to risk of bias and very serious imprecision.

Potential harms of intervention. As noted above, combination therapy with biologic agents + immunomodulators may be associated with a modestly higher risk of serious infections over biologic monotherapy. The combination of thiopurines with TNFα antagonists is associated with a 2- to 3-fold higher risk of lymphoma compared with TNFα antagonist monotherapy.

Discussion. Combining biologic agents with immunomodulators may increase efficacy through several potential mechanisms. First, immunomodulators have their independent efficacy in patients with CD, which may add to the benefits observed with biologics. Second, immunomodulators have been consistently shown to decrease the risk of immunogenicity of biologic agents, and may increase trough concentrations of these agents. The former may explain clear benefits in achieving clinical and endoscopic remission with infliximab + azathioprine in the SONIC trial, as well as higher rates of endoscopic remission with adalimumab + azathioprine in the DIAMOND trial. In contrast, in the COMMIT trial comparing infliximab + methotrexate vs infliximab monotherapy, approximately 25% of patients had failed thiopurines previously.

TNFα antagonists, particularly infliximab, are more immunogenic compared with more recently developed non–TNF-directed biologic agents. In a systematic review, 2.9%–60.8%, 0.3%–35.0%, 3.3%–25.3%, 1%–4.1%, and <1% of infliximab-, adalimumab-, certolizumab pegol-, vedolizumab-, and ustekinumab-treated patients, respectively, developed anti-drug antibodies, with a significant proportion of these being neutralizing antibodies.[92] Hence, adding immunomodulators to prevent immunogenicity in TNFα antagonist–treated patients may be particularly beneficial in patients with unfavorable pharmacokinetics, or those with prior immunogenicity to TNFα antagonists, even in patients who previously failed to respond to immunomodulators. In a recent RCT in patients with IBD with pharmacokinetic failure of first TNFα antagonist, Roblin and colleagues[93] observed that adding thiopurines at the time of starting the second TNFα antagonist significantly decreased risk of clinical relapse and unfavorable pharmacokinetics compared with TNFα antagonist monotherapy. In contrast, with very low rates of immunogenicity with vedolizumab or ustekinumab, the potential benefit of combination therapy with these agents in terms of mitigating antibody formation may be less than with TNFα antagonists.

Question 6. In Adult Outpatients With Quiescent Crohn's Disease on Combination Therapy With Biologic Agents and Immunomodulators for More Than 6 Months, Is Ongoing Combination Therapy Superior to Withdrawal of Immunomodulators or Biologic Agent in Decreasing the Risk of Relapse?

Key messages.

1. In adult patients with quiescent CD on combination therapy with biologic and immunomodulators for more than 6 months, the benefit of ongoing combination therapy over withdrawal of immunomodulators is uncertain (*very low certainty of evidence*).
2. In adult patients with quiescent CD on combination therapy with biologic and immunomodulators for more than 6 months, the benefit of ongoing combination therapy over withdrawal of biologics is uncertain (*very low certainty of evidence*).

Effect estimates and certainty of evidence. We identified 3 RCTs (161 patients) in patients who achieved and maintained remission on combination therapy with TNFα antagonists and immunomodulators (majority on thiopurines) on for at least 6 months (2 trials of infliximab-, 1 trial of adalimumab-based combination therapy).[94–96] On meta-analysis, no significant differences were observed in the risk of relapse over 12–24 months in patients who continued combination therapy vs withdrew immunomodulators (28 of 78 vs 29 of 83; RR, 1.02; 95% CI, 0.71–1.46) (Supplementary Figure 10). The overall body of evidence supporting the continuation of combination therapy was rated as very low certainty, with evidence rated down for serious risk of bias (unblinded trials) and very serious imprecision (due to very wide 95% CI, unable to exclude significant benefit or harm with continuing combination therapy) (Table 11).

No RCTs evaluating systematic withdrawal of biologic therapy in patients with quiescent CD on combination therapy were identified. In a prospective cohort study of 115 CD patients on combination therapy for more than 1 year, with clinical remission for at least more than 6 months, withdrawal of infliximab was associated with 44% and 52% risk of relapse at 1 and 2 years, respectively.[97] The vast majority of patients were able to recapture response with re-introduction of infliximab, and the de-escalation strategy was deemed to be successful in 70% patients over 7 years.[98]

Potential harms of intervention. Primary potential harm of intervention is risk of disease relapse with withdrawal of immunomodulators. In addition, because immunomodulators favorably modify the pharmacokinetics of biologics and decrease risk of immunogenicity, it is possible that patients may lose response to biologic therapy. However, the risk may be small, especially if biologic trough concentrations are monitored closely. Besides risk of relapse, one concern with withdrawal of a biologic (and continuation of immunomodulators) is development of immunogenicity with prolonged drug holiday, which may render the drug ineffective in a small proportion of patients at time of re-introduction and cause infusion reactions. As noted earlier, long-term combination therapy with biologic agents + immunomodulators may be associated with a modestly higher risk of serious infections and 2- to 3-fold higher risk of lymphoma over biologic monotherapy. Lymphoma risks returns to baseline within 12 months of stopping thiopurines.[99]

Discussion. In patients with long-standing quiescent CD, de-escalation of immunosuppressive therapy is one of the most frequently asked questions by patients. Given risk of relapse with treatment de-escalation, shared decision-making and eliciting patients' values and preferences regarding acceptable risks of relapse with de-escalation are important. Systematic withdrawal of immunomodulators with continuation of biologic monotherapy is one favored de-

Table 11. GRADE Evidence Profile Comparing Continuation of Combination of Biologic Agent + Immunomodulator Therapy (Thiopurines, Methotrexate) vs Withdrawal of Immunomodulators for Preventing Relapse in Adult Patients With Quiescent Crohn's Disease on Combination Therapy With Biologic and Immunomodulators for More Than 6 Months

	Study event rates, n (%)					
Outcomes	Risk with continuing combination of biologic agent + immunomodulator therapy	Risk with withdrawal of immunomodulators	Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
Risk of relapse at 12 mo (CRITICAL)	28/78 (35.9)	29/83 (34.9)	RR 1.02 (0.71–1.46)	7 more per 1000 (from 101 fewer to 161 more)	161 (3 RCT)	⊕◯◯◯[b,c] VERY LOW

[a]To calculate absolute effect estimate with intervention, we used observed rates with comparators (continuing combination of biologic agent + immunomodulator therapy).
[b]Rated down for risk of bias (unblinded studies).
[c]Rated down for very serious risk of imprecision (due to very wide 95% CI, unable to exclude significant benefit or harm with continuing combination therapy).

escalation strategy in patients on combination therapy. Based on 3 open-label RCTs, withdrawal of immunomodulators in selected patients with quiescent CD for at least 6 months was not associated with increased risk of relapse over 12–24 months compared with continuation of combination therapy. Moreover, withdrawal of immunomodulators was not associated with emergence of unfavorable pharmacokinetics in patients who continued on biologic monotherapy.

No trials evaluated discontinuation of biologics in patients who were in remission on combination therapy. Most studies suggest a 35%–45% risk of relapse within 1–2 years of discontinuing TNFα antagonists, which may be unacceptable to patients.[100] However, with recognition that endoscopic and/or histologic remission may represent deeper remission in patients with CD, the predicted risk of relapse with de-escalation may be lower in patients who achieve these end points on combination therapy compared with those only in clinical and biochemical remission. In addition, with the emergence of newer therapies with different mechanisms of action and lower immunogenicity, risks of withdrawal of biologic therapy may be lower because alternative therapies may be available to manage relapse in case re-introduction of index biologic therapy is not effective.

Question 7. In Adult Outpatients With Moderate to Severe Crohn's Disease, Is a Top-Down Treatment Strategy (Early Use of Combination Therapy With Biologic Agents With Immunomodulators) Superior to Step Therapy (Escalation to Biologic-Based Therapy Only After Failure of Mesalamine and/or Immunomodulators) for Achieving Remission and Preventing Disease Complications?

Key message. In adult outpatients with moderate to severely active CD, a top-down treatment strategy (early use of combination therapy with biologic agents with immunomodulators) may be more effective than step therapy (escalation to biologic-based therapy only after failure of mesalamine and/or immunomodulators) for achieving remission and preventing disease-related complications (*low certainty of evidence*)

Effect estimates and certainty of evidence. Evidence informing this question was derived from several different types of RCTs. In an open-label RCT in 133 patients with recently diagnosed CD who were naïve to corticosteroids, immunomodulators, and biologics, D'Haens and colleagues[101] randomized patients with active disease to early combined immunosuppression (3 doses of infliximab induction therapy followed by episodic dosing as needed) vs conventional step therapy in which patients received corticosteroids, followed, in sequence, by azathioprine and infliximab. At 52 weeks, 40 of 65 patients (61.5%) in the early combined immunosuppression group were in corticosteroid- and surgery-free remission without corticosteroids, compared with 23 of 64 patients (42.2%) in the step therapy arm (RR for failure to achieve remission, 0.67; 95% CI, 0.46–0.97). Long-term extension of this trial to 8 years suggested lower rates of clinical relapse, corticosteroid use, and TNFα antagonist use in patients randomized to early combined immunosuppression.[102] The evidence from this trial was rated as low certainty due to risk of bias (due to open-label trial evaluating a subjective outcome), and imprecision (because optimal information size not reached) (Table 12). In another open-label cluster randomized trial (REACT), 39 community practices to either an algorithmic approach of early combined immunosuppression, or conventional management of CD, and followed 1982 patients for 2 years.[103] In the early combined immunosuppression group, practitioners were educated on initiation of adalimumab and immunomodulator in case of failure to achieve clinical remission with a 4- to 12-week tapering course of corticosteroids, and practitioners in the usual care group were allowed to manage per preference. At 12 months, there was no significant difference in the rate of

Table 12. GRADE Evidence Profile Comparing Top-Down Treatment Strategy (Early Use of Combination Therapy With Biologic Agents With Immunomodulators) vs Step Therapy (Escalation to Biologic-Based Therapy Only After Failure of Mesalamine and/or Immunomodulators), and Early Thiopurine Therapy vs Conventional Therapy, for Achieving Remission and Preventing Disease Complications for Moderate to Severe Luminal Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with step therapy	Risk with early combined immunosuppression				
Top-down treatment strategy (early use of combination therapy with biologic agents with immunomodulators) vs step therapy (escalation to biologic-based therapy only after failure of mesalamine and/or immunomodulators) for achieving remission and preventing disease complications for moderate to severe luminal CD						
Achieving clinical remission (CRITICAL)	26/65 (40.0)	41/64 (64.1)	RR 0.62 (0.44–0.89)	243 fewer per 1000 (from 359 fewer to 70 fewer)	129 (1 RCT)	⊕⊕◯◯[c,d] LOW
Preventing disease complications (CRITICAL)	342/898 (38.1)	369/1084 (34.0)	HR 0.73 (0.62–0.86)	103 fewer per 1000 (from 145 fewer to 53 fewer)	1982 (1 RCT)	⊕⊕⊕◯[b] MODERATE

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with conventional therapy	Risk with early thiopurine use				
Early thiopurine therapy (at or within 6 mo of diagnosis) vs conventional therapy for preventing disease flare for moderate to severe luminal CD						

Table 12. Continued

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with conventional therapy	Risk with early thiopurine use				
Failure to achieve corticosteroid-free remission (critical)	61/67 (91.0)	58/65 (89.2)	RR 1.02 (0.91–1.14)	18 more per 1000 (from 82 fewer to 127 more)	132 (1 RCT)	⊕⊕◯◯[c,e] low

HR, hazard ratio.
[a]To calculate absolute effect estimate, we used observed rates with in comparator arm for each outcome.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for risk of bias (open-label trial).
[d]Rated down for imprecision because optimal information size not met (<200 events).
[e]Rated down for imprecision because 95% CI crosses unity.

corticosteroid-free clinical remission in the 2 groups (early combined immunosuppression vs usual care: 66% vs 62%), which was the primary outcome of the study. However, at 24 months, patients in practices randomized to early combined immunosuppression had significantly lower rates of major adverse disease-related complications (composite of hospitalization, surgery, or disease complications, including abscess, fistula, stricture, serious worsening of disease activity or extraintestinal manifestations) compared with conventional management (hazard ratio, 0.73; 95% CI, 0.62–0.86). Evidence from REACT was rated as moderate certainty due to risk of bias (open-label trial, with site-level and not patient-level randomization) (Table 12). Both of these trials supposed early use of combination therapy with biologics, specifically infliximab and adalimumab and immunomodulators in patients with active CD. In REACT, the risk of CD-related complications was lower with early combined immunosuppression in a subset of patients with corticosteroid-dependent, or corticosteroid-refractory CD.

In contrast, mesalamines are not effective for the management of moderate to severe CD (see Question 9). Although thiopurines are effective for maintaining remission in patients with quiescent CD, their role in step therapy was informed in an open-label trial of adults with recently diagnosed CD at risk for disabling disease.[79] In this trial, Cosnes and colleagues[79] randomized 122 patients to either early initiation of azathioprine (within 6 months of CD diagnosis) or conventional management in which azathioprine was introduced only in cases of corticosteroid dependency, chronic active disease with frequent flares, poor response to corticosteroids, or development of severe perianal disease. During a 3-year follow-up, time spent in corticosteroid-free clinical remission was comparable between the 2 treatment groups. 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 from this trial was rated as low certainty due to risk of bias (open-label trial) and imprecision (very wide CIs) (Table 12).

Based on these trials, combining direct evidence favoring early combined immunosuppression over conventional management, and indirect evidence suggesting lack of benefit of mesalamine in moderate to severe CD and lack of benefit of early azathioprine use over azathioprine-based step therapy, we inferred that a top-down treatment strategy based on combination therapy may be more effective then step therapy in which biologics are introduced only after failure of mesalamine and/or immunomodulators. Evidence was rated as low certainty due to risk of bias noted in contributing evidence and indirectness (differences in comparators, variability in outcomes).

Potential harms of intervention. Routine implementation of early combined immunosuppression may overtreat some patients, particularly those at low risk of CD-related complications Risks associated with combination therapy have been discussed earlier. However, these risks should be interpreted in the context of risks of CD-related complications that may be associated with step therapy.

Discussion. Registrations trials and subsequent regulatory approval for biologics focused on patients who had failed conventional management with mesalamine and/or immunomodulators. They provide limited guidance on optimal timing of use of these agents in the management of CD. As noted earlier, treatment strategy in which patients gradually step up from mesalamine and/or immunomodulators to biologic-based therapy may not suitable, especially for patients at high risk of developing disease complications, in whom early introduction of biologics agents combined with immunomodulators may be preferred. At the same time, routine use of early combined immunosuppression for all patients may overtreat some patients, exposing them to treatment-related risks and costs without substantial benefit. Optimal risk stratification and subsequent implementation of risk-congruent treatment strategies are warranted to minimize the risk of short- and long-term complications and bowel damage. Unfortunately, prediction models to identify patients at high risk of complications or disease severity indices have not been well validated. Ideally, evidence regarding top-down vs step-up therapy would be best informed by a pragmatic RCT comparing outcomes in patients assigned to risk-congruent therapy vs conventional management.

Question 8. In Adult Outpatients With Moderate to Severe CD, What Is the Efficacy of Corticosteroids (Prednisone or Budesonide) for Induction and Maintenance of Remission?

Key messages.

1. In adult outpatients with moderate to severely active CD involving the distal ileum, controlled ileal release (CIR) budesonide may be effective for inducing remission (*low certainty of evidence*). In patients with quiescent moderate to severe CD involving the distal ileum, CIR budesonide may be effective for maintaining remission (*low certainty of evidence*). However, it is important to note that budesonide has only been approved by the FDA for mild to moderate CD for short-term use.
2. In adult outpatients with moderate to severely active CD, prednisone may be effective for inducing remission (*low certainty of evidence*). In patients with quiescent moderate to severe CD, prednisone may not be effective for maintaining remission (*low certainty of evidence*).
3. In adult outpatients with moderate to severely active CD involving the distal ileum, prednisone is probably more effective than CIR budesonide for inducing remission (*moderate certainty of evidence*).

Effect estimates and certainty of evidence. *Budesonide vs placebo, induction and maintenance of remission.* We identified 3 RCTs (367 patients) comparing CIR budesonide vs placebo in patients with CD involving distal ileum and/or ascending colon for induction of remission; 2 trials were conducted exclusively in patients with mild to moderate CD.[104–106] On meta-analysis, CIR budesonide 9 mg/d was more effective than placebo in inducing remission (RR, 0.74; 95% CI, 0.60–0.91) (Supplementary Figure 11*A*). Quality of evidence was rated as low, being rated down for indirectness (trials focused on patients with mild to moderately active disease, with CDAI between 180 and 400) and imprecision (optimal information size not met) (Table 13).

We identified 4 RCTs (290 patients) comparing CIR budesonide vs placebo in patients with CD involving distal ileum and/or ascending colon for maintenance of budesonide-induced clinical remission.[107–110] On meta-analysis, CIR budesonide 6 mg/d was more effective than placebo in maintaining remission at 1 year (RR, 0.79; 95% CI, 0.62–1.00) (Supplementary Figure 11*B*). Quality of evidence was rated as low, being rated down for indirectness (patients with mild to moderately active disease who may intrinsically be at lower risk of relapse compared with patients with moderate to severely active CD) and imprecision (95% CI reaching unity) (Table 13).

Systemic corticosteroids vs placebo, induction and maintenance of remission. In 2 RCTs (267 patients) conducted in 1979 and 1984 in patients with active CD, systemic corticosteroids at prednisone dose equivalents up to 60 mg/d were more effective than placebo in inducing clinical remission (RR, 0.57; 95% CI, 0.45–0.73) (Supplementary Figure 12*A*).[111,112] The overall quality of evidence was rated as low certainty, being rated down for serious risk of bias (sequence generation and allocation concealment not adequately reported) and imprecision (optimal information size not met); although considerable heterogeneity was observed in effect estimates, both trials demonstrated higher efficacy with the intervention and evidence was not rated down for inconsistency (Table 13).

In 3 RCTs (269 patients), systemic corticosteroids were no more effective than placebo for maintaining corticosteroid-induced remission (RR, 1.02; 95% CI, 0.81–1.29) (Supplementary Figure 12*B*).[111–113] The overall body of evidence was rated down due to risk of bias (unclear randomization scheme) and serious imprecision (wide 95% CI that could not exclude significant benefit or harm) (Table 13).

Budesonide vs systemic corticosteroids, induction and maintenance of remission. In 5 RCTs (651 patients) comparing CIR budesonide vs systemic corticosteroids in patients with CD involving distal ileum and/or ascending colon for induction of remission (majority with mild to moderately active disease) over 8 to 12 weeks, CIR budesonide was inferior to systemic corticosteroids for inducing remission (RR for failure to induce remission, 1.20; 95% CI, 1.01–1.44) (Supplementary Figure 13).[114–118] Overall quality of evidence was rated as moderate, being rated down for risk of bias (sequence generation and allocation concealment not reported adequately) (Table 13).

Potential harms of intervention. Adverse effects of short- and long-term systemic corticosteroid therapy are well known, and include (but are not limited to) weight gain, irritability and mood disturbances, insomnia, increased risk of serious infections, hyperglycemia, hypertension, osteoporosis, cataract, and adrenal insufficiency. CIR budesonide is better tolerated, and due to extensive first-pass metabolism in the liver, systemic corticosteroid exposure is very low. In maintenance trials up to 1 year, budesonide 6 mg/

Table 13. GRADE Evidence Profile Comparing Budesonide vs Systemic Corticosteroids vs Placebo, for Inducing and Maintaining Remission for Moderate to Severe Luminal Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with budesonide				
Budesonide compared with placebo for moderate to severe luminal CD involving distal ileum and/or cecum and ascending colon						
Induction of clinical remission (CRITICAL)	104/133 (78.2)	131/246 (53.3)	RR 0.74 (0.60–0.91)	203 fewer per 1000 (from 313 fewer to 70 fewer)	379 (3 RCT)	⊕⊕◯◯[c,d] LOW
Maintenance of clinical remission (CRITICAL)	78/145 (53.8)	62/145 (42.8)	RR 0.79 (0.62–1.00)	113 fewer per 1000 (from 204 fewer to 0 fewer)	290 (4 RCT)	⊕⊕◯◯[c,d] LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with prednisone				
Systemic corticosteroids compared with placebo for moderate to severe luminal CD						
Induction of clinical remission (CRITICAL)	91/135 (67.4)	53/132 (40.2)	RR 0.57 (0.45–0.72)	290 fewer per 1000 (from 371 fewer to 182 fewer)	267 (2 RCTs)	⊕⊕◯◯[d,e] LOW
Maintenance of clinical remission (CRITICAL)	94/131 (71.8)	95/138 (68.8)	RR 1.01 (0.81–1.29)	7 more per 1000 (from 136 fewer to 208 more)	269 (3 RCTs)	⊕⊕◯◯[f,g] LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with systemic corticosteroids	Risk with budesonide				
Budesonide compared with systemic corticosteroids for moderate to severe luminal CD						

Table 13. Continued

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with systemic corticosteroids	Risk with budesonide				
Induction of clinical remission (CRITICAL)	179/295 (60.7)	186/356 (52.2)	RR 1.20 (1.01–1.44)	79 more per 1000 (from 4 more to 173 more)	651 (5 RCT)	⊕⊕⊕◯[e] MODERATE

[a]To calculate absolute effect estimate, we used observed rates n placebo arms for induction and maintenance of remission.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for indirectness (trials focused on patients with mild to moderately active disease, with CDAI between 180–400).
[d]Rated down for imprecision because optimal information size not met (<200 events).
[e]Rated down for risk of bias (sequence generation and allocation concealment not adequately reported).
[f]Rated down for risk of bias (unclear randomization scheme).
[g]Rated down for imprecision (wide 95% CI that could not exclude significant benefit or harm).

d did not significantly lower serum cortisol levels and did not adversely impact bone density.

Discussion. Corticosteroids play a critical role in the symptomatic management of patients with active luminal CD across the spectrum of disease activity. They are rapidly acting and induce clinical improvement within 1 week in the majority of patients. CIR budesonide, by virtue of its localized release in the distal ileum and high first-pass metabolism, is effective for mild to moderately active distal ileal and/or ascending colon CD and may be better tolerated than systemic corticosteroids. However, neither of these agents are recommended for long-term use. Although systemic corticosteroids were not shown to be effective for maintenance of remission, CIR budesonide was effective in a subset of patients with mild to moderate CD in budesonide-induced clinical remission. There are limited data on budesonide's ability to achieve endoscopic remission, and its effect on modifying the risk of disease-related complications. Use of CIR budesonide for maintenance therapy may distract from use of an optimal and effective maintenance therapy, such as immunomodulators and/or biologic agents. The FDA has approved CIR budesonide for short-term use only, and not as long-term maintenance therapy.

Question 9. In Adult Outpatients With Moderate to Severe Crohn's Disease, What Is the Efficacy of Sulfasalazine and Mesalamine for Induction and Maintenance of Remission?

Key messages.

1. In adult outpatients with moderate to severely active CD, sulfasalazine may be effective for induction of remission (*very low certainty of evidence*). In adult outpatients with quiescent moderate to severe CD, the benefit of sulfasalazine for maintenance of remission is uncertain (*very low certainty of evidence*).
2. In adult outpatients with moderate to severely active CD, the benefit of mesalamine for induction of remission is uncertain (*very low certainty of evidence*). In adult outpatients with quiescent moderate to severe CD, mesalamine is probably not effective for maintenance of remission (*moderate certainty of evidence*).

Effect estimates and certainty of evidence. *Sulfasalazine vs placebo/no treatment, induction and maintenance of remission.* We relied on previously published meta-analysis to inform this body of evidence; these meta-analyses were rated as moderate quality.[119–121] In 3 RCTs (289 patients) conducted between 1979 and 1984 in patients with active CD (unclear disease severity or activity), sulfasalazine was more effective than placebo for induction of remission over 6–17 weeks (RR, 0.78; 95% CI, 0.65–0.93) (Supplementary Figure 14). Overall quality of evidence was rated as very low certainty, being rated down for serious risk of bias (sequence generation and allocation concealment not reported adequately), indirectness (baseline disease activity not well-defined as contemporary trials with inclusion of patients with mild to moderately active disease), and imprecision (optimal information size not met) (Table 14).

In 4 RCTs (415 patients) conducted between 1977 and 1984 in patients with quiescent CD, no significant difference was observed between sulfasalazine and placebo for maintenance of corticosteroid-free clinical remission (RR, 0.98; 95% CI, 0.82–1.17). The overall body of evidence was rated as very low certainty, with evidence being rated down for serious risk of bias (sequence generation and allocation concealment not reported adequately), indirectness (wide variability in patient characteristics and outcome measures), and very serious imprecision (very wide 95% CI) (Table 14).

Mesalamine vs placebo/no treatment, induction and maintenance of remission. In 2 RCTs in patients with active CD (unclear disease severity or activity) comparing mesalamine vs placebo (excluding 2 trials in which concomitant

Table 14. GRADE Evidence Profile Comparing Sulfasalazine and Mesalamine vs Placebo, for Inducing and Maintaining Remission for Moderate to Severe Luminal Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with sulfasalazine				
Sulfasalazine compared with placebo for moderate to severe luminal CD						
Induction of clinical remission (CRITICAL)	105/148 (70.9)	78/141 (55.3)	RR 0.78 (0.65–0.93)	156 fewer per 1000 (from 248 fewer to 50 fewer)	289 (3 RCTs)	⊕◯◯◯[c,d,e] VERY LOW
Maintenance of clinical remission (CRITICAL)	132/225 (58.7)	112/190 (58.9)	RR 0.98 (0.82–1.17)	12 fewer per 1000 (from 106 fewer to 100 more)	415 (4 RCTs)	⊕◯◯◯[c,f,g] VERY LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with mesalamine				
Mesalamine compared with systemic corticosteroids for moderate to severe luminal CD						
Induction of clinical remission (CRITICAL)	109/127 (85.8)	142/185 (76.8)	RR 0.90 (0.80–1.00)	68 more per 1000 (from 72 fewer to 268 more)	312 (2 RCTs)	⊕◯◯◯[c,f,h] VERY LOW
Maintenance of clinical remission (CRITICAL)	472/1016 (46.5)	472/998 (47.3)	RR 1.03 (0.92–1.16)	14 more per 1000 (from 37 fewer to 74 more)	2014 (11 RCTs)	⊕⊕⊕◯[i] MODERATE

[a]To calculate absolute effect estimate, we used observed rates n placebo arms for induction and maintenance of remission.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for risk of bias (sequence generation and allocation concealment not adequately reported).
[d]Rated down for indirectness (baseline disease activity not well-defined as contemporary trials with inclusion of patients with mild to moderately active disease).
[e]Rated down for imprecision because optimal information size not met (<200 events).
[f]Rated down for indirectness (wide variability in patient characteristics and outcome measures).
[g]Rated down for very serious imprecision (wide 95% CI, which could not exclude significant benefit or harm).
[h]Rated down for imprecision (95% CI of effect estimate crosses minimal clinically important difference threshold of 10% over placebo).
[i]Rated down for serious imprecision (wide 95% CI that could not exclude significant benefit or harm).

prednisone was allowed), mesalamine did not reach the prespecified MCID threshold of 10% over placebo (RR, 0.90; 95% CI, 0.81–1.00) (Supplementary Figure 15*A*). Overall quality of evidence was rated as very low, being rated down for risk of bias, indirectness (wide variability in patient characteristics and outcome measures), and imprecision (MCID of 10% over placebo not met) (Table 14).

In 11 RCTs (2014 patients) in patients with quiescent CD, mesalamine was not more effective than placebo for maintaining remission (RR, 1.02; 95% CI, 0.92–1.16) (Supplementary Figure 15*B*). The overall body of evidence favoring lack of difference between mesalamine and placebo for maintenance of remission was rated as moderate, with evidence being rated down for imprecision (modest benefit and harm could not be excluded). Although there was indirectness due to wide variability in patient characteristics and outcome measures, it was deemed that applying these findings to patients with moderate to severe CD would further bias findings toward null (Table 14).

Potential harms of intervention. Mesalamine is well-tolerated and is not an immunosuppressive medication and carries low risk of major adverse effects. In contrast, sulfasalazine is not as well tolerated as mesalamine, with a higher rate of treatment discontinuation due to adverse events. The main risks associated with the use of these therapies with uncertain efficacy for inducing remission in patients with CD are due to delay in initiation of more effective therapies, which leads to higher risk of disease-related complications. These medications have not been shown to be effective for maintenance of remission, which would warrant switching to an alternative therapy that would likely be an immunosuppressive agent. Hence, any potential long-term safety advantage may be lost.

Discussion. Mesalamine is the most commonly used medication for patients with CD, despite evidence suggesting a lack of efficacy for both induction and maintenance of remission.[122] Although the premise of using a non-immunosuppressive oral agent is appealing to both patients and providers, reliance on these ineffective medications in patients with moderate to severe CD at high risk of disease complications is likely to cause harm due to inadequate disease control. These medications are not approved by the FDA for use in patients with CD, let alone patients with moderate to severe CD.

Pharmacologic Management of Adult Patients With Fistulizing Crohn's Disease

Question 10. In Adults With Fistulizing CD, What Is the Efficacy and Safety of the Following Drugs: TNFα Antagonists (Infliximab, Adalimumab, Certolizumab Pegol), Vedolizumab, Ustekinumab, Immunomodulator Monotherapy (Thiopurines, Methotrexate), and Antibiotics?

Key messages.

1. In adults with symptomatic fistulizing CD, infliximab is probably effective for achieving fistula closure (*moderate certainty of evidence*). In patients with fistulizing CD in remission, infliximab is probably effective for maintaining fistula closure (*moderate certainty of evidence*).
2. In adults with symptomatic fistulizing CD, the benefit of adalimumab and certolizumab pegol in achieving fistula closure is uncertain (*very low certainty of evidence*). In patients with fistulizing CD in remission, adalimumab and certolizumab pegol may be effective for maintaining fistula closure (*low certainty of evidence*).
3. In adults with symptomatic fistulizing CD, the benefit of vedolizumab in achieving fistula closure is uncertain (*low quality evidence*). In patients with fistulizing CD in remission, vedolizumab may be effective for maintaining fistula closure (*low certainty of evidence*).
4. In adults with symptomatic fistulizing CD, ustekinumab may be effective for achieving fistula closure (*low quality evidence*). In patients with fistulizing CD in remission, ustekinumab may be effective for maintaining fistula closure (*low certainty of evidence*).
5. In adults with symptomatic fistulizing CD, the benefit of immunomodulator monotherapy in achieving fistula closure is uncertain (*very low certainty of evidence*). In patients with fistulizing CD in remission, immunomodulator monotherapy may be effective for maintaining fistula closure (*low certainty of evidence*).
6. In adults with symptomatic fistulizing CD, antibiotic monotherapy with ciprofloxacin may have a small benefit in achieving fistula closure (*low certainty of evidence*).

Effect estimates and certainty of evidence. *Infliximab vs placebo, achieving and maintaining fistula remission.* In 1 clinical trial of 94 patients with CD with symptomatic draining fistula (90% perianal), infliximab was more effective than placebo for achieving complete fistula closure on 2 consecutive visits (RR, 0.52; 95% CI, 0.34–0.78) within 18 weeks.[123] Quality of evidence was rated as moderate, being rated down for imprecision (optimal information size not met). In 1 RCT of 194 patients with CD who achieved fistula response with induction therapy (90% perianal), maintenance therapy with infliximab was effective in maintaining fistula remission at 54 weeks.[124] Quality of evidence was rated as moderate, being rated down for imprecision (optimal information size not met) (Table 15).

Adalimumab or certolizumab pegol vs placebo, achieving and maintaining fistula remission. In subgroup analyses of 2 RCTs including 77 patients with symptomatic draining fistula, adalimumab was not effective in inducing complete fistula closure (RR, 1.08; 95% CI, 0.93–1.27) within 4 weeks.[49,125] Similarly, in subgroup analysis of 2 RCTs including 165 patients with symptomatic draining fistula, certolizumab pegol was not effective in inducing complete fistula remission (RR, 1.01; 95% CI, 0.80–1.27).[56,126] Overall quality of evidence for both these agents was rated as very low certainty, being rated down for very serious imprecision (wide 95% CI, which could not rule out significant risk of benefit or harm with intervention) and

Table 15. GRADE Evidence Profile Evaluating Biologic Agents vs Placebo for Achieving and Maintaining Fistula Remission in Patients With Moderate to Severe Fistulizing Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with infliximab				
Infliximab compared with placebo for moderate to severe fistulizing CD						
Achieving fistula remission (CRITICAL)	27/31 (87.1)	14/31 (45.2)	RR 0.52 (0.34–0.78)	418 fewer per 1000 (from 575 fewer to 192 fewer)	62 (1 RCT)	⊕⊕⊕◯[c] MODERATE
Maintenance of fistula remission (CRITICAL)	79/99 (79.8)	58/96 (60.4)	RR 0.76 (0.63–0.92)	192 fewer per 1000 (from 295 fewer to 64 fewer)	195 (1 RCT)	⊕⊕⊕◯[c] MODERATE

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with adalimumab				
Adalimumab compared with placebo for moderate to severe fistulizing CD						
Achieving fistula remission (CRITICAL)	28/31 (90.3)	31/32 (90.3)	RR 1.08 (0.93–1.27)	72 more per 1000 (from 63 fewer to 244 more)	63 (2 RCTs)	⊕◯◯◯[d,e] VERY LOW
Maintenance of clinical remission (CRITICAL)	40/47 (85.1)	19/30 (63.3)	RR 0.73 (0.54–0.97)	236 fewer per 1000 (from 401 fewer to 26 fewer)	77 (1 RCT)	⊕⊕◯◯[c,d] LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with certolizumab pegol				
Certolizumab pegol compared with placebo for moderate to severe fistulizing CD						
Achieving fistula remission (CRITICAL)	58/91 (63.7)	47/74 (63.5)	RR 1.01 (0.80–1.27)	6 more per 1000 (from 127 fewer to 171 more)	165 (2 RCTs)	⊕◯◯◯[d,e] VERY LOW

Table 15. Continued

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with certolizumab pegol				
Maintenance of clinical remission (CRITICAL)	25/30 (83.3)	18/28 (64.3)	RR 0.77 (0.56–1.06)	155 fewer per 1000 (from 297 fewer to 41 more)	58 (1 RCT)	⊕⊕◯◯[c,d] LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk of placebo	Risk with vedolizumab				
Vedolizumab compared with placebo for moderate to severe fistulizing CD						
Achieving fistula remission (CRITICAL)	16/18 (88.9)	28/39 (71.8)	RR 0.81 (0.63–1.04)	169 fewer per 1000 (from 329 fewer to 36 more)	57 (1 RCT)	⊕◯◯◯[d,f,g] VERY LOW
Maintenance of clinical remission (CRITICAL)	16/18 (88.9)	27/39 (69.2)	RR 0.78 (0.60–1.02)	196 fewer per 1000 (from 356 fewer to 18 more)	57 (1 RCT)	⊕⊕◯◯[d,f] LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with ustekinumab				
Ustekinumab compared with placebo for moderate to severe fistulizing CD						
Achieving fistula remission (CRITICAL)	67/77 (87.0)	52/70 (74.3)	RR 0.85 (0.73–1.00)	131 fewer per 1000 (from 235 fewer to 0 fewer)	147 (3 RCTs)[h]	⊕⊕◯◯[c,d] LOW
Maintenance of clinical remission (CRITICAL)	6/11 (54.5)	3/15 (20)	RR 0.37 (0.12–1.15)	344 fewer per 1000 (from 480 fewer to 82 more)	26[i] (1 RCT)	⊕⊕◯◯[c,d] LOW

[a]To calculate absolute effect estimate, we used observed rates in placebo arms for induction and maintenance of fistula remission.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision because optimal information size not met (<200 events).
[d]Rated down for risk of bias (because randomization was not stratified by presence or absence of fistula).
[e]Rated down for very serious imprecision (wide 95% CI, which could not rule out significant risk of benefit or harm with intervention).
[f]Rated down for imprecision (95% CI crosses unity).
[g]Rated down for indirectness (all patients received induction therapy with the biologic).
[h]Pooled analysis of patients in 3 ustekinumab RCTs.
[i]Pooled analysis of patients in 2 ustekinumab RCTs.

risk of bias (because randomization was not stratified by presence or absence of fistula) (Table 15).

In subgroup analysis of 1 RCT that included 117 patients with luminal CD with response to induction dose with adalimumab, with active draining fistula at trial initiation (unclear fistula status at time of re-randomization after initial adalimumab dose), adalimumab was more effective than placebo for achieving complete fistula closure by 26 weeks (RR, 0.73; 95% CI, 0.54–0.97).[48] In subgroup analysis of 1 RCT with 58 patients with luminal CD with response to induction dose with certolizumab pegol, with active draining fistula at trial initiation (unclear fistula status at time of re-randomization after initial certolizumab pegol dose), certolizumab pegol was numerically more effective than placebo for achieving complete fistula closure by 26 weeks (RR, 0.77; 95% CI, 0.56–1.06).[126] Overall quality of evidence for both these agents was rated as low certainty, being rated down for serious imprecision (low event rate) and risk of bias (because randomization was not stratified by presence or absence of fistula) (Table 15).

Vedolizumab vs placebo, achieving and maintaining fistula remission. In subgroup analysis of the GEMINI 2 trial including 165 patients with active CD who received induction therapy with vedolizumab with clinical response of luminal disease and had symptomatic draining fistula at baseline (unclear fistula status at time of re-randomization after initial vedolizumab dose), vedolizumab may be more effective than placebo for achieving complete fistula closure (RR, 0.81; 95% CI, 0.63–1.04) within 14 weeks.[127] Of note, all patients in this trial had received initial induction therapy with vedolizumab, and those with clinical response based on CDAI were re-randomized to vedolizumab vs placebo. Overall quality of evidence was rated as very low certainty, being rated down for risk of bias (because randomization was not stratified by presence or absence of fistula), indirectness (because all patients received induction therapy with vedolizumab) and imprecision (95% CI crossing unity). In the same trial, on extension to 52 weeks, maintenance therapy with vedolizumab may be more effective than placebo achieving fistula remission (RR, 0.78; 95% CI, 0.60–1.02). Overall quality of evidence was rated as low certainty, being rated down for risk of bias (because randomization was not stratified by presence or absence of fistula), and imprecision (95% CI crossing unity) (Table 15). In a phase 4 RCT comparing 2 doses of vedolizumab (standard dose vs standard dose + additional dose at week 10) for fistulizing CD, no differences were observed in rates of fistula closure at week 30 between the 2 doses (7 of 14 vs 5 of 14).[128]

Ustekinumab vs placebo, achieving and maintaining fistula remission. In a pooled analysis of 4 trials of induction therapy with ustekinumab, Sands and colleagues[129] identified 238 patients with active draining fistula (100% perianal). Ustekinumab was more effective than placebo in achieving complete closure of fistula (RR, 0.85; 95% CI, 0.73–1.99). Quality of evidence was rated as low certainty, being rated down for risk of bias (because randomization was not stratified by presence or absence of fistula) and imprecision (optimal information size not met). In extension of the IM-UNITI maintenance trial in which all patients received induction therapy with ustekinumab, and responding patients were randomized to ustekinumab vs placebo, ustekinumab was associated with a higher rate of achieving fistula remission at week 44 (RR, 0.37; 95% CI, 0.12–1.15).[129] Quality of evidence was rated as low certainty, being rated down for risk of bias (because randomization was not stratified by presence or absence of fistula) and imprecision (wide 95% CI crossing unity) (Table 15).

Thiopurines vs placebo, achieving and maintaining fistula remission. In subgroup analysis of a single RCT including 10 patients with active draining fistula (80% perianal), azathioprine was not effective in achieving fistula healing, defined as partial or complete closure by 16 weeks (RR, 1.00; 95% CI, 0.08–11.93).[130] Overall quality of evidence was rated as very low certainty due to risk of bias (subgroup analysis where randomization was not stratified by presence or absence of fistula) and very serious imprecision (very wide 95% CI, where significant benefit or harm with thiopurines could not be excluded). In subgroup analysis of 1 trial of maintenance therapy with thiopurines in which 2 patients achieved clinical remission luminally with active draining fistula. In this analysis, the 1 fistula patient who responded to active therapy failed to maintain response, and the 1 fistula patient who responded to placebo successfully maintained response. Overall quality of evidence was rated as very low certainty due to risk of bias and very serious imprecision (Table 16).

No specific studies compared methotrexate vs placebo for fistula remission. In subgroup analysis of 1 RCT comparing methotrexate vs azathioprine in patients with fistulizing CD, methotrexate was slightly better than azathioprine in achieving fistula remission over 26 weeks (failure to achieve fistula remission, methotrexate vs azathioprine: 2 of 6 vs 4 of 6; $P = .28$).

Antibiotics vs placebo, achieving and maintaining fistula remission. In a single 3-arm RCT, 25 patients with active draining perianal fistula were randomized to ciprofloxacin, metronidazole, or placebo for 10 weeks.[131] Neither ciprofloxacin nor metronidazole was more effective than placebo in achieving complete fistula closure (RR, 0.94; 95% CI, 0.67–1.33). None of the patients randomized to metronidazole alone achieved partial or complete fistula closure. Overall quality of evidence was rated as low certainty due to very serious imprecision (very wide 95% CI, where significant benefit or harm with antibiotic monotherapy could not be excluded). No trials of maintenance therapy with antibiotics were identified (Table 16).

Potential harms with interventions. Specific adverse effects with all medications have been discussed previously.

Discussion. Fistulizing or penetrating CD is a particularly severe form of CD, reported in 17%–50% of patients, causes substantial morbidity, and is difficult to treat, often requiring combined medical and surgical management. Pharmacotherapies specifically for fistulizing CD have not been well-studied, and most data on efficacy are drawn from subgroup analyses from pivotal registration trials. In these trials, perianal CD is most common, with limited data on

Table 16. GRADE Evidence Profile Evaluating Thiopurines or Antibiotics vs Placebo for Achieving Fistula Remission in Patients With Moderate to Severe Fistulizing Crohn's Disease

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with thiopurines				
Thiopurines compared with placebo for moderate to severe fistulizing CD						
Achieving fistula remission (CRITICAL)	1/5 (20)	1/5 (20)	RR 1.00 (0.08–11.93)	0 fewer per 1000 (from 184 fewer to 1000 more)	10 (1 RCT)	⊕◯◯◯[c,d] VERY LOW

Outcomes	Study event rates, n (%)		Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with antibiotics				
Antibiotics compared with placebo for moderate to severe fistulizing CD						
Induction of clinical remission (CRITICAL)	7/8 (87.5)	14/17 (82.4)	RR 0.94 (0.67–1.33)	18 fewer per 1000 (from 210 fewer to 315 more)	35 (1 RCT)	⊕⊕◯◯[e] LOW

[a]To calculate absolute effect estimate, we used observed rates in placebo arms for induction and maintenance of fistula remission.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for risk of bias (subgroup analysis where randomization was not stratified by presence or absence of fistula).
[d]Rated down for very serious imprecision (very wide 95% CI where significant benefit or harm with thiopurines could not be excluded).
[e]Rated down for very serious imprecision (very wide 95% CI where significant benefit or harm with thiopurines could not be excluded).

internal penetrating disease, such as enteroenteric, enterovesicular, and enterocutaneous fistulae. There was variability in the definition and timing of outcome assessment. For this technical review, we opted to combine all forms of fistulizing CD, and relied largely on RCTs. Surgical management of fistulizing CD was outside the scope of the guideline and technical review. Infliximab is the only biologic agent that has been evaluated specifically against placebo in patients with fistulizing disease and has the strongest body of evidence supporting its use for achieving fistula closure. For most other medications, low to very low certainty of evidence was available, primarily due to risk of bias in post-hoc subgroup analyses and sparse data.

Question 11. In Adults With Fistulizing Crohn's Disease (Without Abscess), Is Adding Antibiotics to Tumor Necrosis Factor–α Antagonists Superior to Tumor Necrosis Factor–α Antagonists Alone?

Key message. In adults with symptomatic fistulizing CD without perianal abscess, combination of TNFα antagonists with antibiotics is probably more effective than TNFα antagonists alone for achieving fistula closure (*moderate certainty of evidence*).

Effect estimates and certainty of evidence. In 2 RCTs in patients with actively draining perianal fistula,

TNFα antagonists (infliximab and adalimumab) in combination with ciprofloxacin (for 12 weeks) was significantly more effective than corresponding TNFα antagonist alone in achieving fistula closure over 12–18 weeks (RR, 0.42; 95% CI, 0.26–0.68).[132,133] The certainty of evidence was rated as moderate, being rated down for imprecision (optimal information size not met). Although differences were observed in the effect size in the 2 trials, we did not rate down for heterogeneity (Table 17).

Potential harm of intervention. Fluoroquinolones carry a black box warning from the FDA for disabling and potentially irreversible serious adverse reactions, including risk of tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects.

Discussion. Bacteria play a part in fistula development in patients with CD. Hence, adding antibiotics may improve fistula healing by controlling microflora present in the fistula tract. Although current trials suggest a short-term benefit with adding ciprofloxacin for 12 weeks to TNFα antagonists, on extension to 24 weeks (after stopping ciprofloxacin at week 12), Dewint and colleagues[133] observed that 3 patients randomized to the combination treatment group lost response with fistula recurrence, and the number of patients in the adalimumab monotherapy group that reached the primary end point at week 12 remained stable at week 24. This might suggest the need for long-term ciprofloxacin beyond 12 weeks to maintain fistula remission.

Evidence-to-Decision Framework

Patients' Values and Preferences of Crohn's Disease Therapy

Most patients with CD are benefit-driven, preferring the use of therapies with the highest likelihood of maintaining remission; a smaller group of patients are more risk-averse, wishing to minimize potential toxicities, including infection and cancer, even at the expense of reduced likelihood of maintaining remission of CD. In an online patient-preference survey of 812 patients with CD, latent class analysis demonstrated 3 distinct groups of survey responders whose choices were strongly influenced by avoidance of active symptoms (61%); avoidance of corticosteroid use (25%); or avoidance of risks of cancer, infection, or surgery (14%) when choosing a therapy.[134] Class membership was correlated with age, sex, mean short CDAI score and corticosteroid avoidance. Hazlewood and colleagues[135] similarly observed that in a cohort of 155 patients with CD, 55% patients were prioritized treatment benefits, 21% prioritized corticosteroid avoidance, and 20% placed higher importance on avoiding treatments with a risk of cancer or infection. In a discrete choice experiment study of 202 patients with inflammatory bowel disease (77 patients with CD), Bewtra and colleagues[136] observed that to delay relapse by 5 years, patients were willing to accept up to a 28% chance of having a serious infection and 1.8% chance of having a lymphoma. These maximal acceptable risk rates

Table 17. GRADE Evidence Profile Evaluating Antibiotics Combined With Tumor Necrosis Factor–α Antagonists vs Tumor Necrosis Factor–α Antagonists Alone for Achieving Fistula Remission In Patients With Moderate to Severe Fistulizing Crohn's Disease

	Study event rates, n (%)					
Outcomes	Risk with TNFα antagonists alone	Risk with TNFα antagonists and antibiotics	Relative effect (95% CI)	Absolute effect[a]	No. of participants (studies)	Quality of the evidence (GRADE)[b]
TNFα antagonists and antibiotics compared with TNFα antagonists for moderate to severe fistulizing CD						
Achieving fistula remission (CRITICAL)	31/44 (70.5)	13/45 (28.9)	RR 0.42 (0.26–0.68)	409 more per 1000 (from 521 fewer to 225 fewer)	89 (2 RCTs)	⊕⊕⊕◯[c] MODERATE

[a]To calculate absolute effect estimate, we used observed rates in comparator arm for induction and maintenance of fistula remission.
[b]GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[c]Rated down for imprecision (low event rate).

were lower in patients with CD than ulcerative colitis. These rates vary depending on disease state—patients with active disease are willing to accept comparatively less risk than patients with no active symptoms to achieve a given improvement in time to relapse. For example, to delay a relapse for 1.5 years, patients currently in remission would be willing to accept a 15.6% risk of infection and a 1.1% risk of lymphoma, and patients currently experiencing symptoms were willing to accept only 8.5% risk of infection and 0.5% risk of lymphoma. Recognizing the heterogeneity of patient preferences among those with CD, physicians should engage patients in shared decision-making with adequate contextualization of risks and benefits, and tailor treatment options based on patient preference.

Cost-Effectiveness

Although several cost-effectiveness analyses have been performed, they have shown conflicting findings due in part to differences in cost of therapies in diverse health care systems globally. In most analyses, infliximab or adalimumab dominated other biologic agents; however, none of the agents met conventional cost-effectiveness thresholds.[137]

Equity

A recent review on the effects of race and ethnicity on the management of IBD patients highlights issues around access to care, insurance coverage, and use of medical therapies, specifically biologic agents.[138] Although some studies demonstrated that African American, Asian, or Hispanic patients with CD were less likely to receive biologics compared with White patients, other studies found no differences in the use of immunomodulators of TNFα antagonists among patients of different races or ethnicities.[139–141] There is evidence of differences in insurance coverage, however, with African American and Hispanic populations less likely to have commercial insurance and more likely to have Medicaid or be uninsured.[142,143]

Knowledge Gaps and Future Directions

Although several significant advancements have been made in the treatment of patients with moderate to severe luminal and fistulizing CD, this technical review identified some key knowledge gaps that merit further evaluation to inform clinical guidelines and practice.

Risk Stratification and Shared Decision-Making

Several prognostic factors have been identified that predict higher risk of requiring surgery and developing disease complications in patients with CD.[24] There is considerable heterogeneity within CD based on disease location, behavior, and early course and presentation. However, there is a paucity of risk-prediction models based on clinical, biochemical, serologic, genetic, and other factors that can accurately stratify patients in terms of their short- and long-term disease–related risks and disability. This results in frequent over- and undertreatment of patients at low- and high-risk of disease complications, respectively, and delay in appropriate care. Developing such models may allow implementation of risk-congruent treatment strategies and appropriate use of expensive therapies. Similarly, risk-stratification strategies to identify patients at high risk of developing treatment-related complications are limited. Validated risk prediction models to accurately identify patients at high risk of disease- vs treatment-related complications, and how different treatments modify these risks, is vital to know and communicate effectively to patients. Pairing this information with patients' values and preferences would facilitate shared decision-making, as the treatment landscape evolves rapidly in this field.

Personalization and Positioning of Therapies

With increasing availability of different biologic agents and promising targeted immunosuppressive agents in development for treating outpatients with moderate to severe CD, there is clearly a need for identifying biomarkers predictive of response to individual therapies, to facilitate optimal choice of therapies. While awaiting biomarkers, validated clinical prediction models may be helpful, if sufficiently discriminatory to help identify patients who have a low vs high probability of response to specific therapies. Ongoing research efforts using multi-omic platforms using serum, stool, and tissue specimens have potential to inform biomarkers predictive of response to specific therapies. Once these are available, clinical trials or prospective comparative effectiveness studies using integrated clinical-, pharmacokinetic-, and biomarker-based treatment positioning strategies vs usual care could provide guidance on appropriate management strategies.

Management of Crohn's Disease in Special Populations

With rising incidence and prevalence of CD in older patients, evidence-based treatment strategies for this population are much needed.[144] Management of these patients warrants careful consideration of the risks of disease-related vs treatment-related complications and extra-intestinal complications (eg, cardiovascular disease and malignancy) in the context of patients' values and preferences, functional status, and comorbidities. Similarly, racial and ethnic minorities, including African American and Hispanic populations, and immigrants have traditionally been underrepresented in clinical trials.[138] Prior studies have demonstrated lower use of advanced medical and surgical therapies, inferior health care access, lower adherence to therapy, and inferior IBD-related outcomes in these patients. Therefore, a more comprehensive understanding of disease burden, course and treatment effectiveness, and access is warranted in these patients.

Treatment Targets in Crohn's Disease

Although it is well known that there may be significant discrepancies in symptoms and endoscopic findings in patients with CD, particularly small bowel CD, until recently, clinical trials have often not routinely incorporated

endoscopic evaluation in assessing efficacy of therapy. Although treating to a target of symptomatic remission has been shown to decrease risk of disease complications, it remains to be seen whether routinely treating to a target of endoscopic remission, even in asymptomatic patients, offers substantial additional benefit.[145] Such an approach, although suggested in expert consensus statements, can be challenging for several reasons, including the need for frequent biochemical and/or endoscopic monitoring and switching empirically between therapies in the absence of predictive biomarkers of response to specific agents. Such empiric switching may inadvertently result in transitioning to a less effective therapy, potentially increasing the risk of disease flare and causing harm. Such an approach would require careful assessment of the anticipated magnitude of benefit in downstream consequences (eg, decreasing surgery health care use) vs risks and costs, with treating to different treatment targets. Different therapies have different rates of achieving different targets, often incrementally more difficult from clinical and biochemical, to endoscopic, to histologic remission, and may result in different intensity of therapies with associated risks and costs.

Novel Therapies

Even the most effective pharmacologic therapies for patients with moderate to severe CD are effective in achieving clinical remission in 40%–50% of patients, with frequent loss of response. Novel agents targeting different aspects of the inflammatory pathways, novel combinations to optimize response to existing therapies, as well as novel dietary and microbiota-directed therapies, are warranted to improve outcomes in patients with CD.

Management of Fistulizing Crohn's Disease

As noted above, fistulizing CD is a particularly severe form of CD with substantial morbidity, yet there is little evidence to inform optimal treatment approach. Although medical and surgical co-management is often required, optimal management strategies need to be defined. Local injection of mesenchymal stem cells in fistula tracts appears promising.[146]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dxdoi.org/10.1053/j.gastro.2021.04.023.

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Correspondence
Address correspondence to: Chair, Clinical Guidelines Committee, American Gastroenterological Association, National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: natarodian@gastro.org

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Conflicts of interest
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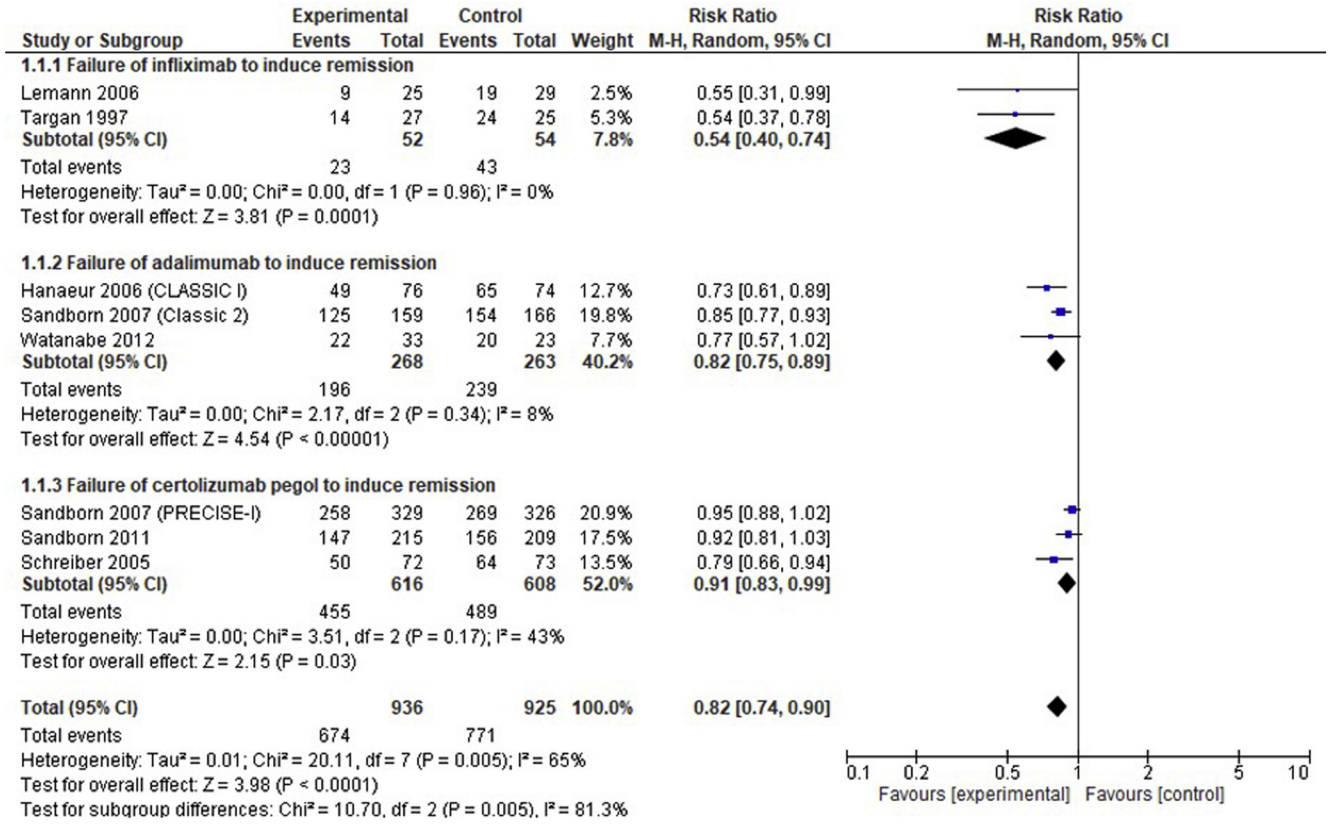
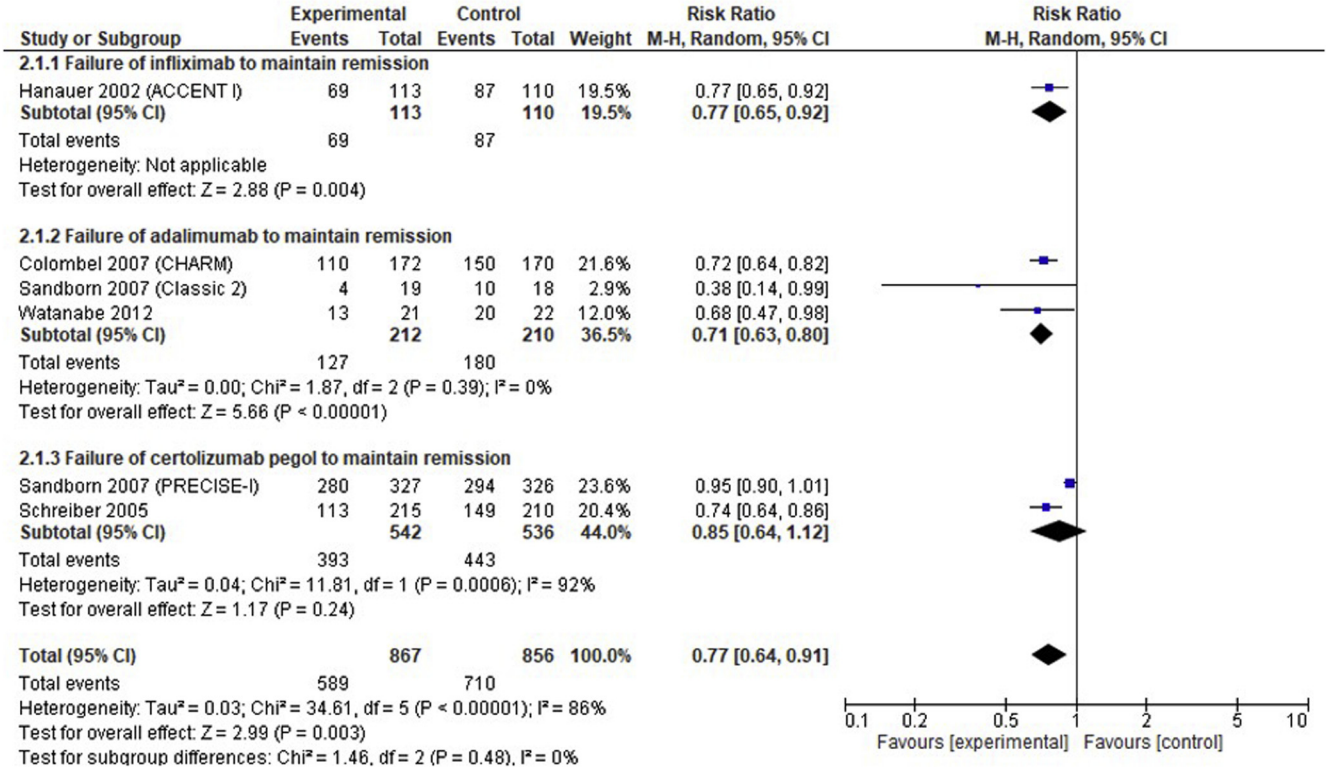
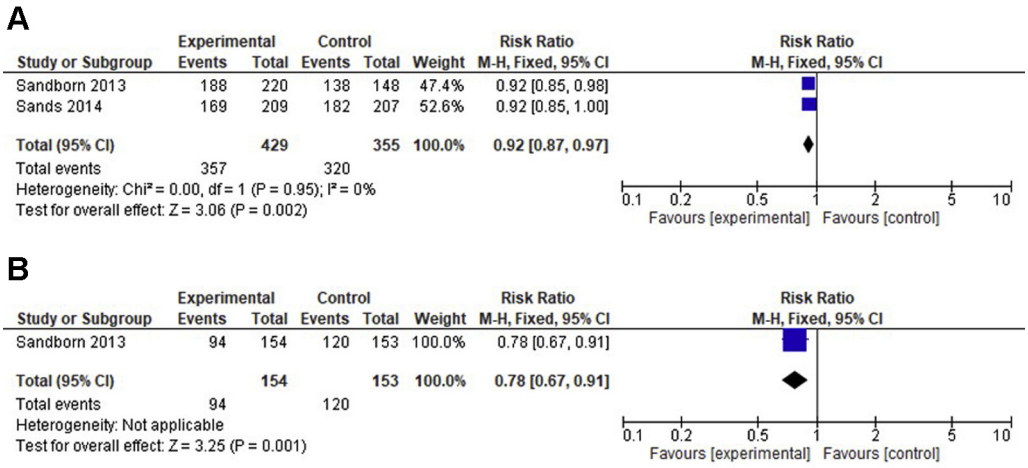


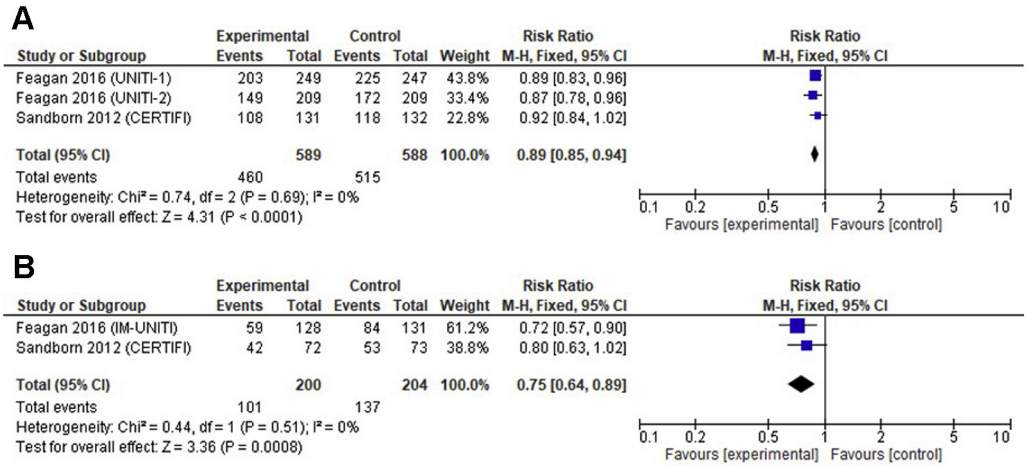
Supplementary Figure 1. Pair-wise meta-analysis: efficacy of tumor necrosis factor-α antagonists for inducing remission in patients with moderate to severely active CD.



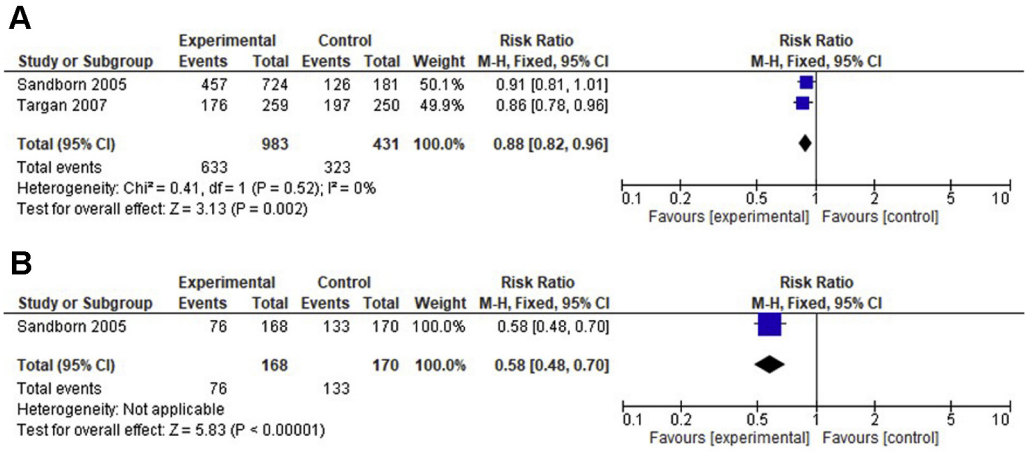
Supplementary Figure 2. Pair-wise meta-analysis: efficacy of tumor necrosis factor-α antagonists for maintaining remission in patients with quiescent moderate to severe CD.



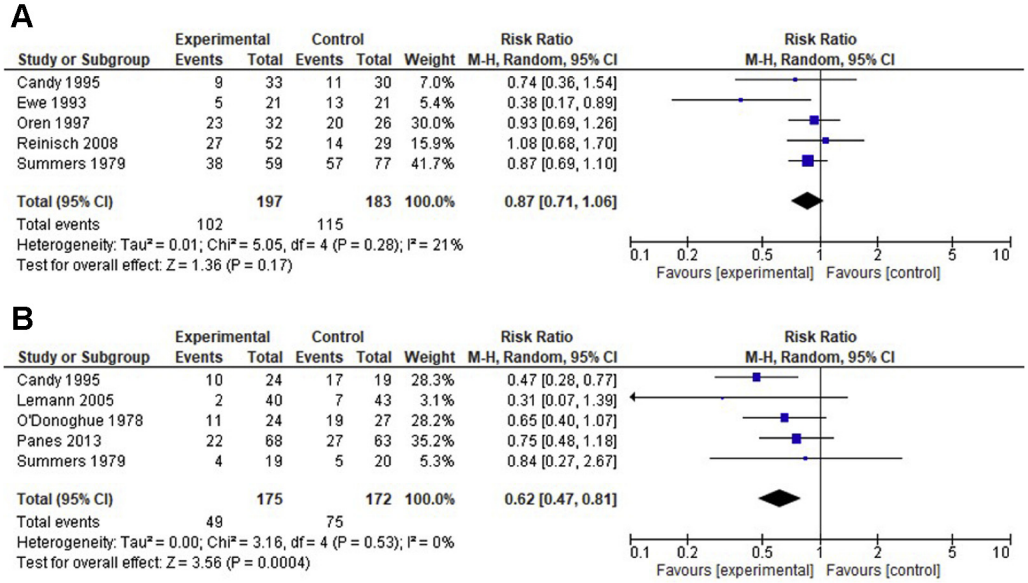
Supplementary Figure 3. Pair-wise meta-analysis: efficacy of vedolizumab for (*A*) induction and (*B*) maintenance remission in patients with moderate to severe CD.



Supplementary Figure 4. Pair-wise meta-analysis: efficacy of ustekinumab for (*A*) induction and (*B*) maintenance remission in patients with moderate to severe CD.

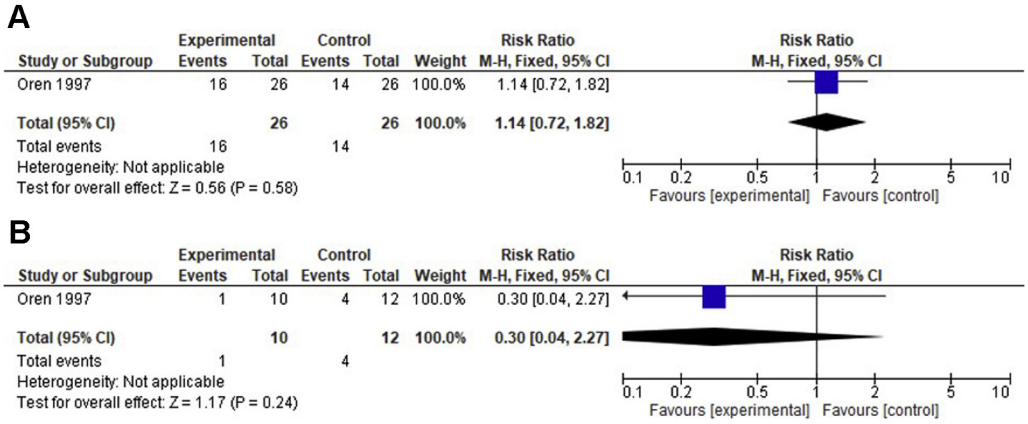


Supplementary Figure 5. Pair-wise meta-analysis: efficacy of natalizumab for (*A*) induction and (*B*) maintenance remission in patients with moderate to severe CD.

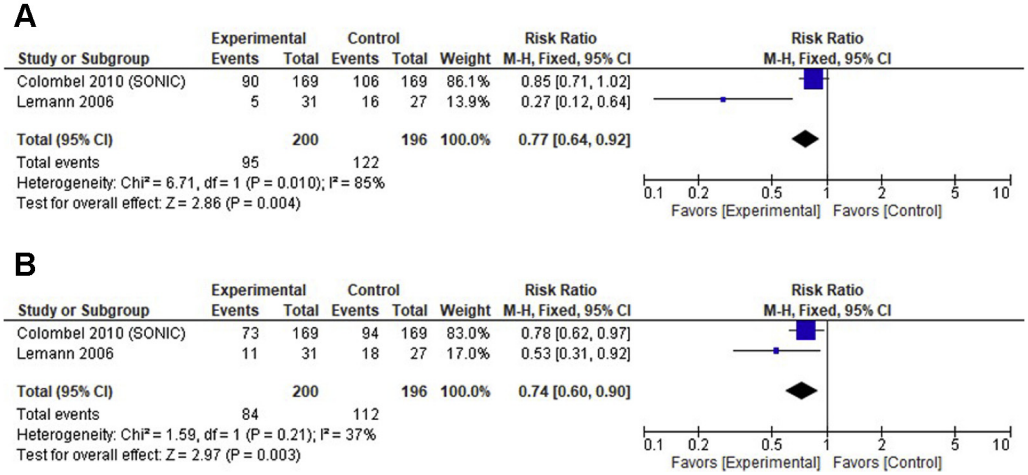


Supplementary Figure 6. Pair-wise meta-analysis: efficacy of thiopurines for (*A*) induction and (*B*) maintenance remission in patients with moderate to severe CD.

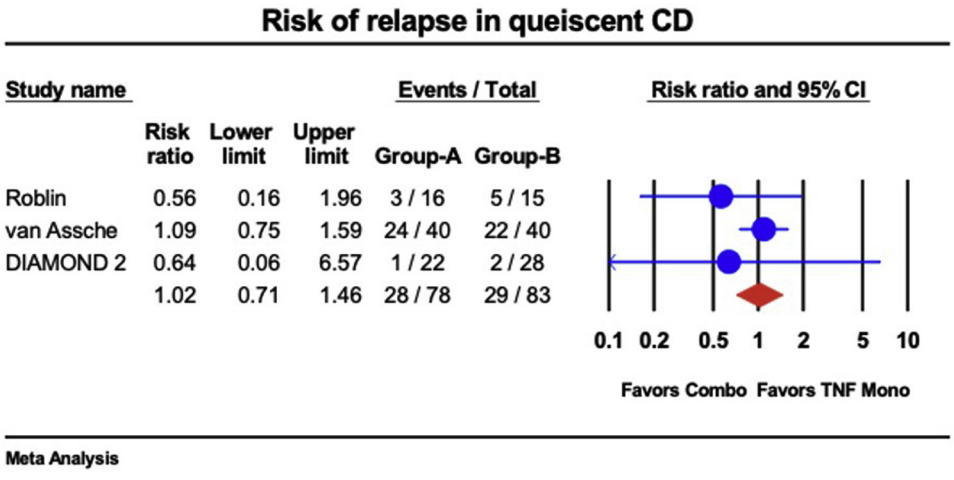
Supplementary Figure 7. Pair-wise meta-analysis: efficacy of subcutaneous methotrexate for (*A*) induction and (*B*) maintenance remission in patients with moderate-severe CD.



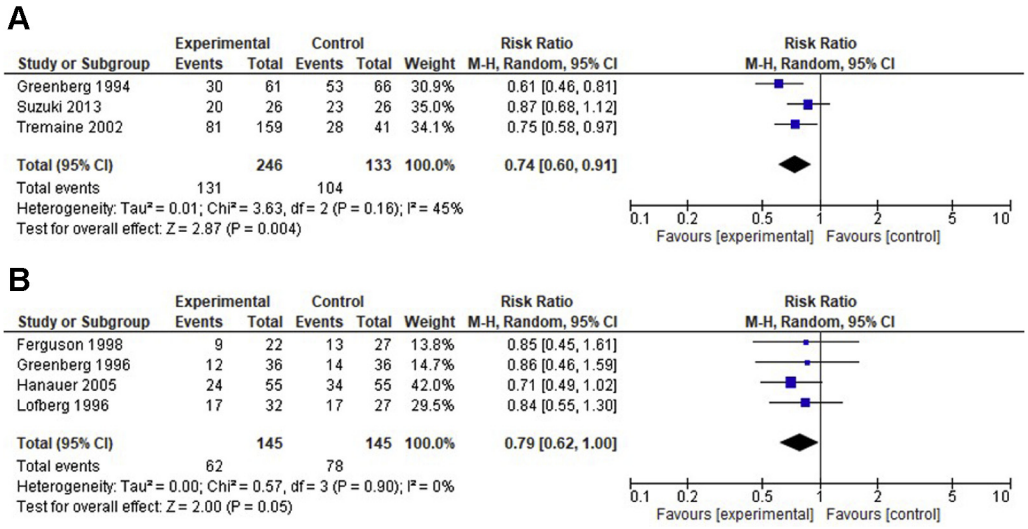
Supplementary Figure 8. Pair-wise meta-analysis: efficacy of oral methotrexate for (*A*) induction and (*B*) maintenance remission in patients with moderate-severe CD.



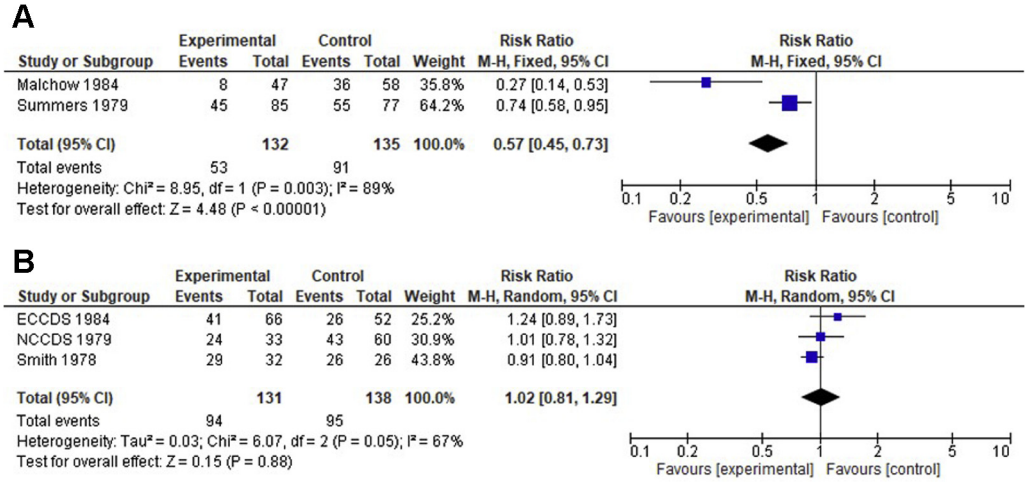
Supplementary Figure 9. Pair-wise meta-analysis: efficacy of infliximab + azathioprine vs infliximab monotherapy for (*A*) induction and (*B*) maintenance of remission in patients with moderate-severe CD.



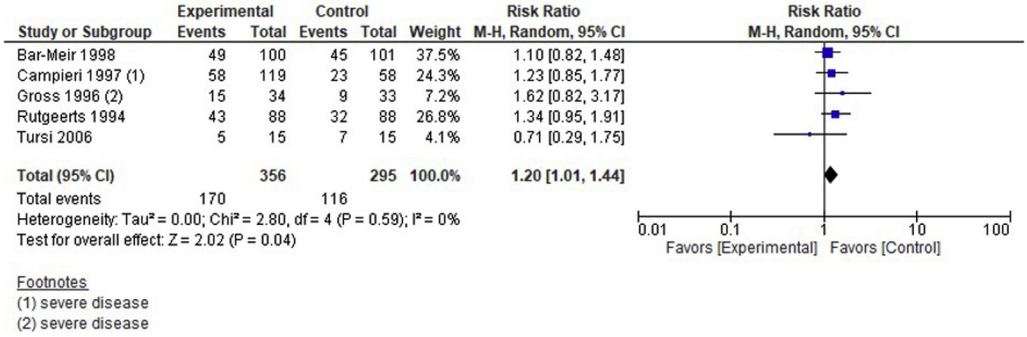
Supplementary Figure 10. Pair-wise meta-analysis: efficacy of continuing combination therapy vs withdrawal of immunomodulator for preventing relapse in patients with quiescent moderate to severe CD on combination therapy.



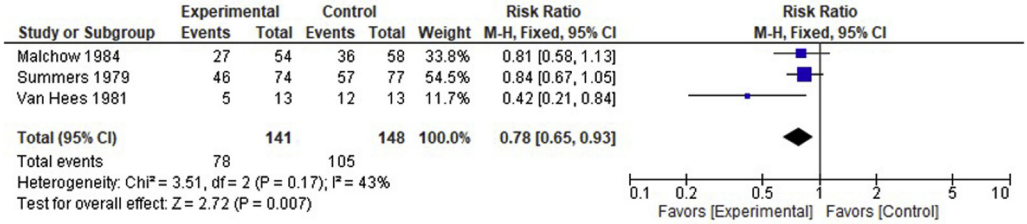
Supplementary Figure 11. Pair-wise meta-analysis: efficacy of controlled ileal release budesonide for (*A*) induction and (*B*) maintenance of remission in patients with moderate-severe CD.



Supplementary Figure 12. Pair-wise meta-analysis: efficacy of oral prednisone for (*A*) induction and (*B*) maintenance of remission in patients with moderate-severe CD.



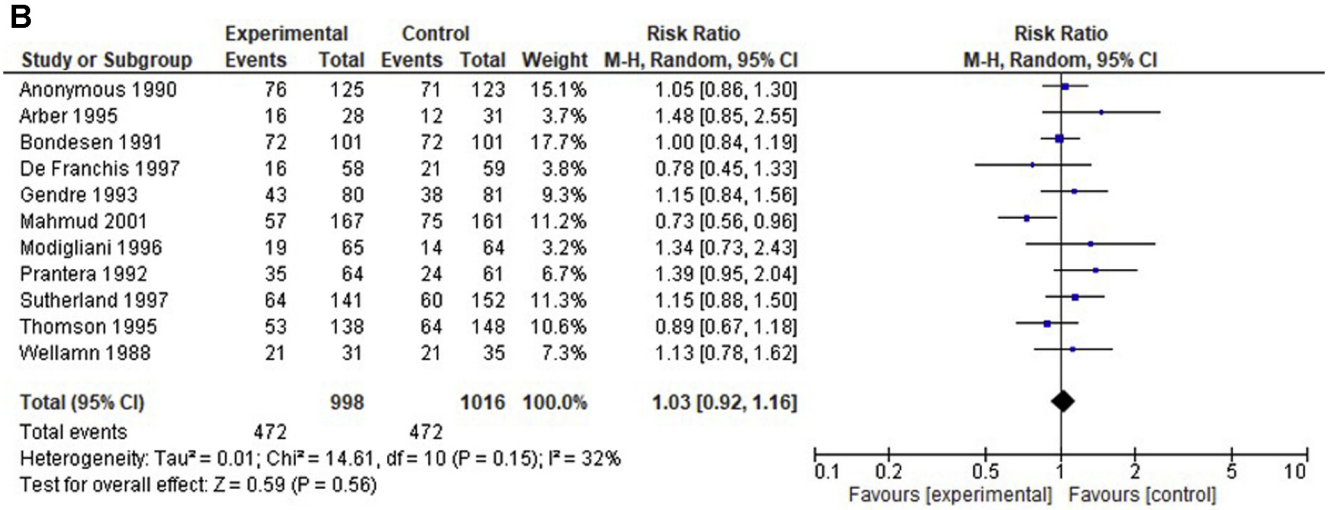
Supplementary Figure 13. Pair-wise meta-analysis: efficacy of controlled ileal release budesonide vs oral prednisone for of remission in patients with moderate to severe CD.



Supplementary Figure 14. Pair-wise meta-analysis: Efficacy of sulfasalazine vs placebo for induction of remission in patients with moderate to severe CD.

A

B



Supplementary Figure 15. Pair-wise meta-analysis: Efficacy of mesalamine vs placebo for (*A*) induction and (*B*) maintenance of remission in patients with moderate to severe CD.

Supplementary Table 1. Risk of Serious and Opportunistic Infections With Immunomodulators and/or Tumor Necrosis Factor–α Antagonists in Key Cohort Studies

Study, first author, year, setting	Patients	Serious infections	Opportunistic infections
Kirchgesner, 2018[29]; France; Nationwide cohort, 2009–2014	190,694 patients with IBD (49.7% UC); 24.9%, 13.8% and 6.3% on IMM monotherapy, TNFα monotherapy and combination therapy, respectively	Incidence rate (per 1000 PY): Unexposed: 8.4 IMM mono: 10.5 TNFα mono: 18.9 Combination: 22.4 Adjusted analysis (HR [95% CI]): TNFα mono vs IMM: 1.71 (1.56–1.88) Combination vs IMM: 2.11 (1.80–2.48) Combination vs TNFα mono: 1.23 (1.05–1.45)	Incidence rate (per 1000 PY): Unexposed: 0.4 IMM mono: 1.7 TNFα mono: 2.1 Combination: 4.1 Adjusted analysis (HR [95% CI]): TNFα mono vs IMM: 1.08 (0.83–1.40) Combination vs IMM: 2.11 (1.45–3.08) Combination vs TNFα mono: 1.96 (1.32–2.91)
Nyboe Andersen, 2015[30]; Denmark; Nationwide register-based propensity score matched cohort study, 2002–2012	52,392 patients with IBD, of whom 4300 received TNFα antagonists; matched 1543 TNFα antagonist users vs 1543 TNFα antagonist nonusers	90-d risk period after start of medication (HR [95% CI]): TNFα antagonist user vs non-user: 1.63 (1.01–2.63) TNFα mono vs IMM: 2.17 (0.85–5.52) 365-d risk period after start of medication (HR [95% CI]): TNFα antagonist user vs non-user: 1.27 (0.92–2.27) TNFα mono vs IMM: 2.05 (0.97–4.36)	Not reported
Grijlava, 2011[147]; United States; multi-institutional collaboration, 1998–2007	45,188 patients with IBD; 9.4% and 6.8% treated with IMM and TNFα antagonist, respectively; 2323 TNFα antagonist users vs 2323 propensity score matched TNFα antagonist nonusers	Incidence rate (per 1000 PY) (HR [95% CI]): IMM therapy: 96.0 TNFα antagonists: 109.1 Adjusted analysis (HR [95% CI]): TNFα user vs IMM user: 1.10 (0.83–1.46)	Herpes zoster Incidence rate (per 1000 PY): IMM therapy: 9.4 TNFα antagonists: 11.3 Adjusted analysis (HR [95% CI]): TNFα user vs IMM user: 0.79 (0.41–1.53)
Schneweiss, 2009[148]; British Columbia; population-based cohort study, 2001–2006	10,622 patients with IBD; 27.0% and 4.9% treated with IMM and TNFα antagonist, respectively	Incidence rate (per 1000 PY): IMM mono: 8.9 TNFα mono: 4.3 Combination: 7.3 Adjusted analysis (HR [95% CI]) TNFα mono vs IMM: 0.74 (0.10–5.53) Combination vs IMM: 1.05 (0.14–7.81)	Not reported
Lewis, 2018[32]; United States; Medicare-Medicaid, 2001–2013	3224 patients with UC treated with TNFα antagonists vs 459 patients treated with prolonged corticosteroids	Incidence rate (per 1000 PY): TNFα antagonist user: 47.0 Prolonged corticosteroid use: 54.9 Adjusted analysis (HR [95% CI]): TNFα antagonist user vs prolonged corticosteroid use: 0.99 (0.78–1.26)	Not reported

HR, hazard ratio; IBD, inflammatory bowel disease; IMM, immunomodulator; UC, ulcerative colitis.

Supplementary Table 2. Risk of Malignancy, in Particular Hematologic Malignancy, With Immunomodulators and/or Tumor Necrosis Factor–α Antagonists in Key Cohort Studies

Study, first author, year, setting	Patients	Malignancy
Lemaitre, 2017[40]; France; nationwide cohort, 2009–2015	189,289 patients with IBD, median follow-up 6.7 y; 65%, 27%, 16%, and 7.5% were unexposed, on IMM monotherapy, TNFα monotherapy, and combination therapy, respectively	Incident lymphoma Incidence rate (per 1000 PY): Unexposed: 0.26 IMM mono: 0.54 TNFα mono: 0.41 Combination: 0.95 Adjusted analysis, HR (95% CI): IMM vs unexposed: 2.60 (1.96–3.44) TNFα mono vs unexposed: 2.41 (1.60–3.64) Combination vs unexposed: 6.11 (3.46–10.8) TNFα mono vs IMM: 0.93 (0.60–1.44) Combination vs IMM: 2.35 (1.31–4.22) Combination vs TNFα mono: 2.53 (1.35–4.77)
Nyboe Andersen, 2014[38]; Denmark; nationwide register-based propensity score–matched cohort study, 1999–2012	56,146 patients with IBD, median follow-up 9.3 y; 8.1% exposed to TNFα antagonists	Overall malignancy Incidence rate (per 1000 PY): TNFα antagonist nonuser: 7.4 TNFα antagonist user: 4.4 Adjusted analysis (including adjusting for IMM use), HR (95% CI): TNFα antagonist user vs non-user: 1.07 (0.85–1.36) Hematopoetic and lymphoid malignancy Incidence rate (per 1000 PY): TNFα antagonist nonuser: 0.55 TNFα antagonist user: 0.43 Adjusted analysis (including adjusting for IMM use), HR (95% CI): TNFα antagonist user vs nonuser: 0.90 (0.42–1.91)
Beaugerie, 2009[149]; France; prospective nationwide observational cohort, 2004–2007	19,486 patients with IBD, median follow-up, 3 y; 30.1% and 5% treated with thiopurines and TNFα antagonists, respectively	Incident lymphoproliferative disorder Incidence rate (per 1000 PY); SIR (95% CI) Unexposed: 0.26; 1.45 (0.53–3.16) IMM: 0.90; 6.86 (3.84-11.31) TNFα antagonist user: 0.48; 4.53 (0.55–16.4) Combination: 1.03; 10.2 (1.24–36.9)
Haynes, 2013[150]; United States; multi-institutional collaboration, 1998–2007	6357 patients with IBD (1508 PY); 58.2% and 41.8% treated with IMM and TNFα antagonist, respectively	Incident lymphoma or leukemia Incidence rate (per 1000 PY): IMM user: 0.5 TNFα antagonist user: 0.6 Any solid organ cancer Incidence rate (per 1000 PY): IMM user: 8.2 TNFα antagonist user: 4.1 Adjusted analysis TNFα antagonist user vs IMM user: 1.42 (0.47–4.26)
Herrinton, 2011; United States; Kaiser Permanente IBD Registry, 1996-2009	16,023 patients with IBD; median follow-up, 5.8 y; 24% and 9% on IMM and TNFα antagonist, respectively	Incident lymphoma Incidence rate (per 1000 PY) (SIR [95% CI]): Unexposed: 0.49; 1.0 (0.95–1.1) IMM mono: 0.46; 1.4 (1.2–1.7) TNFα antagonist mono: 1.49; 5.2 (3.5–6.8) Combination: 1.91; 6.6 (4.4–8.8)

Supplementary Table 3. Rate of Adverse Events in Included Trials of Maintenance Therapy for Moderate to Severe Crohn's Disease

Trial	Any adverse event	Any adverse event leading to drug discontinuation	Serious adverse events	Serious infections
Infliximab				
Hanauer,[47] ACCENT-I, 2002	NR	P: 3	29	4
Rutgeerts,[151] 1999		I: 15	28	4
	P: 97	NR	NR	NR
	I: 95			
Adalimumab				
Sandborn,[54] CLASSIC-II, 2007	P: 100	11	11	0
Colombel,[55] CHARM, 2007	I: 78	5	3	0
Watanabe,[50] 2012				
	P: 85	13	15	1
	I: 89	7	9	3
	P: 84	24	24	8
	I: 80	4	8	4
Certolizumab pegol				
Schreiber,[59] PRECISE 2, 2007	P: 67	13	7	<1
	I: 65	8	6	3
Vedolizumab				
Sandborn,[60] GEMINI II, 2013	P: 82	NR	15	3
	I: 87		24	6
Ustekinumab				
Sandborn,[63] CERTIFI, 2012	P: 83	NR	18	4
Feagan,[62] IM-UNITI, 2016	I: 77		17	2
	P: 84	NR	15	2
	I: 82		10	2

I, intervention; NR, not reported; P, placebo.