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

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

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

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

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

Methods

Overview

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

Outcomes of Interest

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

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

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Table 1. PICO Questions

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

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

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

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

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

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

Literature Search

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

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

harm was performed from this search (see Supplementary Methods for the detailed search strategies). Updated information on serious infection and lymphoma (The Crohn's Therapy, Resource, Evaluation, and Assessment Tool [TREAT] registry) became available during the writing process and was thus included in this review (Lichtenstein et al, manuscript under review).[11,12]

Based on these searches, we identified existing systematic reviews and used AMSTAR,[13] a validated instrument, to evaluate the quality of systematic reviews. Systematic reviews that were of high quality, were up-to-date, and used the aforementioned outcomes of interest (eg, corticosteroid-free remission based on CDAI) were selected for inclusion in the evidence profiles. When systematic reviews were not up-to-date or were incomplete, we performed our own meta-analysis (random effects model for 3 or more studies and fixed effects model for 2 studies) using the Cochrane Collaboration's RevMan 5.1 software.[14]

Harm data from RCTs were sometimes of inadequate quality or had very few events. When this occurred, we identified observational studies and assessed them for risk of bias using the Newcastle–Ottawa tool.[15] We selected the observational studies with the highest methodological quality and greatest number of events for the outcomes of serious infections and lymphoma.

Results

Induction of Remission

Thiopurines versus placebo. Five RCTs in 380 patients (thiopurine, 197; placebo, 183) compared AZA or 6-MP with placebo for the induction of remission.[16–20] All studies were blinded and likely achieved allocation concealment. The patient populations differed with respect to disease duration and location. The majority of patients had ileal or ileocolonic disease for at least 3 to 4 years and had received prior medical therapy and/or had undergone prior surgery. Except for one study that used 6-MP at a low dosage of 50 mg/day,[18] all studies examined the use of AZA at a dosage of 2.5 mg/kg/day. Tapering doses of corticosteroids were given concomitantly in both the placebo and AZA/6-MP arms in all trials except for one study.[19]

Compared with placebo, thiopurine therapy showed a trend toward fewer failures to achieve remission at 12 to 17 weeks (relative risk [RR], 0.87; 95% confidence interval, 0.71–1.06).[21] Based on a placebo failure rate of 62.8%, thiopurine therapy would result in 82 fewer failures per 1000 patients (95% CI, from 182 fewer to 38 more) (Table 2). The CI included substantial benefit but also potential harm (crossing 1.0). The overall quality of evidence was deemed moderate as a result of imprecision. A low dose of 6-MP was used in one trial,[18] but a sensitivity analysis without this trial did not substantially change the overall estimate of the results.

The quality of data on serious infections varied among the primary studies. Only 2 of the 5 studies specifically reported serious infections.[16,17] One study[18] did not provide any data on overall infections, and the remaining 2 studies did not provide any detailed data specific to serious infections.[20,22] Data on the risk of serious infections were thus obtained from a large prospective, observational cohort study of 6273 patients with a mean follow-up of 5.2 years.[11] On multivariate analysis,

Table 2. Should Thiopurines (AZA/6-MP) Versus Placebo Be Used for Adults With Active (Moderate to Severe) CD (CDAI 220–450)?

No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) With control	Study event rates (%) With thiopurines (AZA/6-MP)	Relative effect (95% CI)	Anticipated absolute effects Risk with controls	Anticipated absolute effects Risk difference with thiopurines (AZA/6-MP) (95% CI)
Failure of remission (critical outcome; remission assessed with CDAI <150 or Harvey–Bradshaw Index <4)											
380 (5 studies), 12–17 wk, Khan et al[21]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	Undetected	⊕⊕⊕⊖ Moderate[a] due to imprecision	115/183 (62.8)	102/197 (51.8)	RR, 0.87 (0.71–1.06)	628 per 1000	82 fewer per 1000 (from 182 fewer to 38 more)
Serious infections[b] (important outcome)											
5394 (1 study), 5.2 y (mean follow-up), Lichtenstein et al[11]	Serious[c]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	⊕⊖⊖⊖ Very low[c] due to risk of bias, imprecision	148/3255 (4.6)	146/1849 (7.9)	OR, 1.23 (0.96–1.57)[d]	46 per 1000	10 more per 1000 (from 2 fewer to 24 more)[e]

[a]CI includes substantial benefit but also potential harm (CI crosses 1.0).
[b]Data on serious infections were obtained from the study by Lichtenstein et al, which evaluated risk across all immunomodulators (AZA/6-MP/MTX); however, in 95% of cases, this consisted of treatment with a thiopurine (AZA/6-MP). Serious infection was defined as "any infection reported as serious by the investigator and any infection that required hospitalization."
[c]The following issues were identified for rating down the quality: representativeness of patient population unclear, consecutive patients not enrolled (convenience sample), outcome adjudication not independently confirmed, incomplete outcome reporting, and imprecision.
[d]This was an adjusted effect estimate.
[e]Time frame was not reported in the original manuscript.

thiopurine therapy was associated with a trend toward an increase in serious infections (adjusted odds ratio [OR], 1.23; 95% CI, 0.96–1.57). Patients treated with thiopurines had 10 more serious infections per 1000 patients compared with patients who were not treated with thiopurines (95% CI, from 2 fewer to 24 more; Table 2). The overall quality of evidence was rated very low due to bias and imprecision (Table 2).

MTX versus placebo. Two RCTs compared MTX with placebo for the induction of remission.[18,23] Doses and routes of administration of MTX (intramuscular vs oral) differed between the 2 studies, and MTX may have been underdosed in one study.[18] Additionally, there were differences in disease severity among the populations.

Compared with controls, there was a trend toward fewer failures of remission with MTX versus placebo (RR, 0.82; 95% CI, 0.65–1.03).[21] Based on a placebo failure rate of 79.5%, MTX therapy would result in 143 fewer failures per 1000 patients (from 278 fewer to 24 more; low-quality evidence; Supplementary Table 1). The overall quality of evidence was deemed low as a result of imprecision and indirectness (different dosages and routes of MTX).

The risk of serious infections could not be assessed due to the paucity of data. In the primary studies, data on serious infections were not reported.[18,23] In the large observational TREAT registry, very few patients were treated with MTX (5.5% in the IFX-treated group vs 2.2% in the group not treated with IFX; G. R. Lichtenstein, personal communication, January 2013) and all immunomodulators (AZA, 6-MP, and MTX) were grouped together as potential predictors of serious infections, without any analysis of the thiopurines and MTX separately.[11] In summary, there are no sufficient data to assess the risk of serious infection in patients with CD treated with MTX.

Anti–TNF-α versus placebo. Eleven RCTs compared IFX, ADA, or CZP with placebo for the induction of remission. Among the 3 studies evaluating the efficacy of IFX,[24–26] there was significant heterogeneity due to (1) differing dosing strategies (single IFX dose,[26] 3 doses over 6 weeks,[25] and 5 doses over 22 weeks[24]), (2) varying disease duration (2–13 years), and (3) differences with regards to prior and concomitant thiopurine or corticosteroid therapy.

Among the 3 trials that evaluated the efficacy of ADA,[27–29] one trial included only patients who were anti–TNF-α naïve,[27] one trial included only patients who were treated with IFX but had not tolerated therapy and/or had lost response (secondary nonresponders),[28] and one trial included both anti–TNF-α naïve individuals and IFX secondary nonresponders.[29] All 3 studies contained an ADA arm treated with 160 mg at week 0 and 80 mg at week 2 (160/80). CLASSIC I (CLinical Assessment of adalimumab Safety and efficacy Studied as Induction therapy in Crohn's disease) also contained arms that received doses of 40 mg/20 mg and 80 mg/40 mg,[27] and the third trial also contained an arm that received doses of 80 mg/40 mg.[29] In all 3 studies, cotherapy with immunomodulators (6-MP, AZA, or MTX) and/or corticosteroids was allowed and clinical remission was assessed at week 4. The mean duration of CD was 8 to 10 years in the 2 trials that reported this disease characteristic.[27,29]

The 4 trials of CZP differed in terms of dosing strategy.[30–33] Cotherapy with corticosteroids, immunomodulators, and antibiotics was allowed, as was prior use of anti–TNF-α (as long as it had been discontinued 3 months before study enrollment). The majority of patients had disease duration of 7 to 10 years.

Pooled results from the IFX trials[24–26] (RR, 0.68; 95% CI, 0.52–0.90), ADA trials[27–29] (RR, 0.85; 95% CI, 0.79–0.91), and CZP trials[30–33] (RR, 0.95; 95% CI, 0.90–1.01) showed an overall reduction of failure to induce remission at weeks 4 to 12 (RR, 0.87; 95% CI, 0.80–0.94).[34] A sensitivity analysis that excluded those subjects who received low ADA induction doses in 2 trials[27,29] did not substantially change the overall estimate of the results (RR, 0.81; 95% CI, 0.75–0.88).

Based on a placebo failure rate of 80.7% in the trials, anti–TNF-α biologic agents reduced the number of failures of remission by 105 per 1000 patients (95% CI, from 48 fewer to 161 fewer failures; Table 3). The CI for failure to induce remission (0.80–0.94) crossed the threshold of minimally important effect (0.80). Therefore, the overall quality of evidence was downgraded to moderate due to imprecision. CZP contributed to the overall heterogeneity of results due to overall lower response rates. Despite differences in patient populations, we did not additionally rate down for indirectness, because this was already reflected in the imprecise results.

Our pooled analysis of the IFX, ADA, and CZP trials did not show any differences in the rates of serious infections compared with placebo (RR, 0.87; 95% CI, 0.47–1.60). Of note, one study[25] had insufficient data on serious infections. Based on the control rate for serious infections of 1.8% over 6 months in SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease), patients treated with anti–TNF-α biologic agents are expected to experience 3 fewer serious infections per 1000 patients (95% CI, from 14 fewer to 16 more; Table 3). The overall quality of evidence was rated moderate due to imprecision (the CI crossed 1).

MTX versus thiopurines. Three small RCTs compared MTX with thiopurines for the induction of remission.[18,35,36] Doses and routes of administration varied and, in general, did not reflect current standards of practice, resulting in indirect and imprecise effect estimates. Compared with thiopurines, MTX failed to show or exclude a beneficial or detrimental effect on failure of remission at 24 to 36 weeks (RR, 1.17; 95% CI, 0.82–1.67).[37] Based on the 40% failure of remission rate of thiopurines observed across these studies, MTX therapy would be expected to produce 68 more failures of remission per 1000 patients (from 72 fewer to 268 more per 1000; Supplementary Table 2). The overall quality of the evidence was rated low due to imprecision and indirectness.

Serious infections were not reported in any of the trials. As noted previously, the observational TREAT study did not separate MTX from the thiopurines but instead considered them together under immunomodulator therapy.[11] In summary, there are no sufficient data to

Table 3. Should Anti-TNFs Versus Placebo Be Used in Adults With Active (Moderate to Severe) CD (CDAI 220–450)?

No. of participants (no. of studies), follow-up, author	Quality Assessment						Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With control	With anti-TNFs	Relative effect (95% CI)	Risk with controls	Risk difference with anti-TNFs (95% CI)
Failure of remission (critical outcome; remission assessed with CDAI <150 at wk 12)											
2756 (10 studies), 4–12 wk, Ford et al[34]	No serious risk of bias	No serious inconsistency	No serious indirectness[a]	Serious[a]	Undetected	⊕⊕⊕⊖ Moderate[a] due to imprecision and indirectness	935/1158 (80.7)	1142/1598 (71.5)	RR, 0.87 (0.80–0.94)	807 per 1000	105 fewer per 1000 (from 48 fewer to 161 fewer)
Serious infections[b] (important outcome)											
2756 (10 studies), 12–54 wk, Ford et al[34]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	⊕⊕⊕⊖ Moderate due to imprecision	22/1236 (1.8)	22/1408 (1.6)	RR, 0.87 (0.47–1.60)	18 per 1000	3 fewer per 1000 (from 14 fewer to 16 more)

[a]CI crosses the threshold of minimally important effect (20%). Rated down for imprecision (wide CI), but we did not additionally rate down for indirectness (despite the heterogeneity in patient populations) because this was already reflected in the imprecise results.
[b]Data on serious infections were updated from the study by Ford et al to include serious infections (own analysis).
[c]Wide CI.

inform a comparison between the thiopurines and MTX as to risk of serious infections in the setting of CD.

Anti–TNF-α/AZA combination therapy versus AZA alone versus anti–TNF-α alone. The most common treatment decision in patients with moderately severe inflammatory CD refractory to corticosteroids involves choosing a thiopurine, an anti–TNF-α monoclonal antibody, or both. SONIC was a 3-arm study of AZA monotherapy, IFX monotherapy, and combination therapy that allowed 2-way comparisons between the therapeutic approaches in a population of immunomodulator- and biologic-naïve patients.[24] The investigators randomized 508 patients (most were white) with a median age of 35 years and median disease duration of 2.2 to 2.4 years.

At week 26, more patients achieved remission in the combination group than in the IFX group (risk of failure to achieve remission compared with IFX: RR, 0.78; 95% CI, 0.62–0.97). Based on the IFX failure rate of 55.6%, combination therapy would reduce the number of remission failures associated with IFX therapy alone by 122 per 1000 patients (from 17 fewer to 211 fewer failures per 1000; Table 4). The overall quality of evidence was rated moderate due to imprecision.

IFX monotherapy and combination therapy were associated with fewer failures of remission than AZA monotherapy. For the comparison of IFX versus AZA, the RR was 0.79 (95% CI, 0.67–0.94). Based on the AZA monotherapy failure rate of 70%, IFX therapy would result in 147 fewer failures of remission per 1000 patients for IFX when compared with AZA (42 fewer to 231 fewer; Table 5). The overall quality of evidence was rated moderate due to imprecision.

For the comparison of combination therapy versus AZA, we performed our own analysis, combining data from SONIC[24] and a study by Lemann et al[25] that compared therapy with IFX (3 doses) plus AZA/6-MP (n = 58) with AZA/6-MP therapy alone (n = 57). Fewer patients failed to achieve remission in the combination group than in the AZA group (RR, 0.61; 95% CI, 0.52–0.73). The use of combination therapy reduced the number of remission failures associated with AZA therapy alone by 274 per 1000 patients (from 190 fewer to 337 fewer; Table 6). The overall quality of evidence was rated high.

There were no significant differences in the rates of serious infections in all three 2-way comparisons: IFX versus AZA (RR, 0.88; 95% CI, 0.35–2.22), combination therapy versus AZA (RR, 0.70; 95% CI, 0.27–1.84), and combination therapy versus IFX (RR, 0.80; 95% CI, 0.3–2.1). The overall quality of evidence was rated moderate due to imprecision (Tables 4–6).

Maintenance of Remission

Thiopurines versus placebo. Three RCTs evaluated maintenance of remission with AZA continuation versus AZA withdrawal.[38–40] More patients maintained remission in the group that continued AZA therapy than in the group that stopped AZA therapy (RR of failure to prevent disease relapse, 0.39, 95% CI, 0.21–0.74).[21] This translates

Table 4. Should AZA/6-MP + Anti-TNF Versus Anti-TNF Be Used in Adults With Active (Moderate to Severe) CD (CDAI 220–450)?

No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With anti-TNF	With anti-TNF + AZA/6-MP		Risk with anti-TNF	Risk difference with anti-TNF + AZA/6-MP (95% CI)
Failure of remission (critical outcome; remission assessed with CDAI <150 and corticosteroid-free)											
338 (1 study), 26 wk, Colombel et al[24]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	Undetected	⊕⊕⊕⊖ Moderate[a] due to imprecision	94/169 (55.6)	73/169 (43.2)	RR, 0.78 (0.62–0.97)	556 per 1000	122 fewer per 1000 (from 17 fewer to 211 fewer)
Serious infections (important outcome)											
342 (1 study), 54 wk, Colombel et al[24]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	⊕⊕⊕⊖ Moderate[b] due to imprecision	8/163 (4.9)	7/179 (3.9)	RR, 0.80 (0.3 to 2.1)	49 per 1000	10 fewer per 1000 (from 34 fewer to 54 more)

[a]CI crosses threshold for minimum clinical effect (10%) and total number of events <300.
[b]CI wide and crosses 1.

Table 5. Should Anti-TNF Versus AZA/6-MP Be Used in Adults With Active (Moderate to Severe) CD (CDAI 220–450)?

No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With AZA/6-MP	With anti-TNF		Risk with AZA/6-MP	Risk difference with anti-TNF (95% CI)
Failure of remission (critical outcome; remission assessed with CDAI <150 and corticosteroid-free)											
339 (1 study), 26 wk, Colombel et al[24]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	Undetected	⊕⊕⊕⊖ Moderate[a] due to imprecision	119/170 (70)	94/169 (55.6)	RR, 0.79 (0.67–0.94)[b]	700 per 1000	147 fewer per 1000 (from 42 fewer to 231 fewer)
Serious infections (important outcome)											
324 (1 study), 54 wk, Colombel et al[24]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	⊕⊕⊕⊖ Moderate[c] due to imprecision	9/161 (5.6)	8/163 (4.9)	RR, 0.88 (0.35–2.22)[b]	56 per 1000	7 fewer per 1000 (from 36 fewer to 68 more)

[a]CI crosses the threshold for minimum clinical effect (10%) and total number of events <300.
[b]Not reported in primary paper; used χ^2 function to recalculate RR (openEpi).
[c]CI is wide and crosses 1.

Table 6. Should AZA/6-MP + Anti-TNF Versus AZA/6-MP Be Used in Adults With Active (Moderate to Severe) CD (CDAI 220–450)?

No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With AZA/6-MP	With anti-TNF + AZA/6-MP		Risk with AZA/6-MP	Risk difference with anti-TNF + AZA/6-MP (95% CI)
Failure of remission (critical outcome; remission assessed with CDAI <150 and corticosteroid-free)											
445 (2 studies) 24–26 wk, Colombel et al[24] and Lemann et al[25a]	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ High	156/222 (70.3)	96/223 (43.0)	RR, 0.61 (0.52–0.73)[a]	700 per 1000	274 fewer per 1000 (from 190 fewer to 337 fewer)
Serious infections (important outcome)											
340 (1 study), 54 wk, Colombel et al[24]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	⊕⊕⊕⊖ Moderate[b] due to imprecision	9/161 (5.6)	7/179 (3.9)	RR, 0.70 (0.27–1.84)	56 per 1000	17 fewer per 1000 (from 41 fewer to 47 more)

[a]Data combined from 2 studies using RevMan (fixed effects model) in our own analysis.
[b]CI wide and crosses 1.

into 201 fewer disease relapses per 1000 patients for those continuing AZA when compared with AZA withdrawal (86 fewer to 260 fewer; Table 7). The overall quality of evidence was rated moderate due to risk of bias (one RCT was open label; fragility was present in the results).

Data on serious infections were not available from the 3 primary studies. Therefore, we used data from the observational TREAT registry.[10,11] Treatment with thiopurines was associated with a trend of more frequent serious infections (adjusted OR, 1.23; 95% CI, 0.96–1.57). Patients treated with thiopurines had 10 more serious infections per 1000 patients compared with patients who were not treated with thiopurines (95% CI, from 2 fewer to 24 more; Table 7). The overall quality of evidence was rated very low due to the risk of bias and imprecision.

To assess the thiopurine-related risk of lymphoma, we evaluated several large observational studies[10,41,42] and selected CESAME as the study providing the most conservative estimate.[41] In CESAME, thiopurine therapy was associated with a hazard ratio (HR) for lymphoma of 5.28 (95% CI, 2.0–13.9). Using the background rate for lymphoma of 0.26 per 1000 per year in patients not treated with thiopurines, thiopurine-treated patients are expected to experience 1.1 more cases of lymphoma per 1000 patients per year (95% CI, from 0.26 more to 3.3 more; Table 7). The overall quality of evidence was rated very low due to the risk of bias, indirectness, and imprecision.

MTX versus placebo. Two RCTs with significant differences in study design examined the use of MTX in patients with quiescent disease.[18,43] In one study,[43] subjects who achieved remission after induction with MTX 25 mg intramuscularly once weekly for 16 to 24 weeks were randomized to MTX (15 mg intramuscularly once weekly) versus placebo for 40 weeks, with no cotherapy allowed. In the second study, MTX was given as a weekly oral dose of 12.5 mg for 9 months and cotherapy with corticosteroids and mesalamine agents was allowed.[18] A pooled analysis showed that MTX therapy was associated with fewer relapses (RR, 0.74; 95% CI, 0.54–1.0).[44] Using a placebo relapse rate of 74%, MTX therapy would result in 168 fewer relapses compared with placebo (95% CI, from 297 fewer to 0 fewer; Supplementary Table 3). The overall quality of evidence was rated low due to indirectness and imprecision.

There are no sufficient data on the risk of infection and lymphoma in patients with CD treated with maintenance MTX. Serious infections and lymphoma were not reported in one study[43]; in the second study, the cohort was too small to estimate the rare outcomes of lymphoma and serious infection.[18] In TREAT,[11] very few immunomodulator-treated patients received MTX, and thiopurine and MTX therapies were not analyzed as separate predictors of infection. Our literature search did not retrieve any reliable evidence examining any association between MTX and lymphoma in CD.

Anti–TNF-α versus placebo. Five RCTs compared IFX, ADA, or CZP with placebo in maintaining remission.[45–49] A total of 1390 subjects were followed up for 26 to 60 weeks. In all trials, initial response was induced by anti–TNF-α therapy and remission rates were

Table 7. Should Thiopurines (AZA/6-MP) Versus Placebo Be Used in Adults With CD in Remission (CDAI <150)?

No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) With controls	Study event rates (%) With thiopurines (AZA/6-MP)	Relative effect (95% CI)	Anticipated absolute effects Risk with controls	Anticipated absolute effects Risk difference with thiopurines (AZA/6-MP) (95% CI)
Disease relapse (critical outcome; CDAI ≥150 and/or corticosteroid use or surgery = relapse)											
163 (3 studies), 12–18 mo, Khan et al[21]	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊖ Moderate[a] due to risk of bias	28/85 (32.9)	10/78 (12.8)	RR, 0.39 (0.21–0.74)	329 per 1000	201 fewer per 1000 (from 86 fewer to 260 fewer)
Serious infections[b] (important outcome; physician report)											
5394 (1 study), 5.2 y (mean follow-up), Lichtenstein et al[11]	Serious[c]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	⊕⊖⊖⊖ Very low[c] due to risk of bias and imprecision	148/3255 (4.6)	146/1849 (7.9)	OR, 1.23 (0.96–1.57)[d]	45 per 1000	10 more per 1000 (from 2 fewer to 24 more)[e]
Lymphoma[f] (physician report)											
16,677 (1 study), 35 mo (median), Beaugerie et al[41]	Serious[g]	No serious inconsistency	Serious[g]	Serious[g]	Undetected	⊕⊖⊖⊖ Very low due to indirectness, imprecision, and risk of bias[g]	6/10,810 (0.06)	15/5867 (0.26)	HR, 5.28 (2.0–13.9)[d]	Lymphoma risk, yearly 0.26 per 1000[h]	1.1 more per 1000 (from 0.26 more to 3.3 more)

[a]We rated down these withdrawal studies at the risk of bias level for the following reasons: one was open label and not blinded, and fragility was present in the results.
[b]Data on serious infections were obtained from the study by Lichtenstein et al, which evaluated risk across all immunomodulators (AZA/6-MP/MTX); however, in 95% of cases this consisted of treatment with thiopurines (AZA/6-MP). Serious infection was defined as "any infection reported as serious by the investigator and any infection that required hospitalization."
[c]The following issues were identified for rating down the quality: representativeness of patient population unclear, consecutive patients not enrolled (convenience sample), outcome adjudication not independently confirmed, incomplete outcome reporting, and imprecision.
[d]Only the unadjusted effect estimate was reported.
[e]The time frame was not reported in the original manuscript.
[f]The risk of lymphoma was based on the observational study by Beaugerie et al (CESAME).[41]
[g]This observational study was rated down for the following reasons: representativeness of patient population unclear, convenient sample used, not population based, and unadjusted for cotherapy as well as issues with imprecision and indirectness.
[h]The baseline risk was calculated as follows: 10,810 patients who were never treated with thiopurines were followed up on average for 2.1 years, which is equivalent to 23,073 patient-years of follow-up and translates to a 0.026% lymphoma rate over 1 year (6/23,073 = 0.00026).

determined at the final study visit. Effect estimates of all 3 anti–TNF-α drugs were very similar (recalculated effect estimates using fixed effects modeling) (IFX: RR, 0.72 [95% CI, 0.63–0.82]; ADA: RR, 0.67 [95% CI, 0.61–0.75]; CZP: RR, 0.73 [95% CI: 0.63–0.85]). The overall results showed that anti–TNF-α therapy was associated with fewer disease relapses (RR, 0.71; 95% CI, 0.65–0.76).[34] The use of anti–TNF-α agents is expected to result in 227 fewer relapses per 1000 patients (188 fewer to 274 fewer) compared with placebo. The overall quality of evidence was rated high (Table 8). The risk of bias was low, and heterogeneity statistics showed little or no inconsistency across all 3 drugs.

In our pooled analysis of the IFX, ADA, and CZP trials, anti-TNF therapy failed to show or exclude any effect on serious infections compared with placebo (RR, 0.97; 95% CI, 0.54–1.76; Table 8). The use of anti–TNF-α agents is expected to result in one more serious infection per 1000 patients (from 12 fewer to 20 more). The overall quality of evidence was rated moderate due to imprecision.

The RR of lymphoma was obtained from the TREAT registry.[10,11] IFX therapy was associated with an HR for lymphoma of 0.98 (95% CI, 0.34–2.82). Because the TREAT data did not allow calculation of the lymphoma rate in patients not treated with immunomodulators and IFX, we used the baseline risk of lymphoma from CESAME[41] to calculate absolute risk differences (0 more lymphomas per year per 1000; from 0.2 fewer to 0.5 more; Table 8). The overall quality of evidence was rated very low due to imprecision and risk of bias (Table 8).

MTX versus thiopurines. Only 2 RCTs[18,35] with a total of 50 patients have compared the use of MTX with thiopurines for maintenance of remission. These 2 maintenance studies were extensions of the initial induction studies. Patients who achieved clinical remission in the induction phase were subsequently followed for up to 38 to 76 weeks for the primary outcome of disease relapse. The results failed to show or exclude a beneficial effect of MTX over thiopurines (RR, 0.53; 95% CI 0.22–1.27; Supplementary Table 4). The overall quality of evidence was rated low due to risk of bias and imprecision.

Serious infections and lymphoma were not reported in the 2 trials and, as already noted, we were unable to identify reliable estimates from observational studies. In summary, when comparing MTX and thiopurines for maintenance of remission, the data on relative efficacy and toxicity are insufficient to estimate a net benefit.

Anti–TNF-α + AZA/6-MP versus anti–TNF-α alone. There is a single RCT comparing anti–TNF-α monotherapy to combination therapy with an anti–TNF-α agent and an immunomodulator in maintaining remission. In an open-label trial,[50] subjects who were in remission while treated with IFX and an appropriate dose of an immunomodulator (AZA, 6-MP, or MTX) for at least 6 months were randomized to continued combination therapy (n = 40) versus AZA withdrawal (ie, IFX monotherapy [n = 40]) for 104 weeks. The primary outcome was disease relapse necessitating a change in the dosage of IFX or discontinuation of IFX. Treatment with IFX in combination with an immunomodulator failed to show or exclude a beneficial effect over IFX monotherapy (RR, 1.09; 95% CI, 0.72–1.65; Supplementary Table 5). The overall quality of evidence was rated low due to risk of bias and imprecision.

Because there were too few adverse events in the primary study (one serious infection and no lymphomas), we used TREAT[11] and CESAME[41] to estimate the risks of infection and lymphoma, respectively. As noted in the preceding text (induction of remission, thiopurines vs placebo), thiopurine therapy in TREAT was associated with a trend toward more frequent serious infections (adjusted OR, 1.23; 95% CI, 0.96–1.57). Patients treated with thiopurines had 10 more serious infections per 1000 patients compared with patients who were not treated with thiopurines (95% CI, from 2 fewer to 24 more; very low-quality evidence; Supplementary Table 5). As also noted in the preceding text (maintenance of remission, thiopurines vs placebo), thiopurine therapy in CESAME was associated with an HR for lymphoma of 5.28 (95% CI, 2.0–13.9). Thiopurine-treated patients are expected to experience 1.1 more lymphomas per 1000 patients per year (95% CI, from 0.26 more to 3.3 more; very low-quality evidence; Supplementary Table 5).

Discussion

In this technical review, we assessed the effectiveness and safety of immunomodulators and anti–TNF-α biologic agents as inductive and maintenance therapies for inflammatory CD. Using the GRADE process, we aimed for greater transparency in rating the quality of evidence and for greater explicitness about the comparators used and outcomes assessed. To weigh the trade-offs involved with different interventions, the GRADE process presents the absolute risk differences for both beneficial outcomes and harms. In the following text, we discuss our findings on the effectiveness and safety of inductive and maintenance therapies, compare and explain the differences between our conclusions and those in other published guidelines, and suggest areas of future research.

Induction of Remission

The data on thiopurines and MTX showed nonsignificant trends toward fewer failures compared with placebo in the induction of remission. For the thiopurines, the overall quality of evidence was moderate as a result of imprecision, whereas for MTX the quality of evidence was low as a result of imprecision and indirectness. Our conclusions regarding the immunomodulators are at variance with those of other groups evaluating the evidence. The American College of Gastroenterology (ACG)[51] (AZA and 6-MP, grade A; MTX, grade B), British Society of Gastroenterology (BSG)[52] (EL1b, RG A), and European Crohn's and Colitis Organisation (ECCO)[53] (EL1b, evidence from RCTs with narrow CI; RG B) all have endorsed immunomodulators as inductive therapies in corticosteroid-treated patients. In our assessment of the evidence, immunomodulators were not more effective than placebo in inducing remission.

Table 8. Should Anti-TNF Versus Placebo Be Used in Adults With CD in Remission (CDAI <150)?

No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With controls	With anti-TNF		Risk with controls	Risk difference with anti-TNF (95% CI)
Disease relapse (critical outcome; assessed with CDAI ≥150 and/or corticosteroid use or surgery)											
1390 (5 studies), 26–60 wk, Ford et al[34]	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊕ High	428/546 (78.4)	472/844 (55.9)	RR, 0.71 (0.65–0.76)	784 per 1000	227 fewer per 1000 (from 188 fewer to 274 fewer)
Serious infections[a] (important outcome)											
1907 (5 studies), 26–60 wk, Ford et al[34]	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	⊕⊕⊕⊖ Moderate due to imprecision	19/715 (2.7)	34/1192 (2.9)	RR, 0.97 (0.54–1.76)	27 per 1000	1 fewer per 1000 (from 12 fewer to 20 more)
Lymphoma[b] (important outcome; physician report)											
6273 (1 study), 5.2 y (mean follow-up), Lichtenstein et al (manuscript under review)	Serious[c]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	⊕⊖⊖⊖ Very low due to risk of bias, imprecision	6/4010 (0.15)	8/3764 (0.21)	RR, 0.98 (0.34–2.82)[d]	Lymphoma risk, yearly 0.26 per 1000[e]	0 more per 1000 (from 0.2 fewer to 0.5 more)

[a]This is an update of the meta-analysis by Ford et al to include serious infection events (own analysis).
[b]Data on lymphomas was obtained from the study by Lichtenstein et al (TREAT), which evaluated risk across all immunomodulators (AZA, 6-MP, and MTX); however, in 95% of cases, this consisted of thiopurines.
[c]We rated down for the following issues: representativeness of patient population unclear, consecutive patients not enrolled (convenient sample), outcome adjudication not independently confirmed, incomplete outcome reporting, and imprecision.
[d]Only the unadjusted effect estimate was reported.
[e]Because the study by Lichtenstein et al did not report a rate for an untreated population, the baseline risk of lymphoma was obtained from the study by Beaugerie et al (CESAME).[41] The baseline risk was calculated as follows: 10,810 patients who were never treated with thiopurines were followed up on average for 2.1 years, which is equivalent to 23,073 patient-years of follow-up and translates to a 0.026% lymphoma rate over 1 year (6/23,073 = 0.00026).

Compared with placebo, anti–TNF-α therapy had a lower failure rate in the induction of remission (RR, 0.87; 95% CI, 0.80–0.94), but this 13% difference was smaller than the minimum important difference of 20%. These results stem from the higher failure rate of CZP (RR, 0.95; 95% CI, 0.90–1.01) and the large weight of the CZP trials (43.3%) in the meta-analysis performed by Ford et al.[34] In contrast, there was high-quality evidence that IFX was more effective than placebo (RR, 0.68; 95% CI, 0.52–0.90). The evidence for ADA was of moderate quality due to its modest magnitude of effect, which did not cross the minimal threshold of 20% (RR, 0.85; 95% CI, 0.79–0.91). The observed differences in effectiveness among the 3 agents may reflect differences in their structure, mechanisms of action, and dose equivalence as well as differences in the study populations (disease duration and prior anti–TNF-α therapy) and the timing of study end points.[54–56]

The most common therapeutic dilemma in patients with moderately severe inflammatory CD involves choosing a thiopurine, an anti–TNF-α monoclonal antibody, or both. SONIC showed that combination therapy was the most effective approach, with a failure rate of remission close to 40% lower with a combination of IFX and AZA compared with AZA alone.[24] In turn, subjects on IFX monotherapy had an approximately 20% lower failure rate of remission than those on AZA monotherapy. In agreement with the World Congress of Gastroenterology,[57] we concluded that combination therapy with AZA and IFX is more effective than IFX monotherapy in inducing remission. ECCO[53] recommended anti–TNF-α therapy, with or without immunomodulators, but did not state a preference for or against immunomodulators. ACG[51] and BSG[52] did not address combination therapy with AZA and IFX vis-à-vis IFX monotherapy.

Our different conclusions are due to our use of the most updated meta-analyses on immunomodulators[21] and anti–TNF-α biologic agents[34] as well as by the incorporation of SONIC.[24] For example, ECCO[53] relied on a Cochrane review,[58] which found that induction of thiopurine therapy was associated with a higher odds of clinical improvement or remission (Peto OR, 2.43; 95% CI, 1.62–3.64). In contrast, we relied on a recent meta-analysis[21] that used clinical remission as the only end point and included only inductive trials of up to 17 weeks' duration.

We recognize that there are limitations to the primary studies used in the meta-analyses. For example, there are only 2 studies of MTX as inductive therapy, one of which administered MTX at a low oral dose. With the development of anti–TNF-α biologic agents, we doubt that any future studies will address immunomodulators as adjuncts to corticosteroids in the induction of remission.

Maintenance of Remission

A meta-analysis of trials[38–40] evaluating the maintenance of remission after withdrawal of AZA showed a strong protective effect of continued AZA therapy (a 61% relative risk reduction of relapse compared with AZA withdrawal).[21] The effectiveness of thiopurines versus placebo for the maintenance of remission has also been evaluated by 2 trials that used a different design, assessing relapse after the induction of remission in active disease.[16,19] In the trial by Candy et al,[16] subjects with active disease were treated with a prednisolone taper and AZA 2.5 mg/kg/day vs placebo for 12 weeks. Subjects in remission at week 12 continued into the maintenance phase of the study over a further 12 months. More patients maintained remission in the AZA group (RR of failure to prevent relapse compared with placebo, 0.47; 95% CI, 0.28–0.77).[16] Discrepant results were found in part II of the National Cooperative Crohn's Disease Study.[19] Subjects were randomized to treatment with AZA 1 mg/kg/day vs placebo for 2 years. There were no differences in the remission rates (RR of failure of remission compared with placebo, 0.88; 95% CI, 0.55–1.42).[16] However, the National Cooperative Crohn's Disease Study had significant methodological issues, including underdosing of AZA (1 mg/kg/day) and a heterogeneous population (32% of subjects in recent corticosteroid-induced remission and 13.5% in postsurgical remission). In summary, we found that the thiopurines (RR, 0.39; 95% CI, 0.21–0.74; moderate-quality evidence) and MTX (RR, 0.74; 95% CI, 0.54–1.0; low-quality evidence) are effective maintenance therapies in patients with CD after corticosteroid-induced remission. ACG,[51] BSG,[52] and ECCO[53] reached similar conclusions regarding the evidence on immunomodulators as maintenance therapy.

Based on a recent systematic review,[34] we concluded that IFX, ADA, and CZP were effective in maintaining remission induced by the anti–TNF-α agent. The effect estimates for the 3 agents separately were very similar. Overall, anti–TNF-α therapy was associated with a 29% reduction in the risk of relapse compared with placebo. Evaluating the evidence, the World Congress of Gastroenterology, ECCO, ACG, and BSG similarly found that the 3 anti–TNF-α agents are effective maintenance therapies, except that the BSG endorsed only IFX and ADA (CZP is not approved for CD in the United Kingdom).[51–53,57]

The comparative effectiveness of anti–TNF-α therapy, thiopurine therapy, and/or combination therapy in maintaining remission is an important issue. Only a single study has addressed the question. In an open-label trial, Van Assche et al[50] randomized patients who were in remission after starting combination therapy (IFX plus AZA, 6-MP, or MTX) to continued combination therapy versus withdrawal of the immunomodulator (ie, IFX monotherapy) for 104 weeks. The results failed to show or exclude any benefits to continued combination therapy over IFX monotherapy in preventing disease relapse (RR, 1.09; 95% CI, 0.72–1.65; low-quality evidence; Supplementary Table 5). Critical limitations of the trial included the open-label design and lack of power. Subjects in the combination arm had lower C-reactive protein and higher trough IFX concentrations, suggesting that differences in the clinical end point might have emerged with longer follow-up. There are no maintenance studies comparing anti–TNF-α or combination therapy with immunomodulator therapy after remission induced by anti–TNF-α therapy.

Infection

The results of our pooled analysis of the induction and maintenance trials failed to show or exclude any

differences in the rates of serious infections of anti–TNF-α compared with placebo. In SONIC,[24] the rates of serious infections at 54 weeks were 5.6%, 4.9%, and 3.9% for the AZA, IFX, and combination arms, respectively (not significant for all comparisons; moderate-quality evidence due to imprecision). Thiopurine therapy showed a trend toward an increase in the risk of serious infection in the TREAT cohort (HR, 1.23; 95% CI, 0.96–1.57; very low-quality evidence). The TREAT data were rated down for quality for several reasons: the representativeness of the patient population was unclear, the population was a convenient sample (consecutive patients were not enrolled), the outcome adjudication was not confirmed independently, there was incomplete outcome reporting, and there was imprecision. We did not find any studies adequately addressing the risk of serious infection associated with MTX therapy. We did not include data on serious infections in patients treated with anti–TNF-α agents for other indications because of possible disease-treatment interactions. However, our estimates for serious infections in CD are similar to estimates in other conditions.[59,60]

We conclude that the thiopurines and the anti–TNF-α agents have low rates of serious infections overall. Nonetheless, the anti–TNF-α agents are associated with opportunistic infections with intracellular pathogens, including *Mycobacterium tuberculosis*, histoplasmosis, coccidiomycosis, listeriosis, and others.[11] The risk of *M tuberculosis* is mitigated by screening for latent infection. Caution dictates that patients with active infections should not be started on anti–TNF-α therapy. Thiopurines and MTX have been associated with an increased risk of viral infections, including herpes zoster. Importantly, corticosteroids are associated with a greater risk of serious infections than immunomodulators and anti–TNF-α agents.[11] Finally, inadequately treated CD is associated, in its own right, with serious infections, including intra-abdominal and perianal abscesses.[11]

Lymphoma

Thiopurine therapy appears to increase the risk of lymphoma, but the magnitude of this risk is debated.[61] Several observational studies have compared rates of lymphoma in thiopurine-treated CD versus the general population using standardized incidence ratios (SIR). A meta-analysis from 2005 found an increased risk of lymphoproliferative disorders in patients with IBD receiving ongoing thiopurine therapy, with a SIR of 4.18 (95% CI, 2.07–7.51).[62] The single-center and population-based studies included in that meta-analysis were heterogeneous and generally small.[61] More recently, analyses of 3 large cohorts have produced different risk estimates. CESAME[41] and TREAT[10] were prospective studies, similar in sample size and number of events, which studied French and US populations, respectively. The Kaiser Permanente study was a retrospective analysis of administrative data from an integrated managed care organization in California.[42] The CESAME estimate was the highest and had wide CIs, with an HR of 5.28 (95% CI, 2.01–13.9) and SIR of 6.86 (95% CI, 3.84–11.31). An increase in risk of lymphoma was reported by TREAT (unadjusted RR, 1.17; 95% CI, 0.37–3.71).[10] The Kaiser study reported a SIR of 1.4 (95% CI, 1.2–2.7).[42] Because the incidence of lymphoma among patients with CD not receiving immunomodulators was not increased compared with the general population,[41,42,61,63] the SIR may approximate the RR. We selected the CESAME data in the evidence profile to provide the most conservative risk of lymphoma and not because CESAME represented the highest-quality evidence available. Indeed, all the data sources we identified had limitations that were serious enough to mandate rating down to very low-quality evidence due to a number of serious confounders. CESAME was the only study that provided effect estimates in the CD population and attempted to control for additional factors such as age and disease duration.

The risk of lymphoma on combination therapy is higher than the risk on thiopurine monotherapy, as shown by both the CESAME study[41] (combination therapy: SIR, 10.2 [95% CI, 1.24–36.9]; thiopurine monotherapy: SIR, 6.86 [95% CI, 3.84–11.31]) and the Kaiser study[42] (combination therapy: SIR, 6.6 [95% CI, 4.4–8.8]; thiopurine monotherapy: SIR, 1.4 [95% CI, 1.2–1.7]). Due to short cumulative follow-up, there are little data on the risk of lymphoma on anti–TNF-α monotherapy. Nonetheless, it appears that lymphoma associated with anti–TNF-α therapy is rare. In the CESAME and Kaiser cohorts, no cases of lymphoma occurred during 2199 and 303 patient-years of IFX monotherapy, respectively.[41,42] In the TREAT population, IFX therapy was not associated with an increased risk of lymphoma (unadjusted RR, 0.98; 95% CI, 0.34–2.82). Data from the ADA trials suggest an increased risk but are confounded by disease state and concomitant immunomodulatory therapy.[64] We did not include data on lymphoma in patients treated with anti–TNF-α agents for other indications because of possible disease-treatment interactions. Nonetheless, similar to our findings, meta-analyses in rheumatoid arthritis found no excess risk of hematologic malignancies or lymphoma in patients treated with anti–TNF-α agents.[65,66]

We did not identify any reliable evidence assessing the risk of lymphoma in MTX-treated patients with IBD. Given the limited use of MTX in IBD, we do not anticipate that studies of any association between MTX therapy and lymphoma will be forthcoming. No increase in risk of lymphoproliferative disorders was reported in a study of patients with rheumatoid arthritis treated with MTX.[67] Overall, the risk of lymphoma associated with MTX therapy seems to be low.[61]

Limitations of Current Evidence and Future Directions

This review has identified a number of areas in need of more data. (1) There are insufficient data on the safety of MTX at the doses used in the CD population. (2) There are few comparative data on thiopurines and MTX. (3) There are no direct comparisons of the 3 anti–TNF-α agents. (4) More data are needed on the role of

immunomodulators in maintaining remission induced by anti–TNF-α therapy. (5) There are only limited data on the risk of lymphoma with anti–TNF-α monotherapy. (6) Uncertainty remains about the magnitude of the risk of lymphoma on thiopurine therapy and combination therapy with a thiopurine and anti–TNF-α. In particular, we need an estimate of the risk of hepatosplenic T-cell lymphoma, a rare, lethal lymphoma that has typically been seen in young male patients treated with thiopurines alone or in combination with anti–TNF-α agents.[61] No cases occurred in the CESAME cohort, suggesting that this type of lymphoma is very rare.[41] Because the anti–TNF-α agents differ with respect to structure, mechanisms of action, and dose equivalence, we should exercise caution in extrapolating findings from one agent to another. For example, we do not know whether the benefits of a thiopurine for induction therapy with IFX also extend to induction therapy with ADA and CZP.

SONIC showed the superiority of IFX induction therapy (with or without AZA) over AZA induction therapy in achieving the primary end point of corticosteroid-free clinical remission at 26 weeks, mucosal healing at 26 weeks, and multiple secondary end points during the extension phase of the trial to 50 weeks. The major finding of SONIC concerns the superiority of combination therapy over IFX monotherapy. The advantage of combination therapy was at least partly mediated by the lower frequency of antibodies to infliximab and the higher trough IFX concentrations. Whether the same therapeutic benefits could be achieved with higher dosing of infliximab monotherapy (without thiopurines) remains to be determined. The benefits of combination therapy should be weighed against the potential toxicity. A modeling study[68] found that although combination therapy led to more deaths from lymphoma, these events were very rare, and there were more deaths overall in the IFX monotherapy group from severe CD, infection, and surgery. Combination therapy yielded more quality-adjusted life years, because more patients were in remission and fewer died. These conclusions proved robust on the sensitivity analysis. Combination therapy remained superior unless it was complicated by serious infections in 20% or more of patients or by lymphoma in 3.9% or more of patients. These thresholds were 5-fold and 65-fold higher, respectively, than the base-case estimate.[68] Although modeling studies can inform the choice between combination therapy and anti–TNF-α monotherapy, individual patients will differ on the value they place on avoiding lymphoma and infection versus avoiding active disease.

Despite the increasing use of the anti–TNF-α agents, the thiopurines remain an important part of the therapeutic arsenal in CD. As noted, these agents are effective maintenance therapy in patients with corticosteroid-induced remission and augment the inductive benefits of IFX. Although the thiopurines do not augment the benefits of corticosteroids in short-term (12- to 17-week-long) inductive studies, they have delayed effects that account for their maintenance, corticosteroid-sparing properties. In SONIC, depending on the analysis performed, 24% to 28% of AZA-treated patients were expected to be in corticosteroid-free clinical remission at 1 year.[24] Thus, a significant proportion of patients with moderately severe CD do not need anti-TNF therapy. In addition, loss of effectiveness of thiopurine appears to occur less frequently than loss of effectiveness of the anti–TNF-α drugs.[38,69,70]

The fundamental dilemma in patients with moderately severe inflammatory CD remains unanswered: whether to initiate treatment with an immunomodulator plus induction with corticosteroids until the immunomodulator maintenance benefits appear, reserving anti–TNF-α therapy (adding the anti–TNF-α agent or switching to anti–TNF-α monotherapy) for cases of failure of the immunomodulator, or whether to use anti–TNF-α therapy for induction and maintenance. Such a study would need to compare the long-term outcomes of these alternate approaches in terms of effectiveness, safety, need for surgery and corticosteroids, and costs.

Several other questions beg exploration. Do higher doses of anti–TNF-α monotherapy provide better outcomes than combination therapy? How do thiopurine monotherapy, anti–TNF-α monotherapy, and combination therapy compare in the maintenance of remission induced by anti–TNF-α therapy in immunomodulator-naïve patients? How do anti–TNF-α monotherapy and combination therapy compare in the maintenance of remission induced by anti–TNF-α therapy in immunomodulator-experienced patients?

An important gap in our knowledge concerns patients with mild disease. All inductive studies in CD have studied patients with moderately active disease as defined by a CDAI of 220 to 450. Calculation of the CDAI is cumbersome in routine practice. Nonetheless, moderately active CD is operationally defined as disease requiring initiation of oral corticosteroid therapy.[51] Patients with mild CD have not been studied in clinical trials. In this population, how would upfront immunomodulatory and/or anti–TNF-α therapy compare with a step-up approach consisting of corticosteroids followed by immunomodulators and/or anti–TNF-α agents?

Future clinical trials and observational studies should be designed not solely for the explicit aim of drug approval or monitoring by the regulatory authorities. The studies should also inform us about the role of an agent in the existing therapeutic landscape. For example, study populations have varied with regard to disease duration, objectively demonstrated disease activity, and prior therapies. Future studies should be large enough to perform prespecified analyses in well-characterized patient subsets. These analyses would thus also permit indirect comparisons with other studies. Academia, the pharmaceutical industry, government agencies, and patient advocacy groups will need to collaborate in setting research priorities and optimizing study designs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of

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Themistocles Dassopoulos
Division of Gastroenterology
Washington University School of Medicine
Saint Louis, Missouri

Shahnaz Sultan
Division of Gastroenterology, Hepatology and Nutrition
Malcom Randall VA Medical Center
University of Florida College of Medicine
Gainesville, Florida

Yngve T. Falck–Ytter
Division of Gastroenterology
Case and VA Medical Center
Case Western Reserve University
Cleveland, Ohio

John M. Inadomi
Division of Gastroenterology
University of Washington School of Medicine
Seattle, Washington

Stephen B. Hanauer
Section of Gastroenterology and Nutrition
University of Chicago
Chicago, Illinois

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Reprint requests

Address requests for reprints to: Chair, Clinical Practice and Quality Management Committee, AGA National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: ischarf@gastro.org; telephone: (301) 222-4003.

Conflicts of interest

The authors disclose the following: Dr Inadomi has served as a consultant for Takeda, AstraZeneca, and Roche and as associate editor of *American Journal of Gastroenterology*. Dr Hanauer has served as a consultant for Abbott Laboratories, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Elan, Exagen Diagnostics, Ferring Pharmaceuticals, Genentech, Gilead, Glycominds, GlaxoSmithKline, Hospira, Janssen, Lilly, Meda, Millennium Pharmaceuticals, Novartis, Novo Nordisk, Pfizer, Prometheus, Salix Pharmaceuticals, Sanofi-Aventis, Shire, Takeda, UCB, and Warner Chilcott. The remaining authors disclose no conflicts.

Supplementary Methods

Search Strategy

Main searches. Databases searched were OVID MEDLINE, OVID In-Process and Other Non-Indexed Citations, OVID EMBASE, Centre for Reviews and Dissemination, and Wiley Cochrane. Note that only the database searches for the first 3 databases appear in the following text; the same combinations of text words and subject headings were used to search the other databases.

Database: Ovid MEDLINE <1948 to November Week 3 2011>, Ovid MEDLINE In-Process & Other Non-Indexed Citations <December 02, 2011>, EMBASE <1980 to 2011 Week 48>

1 exp Crohn Disease/ (70752)
2 (granulomatous adj (enteritis or colitis)).ti,ab. (819)
3 (enteritis adj regional).ti,ab. (10)
4 (crohn* or Ileitis).ti,ab. (65395)
5 or/1-4 (85865)
6 exp Methotrexate/ (134220)
7 (mexate or methotrexate or amethopterin or mtx or Rheumatrex or Trexall).af. (148741)
8 exp 6-Mercaptopurine/ use mesz (16900)
9 exp mercaptopurine/ use emez (16701)
10 (6-thiopurine or leupurin or 6-mercaptopurine or 6 thiohypoxanthine or puri-?ethol or puri?ethol or mercaptopurina or mercaptopurine or 6mp).af. (24455)
11 exp azathioprine/ use emez (60817)
12 (AZASAN or Azathioprine or murel or immuran or imuran or azothioprine or aza).af. (105270)
13 exp Antibodies, Monoclonal/ use mesz (163192)
14 exp infliximab/ use emez (20285)
15 exp adalimumab/ use emez (8756)
16 exp certolizumab pegol/ use emez (1592)
17 (adalimumab or infliximab or certolizumab or anti-tnf* or Anti-tumor Necrosis Factor or Antitumor Necrosis Factor or Remicade or Humira or Cimzia).af. (40917)
18 or/6-17 (427585)
19 5 and 18 (14949)
20 limit 19 to English language (12851)
21 limit 20 to human (11445)
22 limit 21 to yr="1995 -Current" (10757)
23 limit 22 to randomized controlled trial (528)
24 exp Random Allocation/ or exp Double-Blind Method/ or exp Control Groups/ or exp Placebos/ use mesz (379825)
25 Randomized Controlled Trial/ or exp Randomization/ or exp RANDOM SAMPLE/ or Double Blind Procedure/ or exp Triple Blind Procedure/ or exp Control Group/ or exp PLACEBO/ use emez (900711)
26 (random* or RCT).ti,ab. (1256687)
27 (placebo* or sham*).ti,ab. (415354)
28 (control* adj2 clinical trial*).ti,ab. (35208)
29 or/23-28 (1811699)
30 22 and 29 (2028)
31 remove duplicates from 30 (1681)

Harms subsearch. Databases searched were OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane, and Centre for Reviews and Dissemination.

No non-RCTs/systematic reviews/meta-analyses were identified in Cochrane and Centre for Reviews and Dissemination.

Database: Ovid MEDLINE <1946 to March Week 2 2012>, Ovid MEDLINE In-Process & Other Non-Indexed Citations <March 23, 2012>, EMBASE <1980 to 2012 Week 12>

1 exp Crohn Disease/ (72894)
2 (granulomatous adj (enteritis or colitis)).ti,ab. (834)
3 (enteritis adj regional).ti,ab. (10)
4 (crohn* or Ileitis).ti,ab. (67727)
5 or/1-4 (88579)
6 exp Methotrexate/ (136959)
7 (mexate or methotrexate or amethopterin or mtx or Rheumatrex or Trexall).af. (152055)
8 exp 6-Mercaptopurine/ use mesz (16760)
9 exp mercaptopurine/ use emez (17161)
10 (6-thiopurine or leupurin or 6-mercaptopurine or 6 thiohypoxanthine or puri-?ethol or puri?ethol or mercaptopurina or mercaptopurine or 6mp).af. (24910)
11 exp azathioprine/ use emez (62115)
12 (AZASAN or Azathioprine or murel or immuran or imuran or azothioprine or aza).af. (107686)
13 exp Antibodies, Monoclonal/ use mesz (161420)
14 exp infliximab/ use emez (21594)
15 exp adalimumab/ use emez (9430)
16 exp certolizumab pegol/ use emez (1697)
17 (adalimumab or infliximab or certolizumab or anti-tnf* or Anti-tumor Necrosis Factor or Antitumor Necrosis Factor or Remicade or Humira or Cimzia).af. (43116)
18 or/6-17 (432517)
19 5 and 18 (15689)
20 exp Lymphoma/ (317027)
21 (Lympho* or reticulolymphosarcoma* or germinoblast* or adenolymphoma* or lymph node tumo?r*).ti,ab. (1044306)
22 20 or 21 (1145728)
23 19 and 22 (1808)
24 limit 23 to English language (1669)
25 limit 24 to yr="2010 -Current" (486)
26 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ use mesz (64657)
27 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ use emez (556189)
28 (health technology adj2 assess$).ti,ab. (3241)
29 exp Random Allocation/ or exp Double-Blind Method/ or exp Control Groups/ or exp Placebos/ use mesz (389869)
30 Randomized Controlled Trial/ or exp Randomization/ or exp RANDOM SAMPLE/ or Double Blind

Procedure/ or exp Triple Blind Procedure/ or exp Control Group/ or exp PLACEBO/ use emez (934580)
31 (random* or RCT).ti,ab. (1298923)
32 (placebo* or sham*).ti,ab. (426201)
33 (control* adj2 clinical trial*).ti,ab. (36297)
34 meta analysis/ use emez (61737)
35 (meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (264960)
36 or/26-35 (2239263)
37 25 (486)
38 limit 37 to (controlled clinical trial or meta analysis or randomized controlled trial) (17)
39 25 not (36 or 38) (354)
40 remove duplicates from 39 (305)

Glossary of Terms

Baseline risk is a synonym of "control event rate" or "control group risk." It is the observed risk of the event in the control group.

Estimate of effect is the observed relationship between an intervention and an outcome expressed as, for example, a number needed to treat, odds ratio, risk difference, risk ratio, relative risk reduction, standardized mean difference, or weighted mean difference.

Evidence profile contains detailed information about the quality of evidence and the summary of findings for each of the included outcomes. A GRADE evidence profile allows presentation of key information about all relevant outcomes for a given health care question. It presents information about the body of evidence (eg, number of studies), the judgments about the underlying quality of evidence, key statistical results, and a grade for the quality of evidence for each outcome.

Fragility refers to the effect a few events may have on a seemingly robust confidence interval. Changing a small number of events can lead to loss of statistical significance.

Inconsistency refers to heterogeneity or widely differing estimates of the treatment effect. When heterogeneity exists but no plausible explanation can be identified, one may consider downgrading the quality of the evidence.

Indirectness refers to differences between the question being addressed and the available evidence regarding the population, intervention, comparator, or outcome. The lack of direct (head-to-head) comparisons of 2 interventions is an additional source of indirectness.

Imprecision refers to wide confidence intervals around the estimate of effect often attributable to few events or relatively few patients.

Limitations of study design include lack of allocation concealment, lack of blinding (particularly if outcomes are subjective and their assessment is highly susceptible to bias), large loss to follow-up, and failure to adhere to an analysis according to intention-to-treat principle.

PICO: Every health care management question has 4 components: **patients** (population), **interventions** (therapeutic, diagnostic) under investigation (the experimental intervention or in observational studies this may be exposure), **comparison** (alternative intervention; intervention in the control group), and **outcomes** of interest.

Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies (publication bias). Investigators may fail to report studies they have undertaken (typically those that show no effect) or journals may not accept studies that show no effect for publication.

Quality of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation. In the GRADE approach to quality of evidence, randomized trials without important limitations provide high-quality evidence and observational studies without special strengths or important limitations provide low-quality evidence. Limitations or special strengths (ie, criteria for rating down or rating up) can, however, modify the quality of the evidence of both randomized trials and observational studies.

Rating down the quality of the evidence for an outcome: criteria/explanations for rating down include (1) limitations in study design, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias.

Rating up the quality of the evidence for an outcome: criteria/explanations for rating down include (1) large or very large effect, (2) all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect, and (3) presence of a dose-response relation. Only studies with no threats to validity (not downgraded for any reason) may be upgraded.

Relative risk (RR) is a synonym of risk ratio. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Relative risk reduction (RRR) is the proportional reduction in risk in one treatment group compared with another. It is 1 minus the risk ratio. If the risk ratio is 0.25, then the relative risk reduction is $1 - 0.25 = 0.75$ (75%).

Supplementary Table 1. Should MTX Versus Placebo Be Used in Adults With Active (Moderate to Severe) CD (CDAI 220–450)?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With control	With MTX	Relative effect (95% CI)	Risk with controls	Risk difference with MTX (95% CI)
Failure of remission (critical outcome; remission assessed with CDAI <150 or Harvey–Bradshaw Index < 4)											
193 (2 studies), 16 wk, Khan et al[21]	No serious risk of bias	No serious inconsistency	Serious[a]	Serious[b]	Undetected	⊕⊕⊖⊖ Low[a,b] due to indirectness, imprecision	58/73 (79.5)	76/120 (63.3)	RR, 0.82 (0.65–1.03)	795 per 1000	143 fewer per 1000 (from 278 fewer to 24 more)
Serious infections[c] (important outcome, not reported)											

[a]Doses and routes of administration of MTX were different (Feagan et al,[43] 25 mg/wk intramuscularly; Oren et al[18], 12.5 mg/wk orally) and MTX may have been underdosed in one study. Additionally, there were differences in disease severity among the populations.
[b]The CI was wide and included both beneficial and harmful effects.
[c]Data on serious infections were not reported in the primary study, and data from the study by Lichtenstein et al[11] could not be used because the investigators evaluated risk across all immunomodulators (AZA/6-MP/MTX) and only a small percentage had been exposed to MTX.

Supplementary Table 2. Should MTX Versus Thiopurines (AZA/6-MP) Be Used in Adults With Active (Moderate to Severe) CD (CDAI 220–450)?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With thiopurines (AZA/6-MP)	With MTX	Relative effect (95% CI)	Risk with thiopurines (AZA/6-MP)	Risk difference with MTX (95% CI)
Failure of remission (critical outcome; remission assessed with CDAI <150 and corticosteroid-free or Harvey–Bradshaw Index < 4)											
143 (3 studies), Alfadhli et al[37]	No serious risk of bias	No serious inconsistency	Serious[a]	Serious[b]	Undetected	⊕⊕⊖⊖ Low[a,b] due to indirectness, imprecision	30/75 (40)	31/68 (45.6)	RR, 1.17 (0.82–1.67)	400 per 1000	68 more per 1000 (from 72 fewer to 268 more); follow up is 3–6 months
Serious infections (not reported)											

[a]Doses and route of administration varied between studies and do not reflect current practice standards.
[b]The CI was wide and included both beneficial and harmful effects.

Supplementary Table 3. Should MTX Versus Placebo Be Used in Adults With CD in Remission (CDAI <150)?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With controls	With MTX	Relative effect (95% CI)	Risk with controls	Risk difference with MTX (95% CI)
Disease relapse (critical outcome; CDAI ≥150 and/or corticosteroid use or surgery OR Harvey–Bradshaw Index >4)											
128 (2 studies), 38–40 wk, Patel et al[44]	No serious risk of bias	No serious inconsistency	Serious[a]	Serious[b]	Undetected	⊕⊕⊖⊖ Low[a,b] due to indirectness, imprecision	40/62 (64.5)	31/66 (47)	RR, 0.74[c] (0.54 to 1.0)	645 per 1000	168 fewer per 1000 (from 297 fewer to 0 fewer)
Serious infections[d] (important outcome; not reported)											
Lymphoma[e] (important outcome; not reported)											

[a]One of the 2 studies (Oren et al[18]) used a low dose of MTX of 12.5 mg/wk orally as compared with 25 mg/wk intramuscularly (Feagan et al[43]). The use of oral MTX does not reflect current practice because there are concerns about absorption and bioavailability in patients with active disease.
[b]The CI was wide and included both beneficial and harmful effects.
[c]Data are from Patel et al[44] but were recalculated to reflect the outcome of disease relapse.
[d]Serious risk of infection was not reported in the primary study and the study by Lichtenstein et al[11] could not be used because the majority of patients were being treated with thiopurines and not MTX.
[e]The risk of lymphoma was not reported.

Supplementary Table 4. Should MTX Versus Thiopurines (AZA/6-MP) Be Used in Adults With CD in Remission (CDAI <150)?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
No. of participants (no. of studies), follow-up, author	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With thiopurines (AZA/6-MP)	With MTX	Relative effect (95% CI)	Risk with thiopurines (AZA/6-MP)	Risk difference with MTX (95% CI)
Disease relapse (critical outcome; assessed with CDAI ≥150 and/or corticosteroid use or surgery (relapse) or increase of ≥3 points in Harvey–Bradshaw Index and/or reintroduction of corticosteroids)											
50 (2 studies), 38–76 wk, Patel et al[44]	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	⊕⊖⊖⊖ Very low due to risk of bias and imprecision	12/28 (42.9)	5/22 (22.7)	RR, 0.53 (0.22–1.27)	429 per 1000	201 fewer per 1000 (from 334 fewer to 116 more)
Serious infections (important outcome; not reported)											
Lymphoma (important outcome; not reported)											

[a]No randomization at the start of the maintenance phase of the studies. Patients who achieved clinical remission in the induction of remission portion of the study were included in the maintenance of remission study.
[b]The CI was wide and included both beneficial and harmful effects.

Supplementary Table 5. Should AZA/6-MP + Anti-TNF Versus Anti-TNF Be Used in Adults With CD in Remission (CDAI <150)?

Quality assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
No. of participants (no. of studies), follow-up, authors	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With anti-TNF	With anti-TNF + AZA/6-MP	Relative effect (95% CI)	Risk with anti-TNF	Risk difference with anti-TNF + AZA/6-MP (95% CI)
Disease relapse (critical outcome; assessed with subjective global assessment)											
80 (1 study), 104 wk, Van Assche et al[50]	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	⊕⊕⊖⊖ Low[a,b] due to risk of bias, imprecision	22/40 (55)	24/40 (60)	RR, 1.09 (0.72–1.65)	550 per 1000	50 more per 1000 (from 154 fewer to 357 more)
Serious infections (important outcome; physician report)											
5394 (1 study), 5.2 y (mean), Lichtenstein et al[11]	Serious[c]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	⊕⊖⊖⊖ Very low[c] due to risk of bias, imprecision	148/3255 (4.6)	146/1849 (7.9)	OR, 1.23 (0.96–1.57)[d]	45 per 1000	10 more per 1000 (from 2 fewer to 24 more)[e]
Lymphoma[f] (important outcome; physician report)											
16,677 (1 study), 35 mo (median), Beaugerie et al[41]	Serious[g]	No serious inconsistency	Serious[g]	Serious[g]	Undetected	⊕⊖⊖⊖ Very low due to indirectness, imprecision, and risk of bias[g]	6/10,810 (0.06)	15/5867 (0.26)	HR, 5.28 (2.0–13.9)[d]	Lymphoma risk, yearly 0.26 per 1000[e]	1.1 more per 1000 (from 0.26 more to 3.3 more)

NOTE. The baseline risk was calculated as follows: 10,810 patients who were never treated with thiopurines were followed up on average for 2.1 years, which is equivalent to 23,073 patient-years of follow-up and translates to a 0.026% lymphoma rate over 1 year (6/23,073 = 0.00026).

[a]This was an open-label study; patients and physicians (who were also the outcome assessors) were unblinded. There was lack of a clear definition of disease relapse necessitating a dose change or discontinuation.

[b]The CI was wide and included both beneficial and harmful effects.

[c]The following issues were identified for rating down the quality: representativeness of patient population unclear, consecutive patients not enrolled (convenient sample), outcome adjudication not independently confirmed, incomplete outcome reporting, and imprecision.

[d]Only the unadjusted effect estimate was reported.

[e]The time frame was not reported in the original report.

[f]The baseline risk of lymphoma was based on the observational study by Beaugerie et al (CESAME).[41]

[g]This observational study was rated down for the following reasons: representativeness of patient population unclear, convenience sample used, not population based, and unadjusted for cotherapy as well as issues with imprecision and indirectness.