Comparative Effectiveness Review
Number 131

Effective Health Care Program

Pharmacologic Therapies for the Management of Crohn's Disease: Comparative Effectiveness

Executive Summary

Description of Crohn's Disease

Crohn's disease is a type of inflammatory bowel disease. Other types of inflammatory bowel disease include ulcerative colitis and indeterminate colitis. The medical community characterizes Crohn's disease as chronic full-thickness inflammation that can occur anywhere in the gastrointestinal tract but that most often affects the small bowel and colon. Typical symptoms of Crohn's disease include abdominal pain, chronic diarrhea, and gastrointestinal bleeding. Crohn's disease affects between 400,000 and 600,000 North Americans.[1] Ten percent of Crohn's disease patients are children aged 17 years or younger.[2]

The activity of Crohn's disease fluctuates over time, frequently leading to complications that require surgical intervention. One study estimated that during the first 7 years after diagnosis, 20 percent of Crohn's disease patients will have active disease at least once each year, 67 percent will fluctuate between years of active disease and years in remission, and 13 percent will have no relapses after the initial disease episode.[3]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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The clinical management of Crohn's disease is complicated. Clinical practice guidelines for Crohn's disease recommend that clinicians take into account the disease location, severity, complications, and extraintestinal manifestations when choosing a treatment strategy. However, no universal treatment strategy exists for patients.[4] The lack of consensus about the best treatment strategy can result in confusion and frustration for both the clinicians who treat Crohn's disease patients and the patients themselves.

Interventions To Treat Crohn's Disease

Medical therapy in Crohn's disease targets intestinal inflammation with the intent of altering the natural history of the disease. Clinicians have prescribed corticosteroids and aminosalicylates such as sulfasalazine since the mid-1900s to treat Crohn's disease. Clinicians have prescribed immunomodulators (e.g., 6-mercaptopurine, azathioprine, and methotrexate) for the treatment of Crohn's disease since the 1970s, although they did not routinely prescribe these medications until the 1990s.[5] The biologics are a class comprised of four agents: three inhibit tumor necrosis factor-alpha (TNF-alpha) and one inhibits the cellular adhesion molecule alpha-4-integrin. The U.S. Food and Drug Administration (FDA) approved the first biologic TNF-alpha inhibitor, infliximab, for the treatment of Crohn's disease in adults in 1998. The FDA-approved TNF-alpha inhibitor biologics also include adalimumab and certolizumab pegol.[4] Natalizumab is another FDA-approved biologic for adults with Crohn's disease, which works by inhibiting the cellular adhesion molecule alpha 4-integrin (Table A).[6] Biologic treatments differ from other medication classes because they are synthesized using biologic, rather than chemical, processes.

When patients have active disease, clinicians prescribe medications to induce remission. After the patient is in remission (no longer has active disease), clinicians prescribe medications to maintain the remission. If a patient is in a state of remission and symptoms increase to an active state, clinicians refer to the symptom increase as a relapse. Clinicians recommend surgery to induce remission when Crohn's disease or its complications are resistant to medical therapy. Surgery is not a cure for disease, as recurrence is common.

Table A. Medications used for the treatment of Crohn's disease

Class	Generic Name	U.S. Trade Name	Route	Half-Life	Mechanism of Action	FDA Approved for CD in Adults	FDA Approved for CD in Children
Biologic	Adalimumab	Humira	Subcutaneous	10-18 days	TNF-alpha inhibitor	Yes	No
Biologic	Certolizumab pegol	Cimzia	Subcutaneous	~14 days	TNF-alpha inhibitor	Yes	No
Biologic	Infliximab	Remicade	Intravenous	7.7-9.5 days	TNF-alpha inhibitor	Yes	Yes
Biologic	Natalizumab	Tysabri	Intravenous	7-15 days	Prevents attachment of inflammatory immune cells to intestinal cell layers	Yes	No
Immunomodulator	Azathioprine	Azasan, Imuran	Oral, intravenous	5 hours	Purine synthesis inhibitor	No	No
Immunomodulator	6-Mercaptopurine	Purinethol	Oral	1-2 hours	Purine synthesis inhibitor	No	No
Immunomodulator	Methotrexate	Methotrexate	Intravenous, oral	3-15 hours	Dihydrofolate reductase inhibitor	No	No
Corticosteroid	Prednisone, prednisolone, 6-methyl-prednisolone, hydrocortisone, budesonide	Cortef, Entocort	Oral, topical, intravenous	8-54 hours	Binds glucocorticoid receptors in cytoplasm, where it upregulates anti-inflammatory genes	No*	No
Aminosalicylate	Mesalamine	Asacol, Canasa, Pentasa, Lialda, Rowasa	Oral, rectal	2-15 hours	Unknown	No	No
Aminosalicylate	Sulfasalazine	Azulfidine	Oral	5-10 hours	Unknown	No	No

CD = Crohn's disease; FDA = U.S. Food and Drug Administration; TNF = tumor necrosis factor

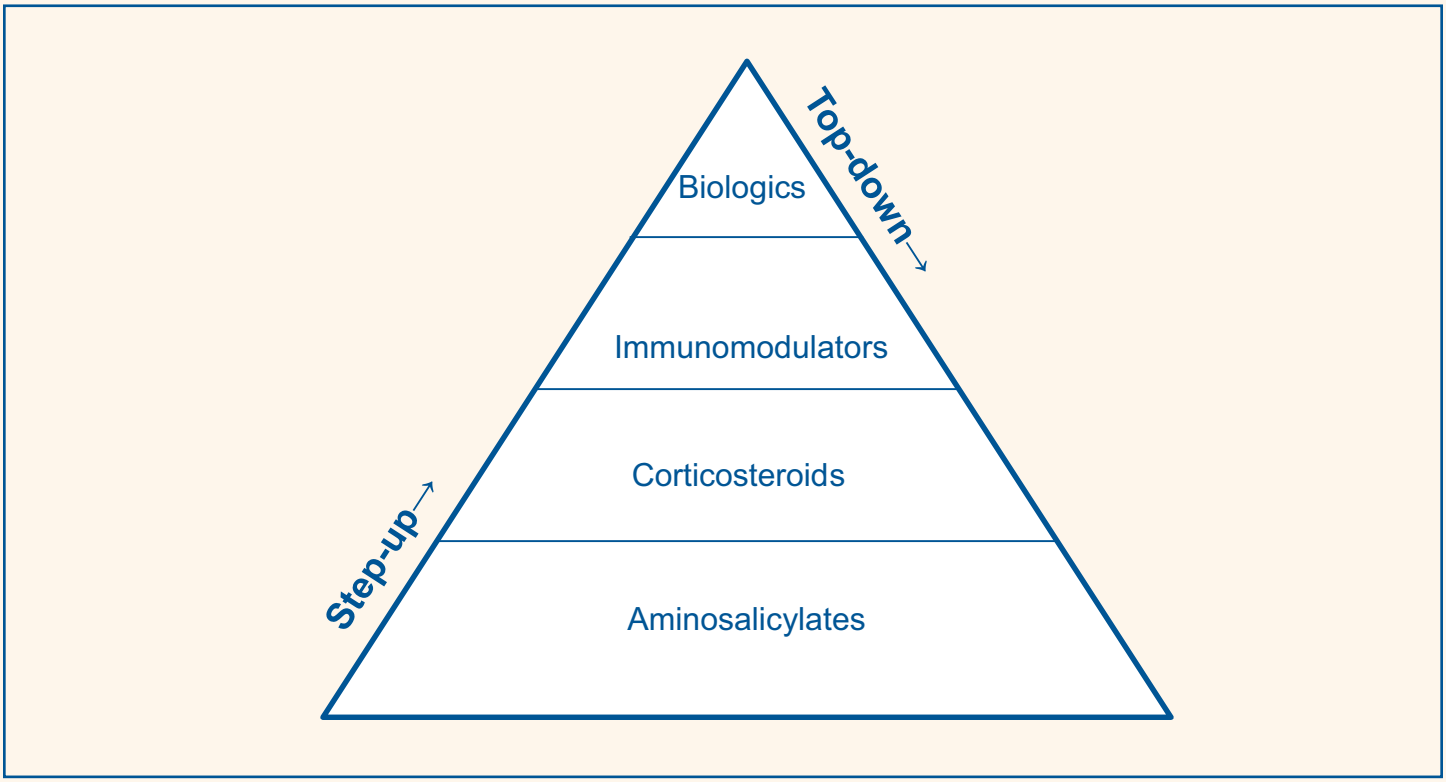
*Budesonide is FDA approved for mild to moderate Crohn's disease.

Current Uncertainties and Controversies in the Treatment of Crohn's Disease

A 2009 report from the Institute of Medicine stated that a priority for comparative effectiveness research is the comparison of algorithms for treating Crohn's disease that introduce biologics at different time points in the disease course.[7] Some experts believe that patients have better long-term outcomes taking immunomodulators and biologics early ("top-down therapy"), as opposed to taking them after prolonged steroid use ("step-up therapy"). Experts have cautioned, however, that the long-term safety of these treatments, particularly when used in combination, remains unknown.[8,9] The disease treatment pyramid shown in Figure A summarizes the two treatment strategies from the onset of disease.[10]

The treatment guidelines point to controversial areas in need of future research. These areas include treatments to achieve long-term remission, the benefits and harms of step-up versus top-down treatment strategies, and how to optimize the use of biologic agents, given that many patients' disease can be managed without the use of biologics.[4]

Figure A. Treatment pyramid for patients with Crohn's disease



Purpose of This Report

The purpose of this review is to give clinicians involved in the care of patients with Crohn's disease a comprehensive comparison of the effectiveness and safety of biologics, immunomodulators, corticosteroids, and aminosalicylates in the treatment of Crohn's disease. The specific Key Questions (KQs) of interest are listed below.

KQ1. What is the comparative effectiveness of therapies, alone or in combination, used to induce remission in adults and children with active Crohn's disease?

Remission is a decrease in or absence of Crohn's disease symptoms. We define remission using the following markers: the Crohn's Disease Activity Index (CDAI), mucosal healing, the absence of Crohn's disease hospitalizations or surgeries, reduction of steroids, fistula healing, and patient-reported outcomes. We looked for data on remission rates at the following time points after randomization: 2–4 weeks, 2–16 weeks, and last reported time point (Table B).

KQ2. What is the comparative effectiveness of therapies, alone or in combination, used to maintain remission in adults and children with inactive Crohn's disease?

We looked for data on the maintenance of remission from inactive disease or response to a medication in a previous induction trial at the following time points after randomization: 48–54 weeks and last reported time point.

KQ3. What is the comparative safety of therapies, alone or in combination, used in adults and children with Crohn's disease in terms of minimizing short- and long-term adverse effects?

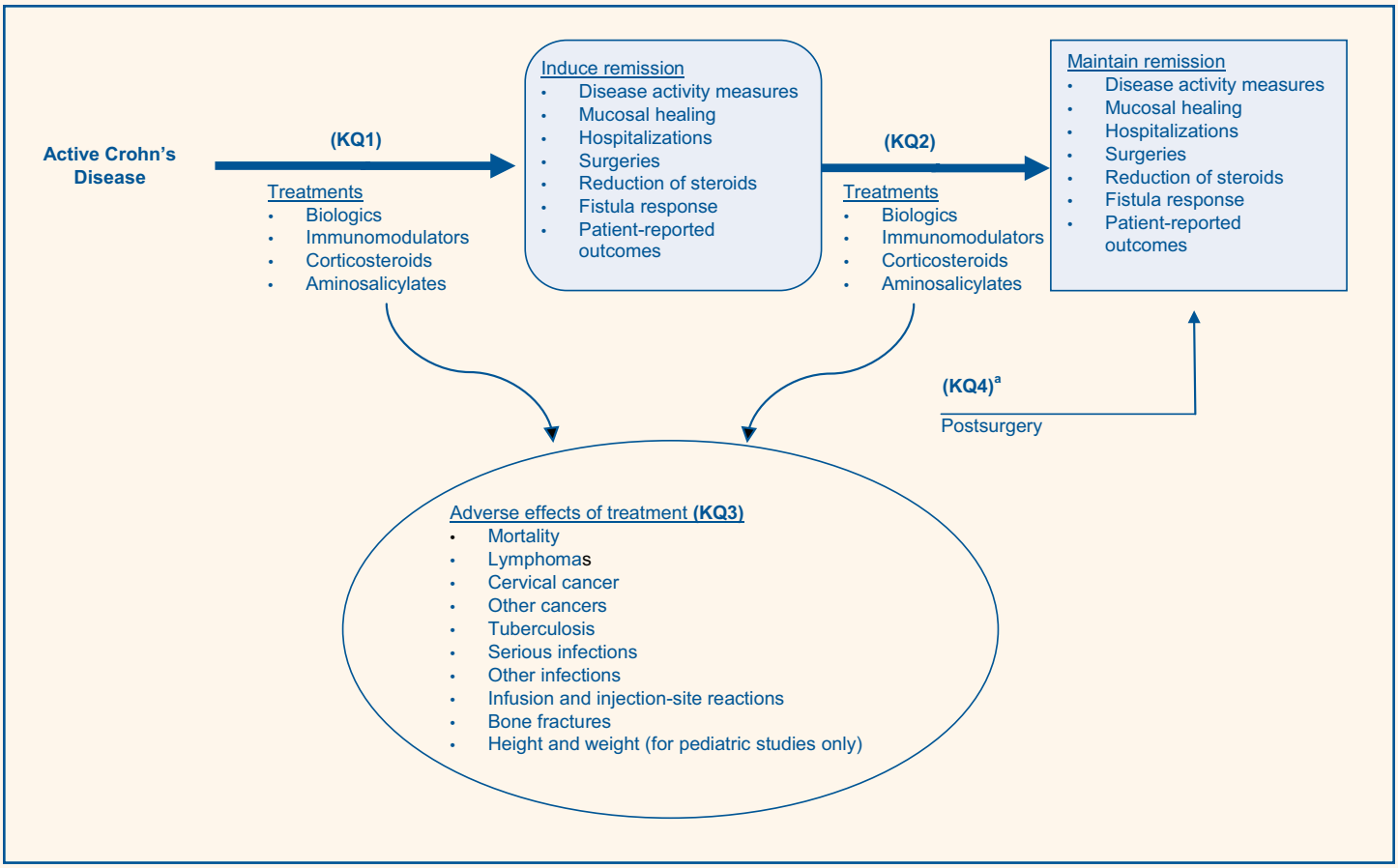
The safety outcomes of interest were mortality, occurrence of lymphomas and/or other cancers, infections, infusion- and injection-site reactions, bone fractures, and growth in children. We looked for data on these outcomes at the last reported time point. Short-term adverse effects are events that occur within 1 year of initiating a medication. Long-term adverse effects occur at least 1 year after initiating a medication.

KQ4. What is the comparative effectiveness of agents used to prevent postoperative recurrence in Crohn's disease as pertains to patient-reported outcomes?

The patient-reported outcomes of interest were standard quality-of-life indexes and specialty indexes (Inflammatory Bowel Disease Questionnaire [IBDQ], Short Inflammatory Bowel Disease Questionnaire), and days of work or school missed. We looked for data on patient-reported outcomes at the following time points after randomization: 48–54 weeks and last reported time point.

Figure B graphically depicts the KQs.

Figure B. Analytic framework for assessing the comparative effectiveness and safety of pharmacologic therapies for Crohn's disease



KQ = Key Question

Note: KQ1: comparative effectiveness in inducing remission; KQ2: comparative effectiveness in maintaining remission; KQ3: comparative safety; KQ4: comparative effectiveness of treatments for postsurgical patient-reported outcomes.

[a]For KQ4, the only examined endpoint is patient-reported outcomes.

Table B. Outcomes considered for each Key Question concerning the comparative effectiveness and safety of medications for the treatment of Crohn's disease

Key Question	Outcomes	Time Points
KQ1	• Disease activity measures (remission as measured by the CDAI, PCDAI, HBI, or other disease activity measurements) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (complete or partial fistula closure or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life, IBDQ, days of work or school missed)	• 2 to 4 weeks after randomization • 12 to 16 weeks after randomization • Last reported time point
KQ2	• Disease activity measures (relapse, CDAI, PCDAI, HBI, or other disease activity measurements) • Mucosal healing (presence of ulcers, CDEIS) • Hospitalizations • Surgeries • Reduction of steroids • Fistula response (fistula recurrence or other measure of perianal disease) • Patient-reported outcomes (health-related quality of life, IBDQ, days of work or school missed)	• 48 to 54 weeks after randomization • Last reported time point
KQ3	• Mortality • Lymphomas • Cervical cancer • Other cancers • Tuberculosis • Serious infections • Other infections • Infusion- and injection-site reactions • Bone fractures • Height and weight as indicators of growth (for pediatric studies only)	• Last reported time point
KQ4	• Patient-reported outcomes (health-related quality of life, IBDQ, days of work or school missed)	• 48 to 54 weeks after randomization • Last reported time point

CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity; HBI = Harvey-Bradshaw Index; IBDQ = Inflammatory Bowel Disease Questionnaire; KQ = Key Question; PCDAI = Pediatric Crohn's Disease Activity Index.

Note: KQ1: comparative effectiveness in inducing remission; KQ2: comparative effectiveness in maintaining remission; KQ3: comparative safety; KQ4: comparative effectiveness of treatments for postsurgical patient-reported outcomes.

Total scores for the CDAI range from 0 to 600, with higher scores indicating more severe disease activity. Total scores for the PCDAI range from 0 to 100, with higher scores indicating more severe disease activity. Total scores for the HBI range from 0 to 19, with higher scores indicating more severe disease activity. Total scores for the CDEIS range from 0 to 44, with higher scores indicating more severe disease activity. Total scores for the IBDQ range from 32 to 224, with higher scores indicating better quality of life.

Methods

Topic Development

The topic for this report was nominated in a public process. At the beginning of the project, we recruited a panel of Key Informants and Technical Experts to give input on the selection and refinement of the questions to be examined. In March 2010, we posted preliminary questions on the Effective Health Care Program Web site for public comment. With the Key Informants, Technical Experts, representatives of the Agency for Healthcare Research and Quality, and public comments, we finalized the KQs listed above.

Search Strategy

We searched the following databases for primary studies for the dates shown in parentheses: MEDLINE® (1966 through June 2011), Embase® (1974 through June 2011), and the Cochrane Central Register of Controlled Trials (Issue 2, 2011). We also reviewed the reference lists of each included article and relevant review articles. To assess the risk of two serious and rare complications that may be associated with the treatment for Crohn's disease, hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy, we supplemented our primary search strategy by also searching for cases reported to the FDA's Adverse Event Reporting System. To identify additional studies, we reviewed the Scientific Information Packets provided by the pharmaceutical manufacturers.

Study Selection

Two reviewers independently reviewed titles and abstracts. We excluded titles and abstracts when both reviewers agreed on exclusion. We resolved differences regarding article inclusion through consensus adjudication. A third reviewer audited a random sample of abstract and article reviews to ensure consistency in the reviewing process. We included relevant English-language studies evaluating nonpregnant patients with Crohn's disease.

For KQ1 and KQ2, on induction and maintenance of remission, we included only randomized controlled trials (RCTs). Both placebo-controlled and head-to-head trials were eligible. We did not include RCTs that examined only the same medication administered at different dosages. We did not include nonrandomized trials. We chose the outcomes of interest for KQ1 and KQ2 to represent important clinical and patient-reported outcomes.

For KQ3, on safety, we included RCTs and observational studies. We chose specific safety outcomes on the basis of the severity of the outcome, impact on quality of life, and potential for safety to differ by medication class. We selected clinical outcomes a priori for inclusion in the review. All RCTs that reported on safety-related outcomes were eligible. Observational studies were eligible if they reported: (1) clear comparison groups specified in the study aims or methods; (2) clear denominators (patients on groups of medications); and (3) clear numerators (patients who experienced the safety event of interest according to group of medication). We also included studies that reported an effect estimate or p-value for a safety outcome by medication use if they met the first criterion (clear comparison groups).

For KQ4, on postoperative outcomes, we focused on the comparative effectiveness of medications only in terms of patient-reported outcomes. We chose this approach because a rigorously conducted systematic review[11] recently assessed the other clinical outcomes associated with the use of medications to maintain remission after intestinal resection in patients with Crohn's disease.

Data Abstraction

For all articles, reviewers extracted information on general study characteristics, study participants, study eligibility criteria, interventions, outcome measures and their method of ascertainment, and the results of each outcome (including measures of variability). We abstracted information on subgroup analyses to understand how disease characteristics could modify the relationship between medications and remission, including baseline C-reactive protein or elevated inflammatory markers, medication history, concomitant use of medications during the trial, disease duration, disease location, and prior surgery related to Crohn's disease.

Quality Assessment

We used study quality assessment to help us understand differences in results between studies. For RCTs, we based the dual independent review of article quality on the Cochrane Collaboration's Risk of Bias Tool.[12] For nonrandomized observational studies, we selected items from the Downs and Black quality checklist.[13] We supplemented both quality assessment tools with items from the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[14] The overall study quality was assessed as—

- Good (low risk of bias). These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison

groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.

- Fair. These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- Poor (high risk of bias). These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.[14]

Applicability

We assessed the applicability of the bodies of evidence for each KQ in terms of the degree to which the study population, interventions, comparisons, outcomes, timing, and settings (PICOTS) were typical of the treatment of individuals with Crohn's disease.

Data Synthesis and Meta-Analysis

We synthesized the evidence for children separately from adults for all KQs. For each KQ, we created a set of detailed evidence tables containing the information we abstracted from eligible studies. We conducted meta-analyses when there were sufficient data (at least three studies) and when studies were sufficiently homogeneous with regard to study characteristics (PICOTS). For studies amenable to pooling for meta-analyses, we calculated pooled relative risks using a DerSimonian and Laird random-effects model.[15] We looked for statistical heterogeneity between the studies in meta-analyses using: (1) a chi-squared test with a significance level of alpha less than or equal to 0.10 and (2) an I-squared statistic with a value of 50 percent or more, indicating substantial heterogeneity.[16] We did not report the pooled result if we found substantial heterogeneity.

We conducted sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate. For all meta-analyses, we conducted formal tests for publication bias using Begg's[17] and Egger's tests;[18] including an evaluation of the asymmetry of funnel plots for each comparison of interest. We conducted all meta-analyses using Intercooled STATA 9.2 (College Station, TX).

When we were unable to pool studies for an outcome, we calculated and displayed absolute risk differences with 95-percent confidence intervals for the individual studies. For KQ1 and KQ2, we considered a difference to be clinically meaningful when there was an absolute difference of 10 percentage points in the outcome between the groups compared, even when the difference was not statistically significant at a p-value less than 0.05. For the IBDQ (the most commonly used patient-reported outcome), we considered a meaningful difference to be a between-group absolute difference of 17 points or greater in the change from baseline.[19]

In terms of adverse effects, when a study did not report an effect estimate, we calculated a Peto odds ratio if the combined number of events in each group was greater than 5.[20,21] We also calculated incidence rate ratios for person-time data when the authors did not report an effect estimate or when the reported effect estimate appeared to contradict the reported events per person-time. We did not specify a standard for a clinically meaningful difference in adverse events, because an absolute rate was rare for most of the adverse events. After performing the main analyses on adverse events, we carried out a sensitivity analysis with studies that evaluated patients with inflammatory bowel disease but did not report results separately for patients with Crohn's disease.

Grading the Strength of Evidence

At the completion of our review, we graded the strength of the evidence addressing the KQs by using the evidence-grading scheme recommended by the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[22] We based the strength-of-evidence grade on four domains: risk of bias, consistency, directness, and precision.

We classified the strength of evidence pertaining to KQs 1 through 4 into four grades:

- "High" grade, indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect
- "Moderate" grade, indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate
- "Low" grade, indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate
- "Insufficient" grade: evidence is unavailable; no studies observed

If the evidence grade or direction of the effect differed at two time points of interest, we reported the evidence grade separately for each time point.

Results

Search Results

We identified 136 studies involving 148,733 patients that met our inclusion criteria for one or more of the KQs. Combining KQ1 and KQ2 yielded 64 studies (94 publications) with 11,377 patients. For KQ3, we found 47 RCTs involving 9,884 Crohn's disease patients and 46 observational studies involving 121,649 Crohn's disease patients. We included an additional 15 studies with 14,934 patients with inflammatory bowel disease as a sensitivity analysis. For KQ4, we found one RCT with 78 patients with Crohn's disease. Five pediatric RCTs examined a total of 298 children, and five observational studies involving 397 children with Crohn's disease reported data for KQs 1-3 but not KQ4.

We reported the results of our systematic review first according to KQ and separated adult from pediatric results. When a study compared multiple medication classes, our report of the study begins with the first medication in our ordered list of medication classes, which we organized according to the top-down approach in the treatment pyramid (Figure A). The medication classes are: biologics (natalizumab, TNF-alpha inhibitor), immunomodulators (thiopurines, methotrexate), corticosteroids, and aminosalicylates.

Key Questions 1 and 2. Induction and Maintenance of Remission

Study Characteristics

The duration of the 64 RCTs ranged from 2 weeks to 4 years. Most RCTs were multicenter (76 percent) and located in Europe and North America, with fewer than 10 multicenter or single-center RCTs in Africa, Australia, Israel, or Asia.

Most patients with active disease (whom we considered in KQ1 on induction of remission) were identified using the CDAI (lower limit, 150 to 220; upper limit, 350 to 600; 43 studies). Most patients with inactive disease (whom we considered in KQ2 on maintenance of remission) were also identified using the CDAI (upper limit, 120 to 220; 23 studies). One study used the Harvey-Bradshaw Index. Twenty-two studies did not report a scoring system to identify disease activity.

Most studies allowed patients to use other medications during the RCT. Many specified that patients had to be on a stable dose at the time of randomization. These trials considered it a failure of treatment if patients made major dose changes during the trial.

Population Characteristics

A small percentage of RCTs reported on race. Of those studies, 84 to 100 percent of the patients were White. The largest non-White racial group in any individual study was 10 percent African American,[23] 8 percent Asian,[24] and 7 percent unspecified other race.[25] The mean or median disease duration ranged from 7 months to 14 years. The mean and median age at the time of randomization ranged from 26 to 47 years. The minimum age reported in any one study was 14 years,[26] and the maximum age was 78 years.[27]

Remission Results

Despite the large number of studies, we were able to perform very few meta-analyses because of the heterogeneity in the definition of the inclusion criteria and outcomes between studies. Recently published studies tended to define remission using the CDAI, with scores below 150 indicating remission and scores of 150 or more indicating active disease. Older studies, including the study for which researchers developed the CDAI,[28] tended to use disease activity measures with or without clinical outcomes, such as the need for surgery or laboratory measures, to indicate remission status. We found very few studies that used measures of remission other than the CDAI (e.g., mucosal healing, hospitalizations, surgeries, reduction of corticosteroid use, fistula response, or patient-reported outcomes).

Key Question 1. Induction of Remission

Of the 78 comparisons with evidence, 4 resulted in high strength of evidence and 20 resulted in moderate strength of evidence (Table C). Most patient-reported outcomes were measured by the IBDQ. Total scores for the IBDQ range from 32 to 224, with higher scores indicating better quality of life.[29]

Key Question 2. Maintenance of Remission

Of the 55 comparisons with evidence, none resulted in high strength of evidence and 11 resulted in moderate strength of evidence (Table D).

Subgroup Analyses

Six trials reported a statistical interaction test on disease characteristics that might modify the relationship between medications and remission. No consistent relationship for a disease characteristic subgroup of interest was observed among the six comparisons.

Table C. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to induce remission*

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 2–4	Disease Activity Measure: Weeks 12–16	Disease Activity Measure: After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Natalizumab vs. placebo 12 weeks	Favors natalizumab; moderate SOE	Favors natalizumab; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 12*: Favors neither; moderate SOE
Natalizumab + infliximab vs. infliximab 10 weeks	Favors neither; low SOE	Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 10*: Favors neither; low SOE
Adalimumab vs. placebo 4 weeks	*>160 mg SC dose*: Favors adalimumab; high SOE *≤80 mg SC dose*: Favors neither; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 4*: Favors neither; low SOE	*Week 4*: Favors neither; high SOE
CP vs. placebo 26 weeks	Favors neither; low SOE	Favors neither; low SOE	*Week 26*: Favors CP; low SOE	Insufficient	Insufficient	Insufficient	*Week 26*: Favors neither; low SOE	*Week 12 and Week 26*: Favors neither; low SOE
Infliximab vs. placebo 12 weeks	Favors infliximab; moderate SOE	Favors infliximab; low SOE	Insufficient	*Week 4*: Favors infliximab; low SOE	Insufficient	Insufficient	*Week 6*: Favors infliximab; high SOE	*Week 4*: Favors infliximab; moderate SOE
Infliximab vs. azathioprine 26 weeks	Insufficient	Favors infliximab; moderate SOE	*Week 26*: Favors infliximab; moderate SOE	*Week 26*: Favors infliximab; low SOE	Insufficient	Insufficient	Insufficient	*Week 26*: Favors neither; moderate SOE
Infliximab + azathioprine vs. infliximab 26 weeks	Insufficient	Favors infliximab + azathioprine; moderate SOE	*Week 26*: Favors infliximab + azathioprine; moderate SOE	*Week 26*: Favors infliximab + azathioprine; low SOE	Insufficient	Insufficient	Insufficient	*Week 26*: Favors neither; moderate SOE

Table C. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 2–4	Disease Activity Measure: Weeks 12–16	Disease Activity Measure: After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Infliximab + azathioprine vs. azathioprine 26 weeks	Insufficient	Favors infliximab + azathioprine; moderate SOE	*Week 26*: Favors infliximab + azathioprine; moderate SOE	*Week 26*; Favors infliximab + azathioprine; low SOE	Insufficient	Insufficient	Insufficient	*Week 26*: Favors neither; moderate SOE
Infliximab + azathioprine vs. steroids 104 weeks	Insufficient	Insufficient	*Week 104*: Favors neither; low SOE	*Week 104*: Favors infliximab + azathioprine; low SOE	Insufficient	Insufficient	Insufficient	*Week 10*: Favors infliximab + azathioprine; low SOE
Infliximab + methotrexate vs. infliximab 48 weeks	Favors infliximab + methotrexate; low SOE	Favors infliximab + methotrexate; low SOE	*Week 48*: Favors infliximab + methotrexate; low SOE	Insufficient	Insufficient	*Week 48*: Favors infliximab + methotrexate; low SOE	Insufficient	*Week 4 and Week 8*: Favors infliximab + methotrexate; low SOE
Thiopurines vs. placebo 104 weeks	Favors neither; low SOE	Insufficient	*Weeks 17-38*: Favors neither; low SOE *Week 104*: Favors 6-MP; low SOE	Insufficient	Insufficient	*Week 16*: Favors neither; low SOE	*Week 17*: Favors neither; low SOE *Week 104*: Favors 6-MP; low SOE	*Week 16*: Favors neither; low SOE‡
Thiopurines vs. oral methotrexate 38 weeks	Favors neither; low SOE	Favors neither; low SOE	*Week 38*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines vs. steroids 17 weeks	Favors steroids; low SOE	Favors steroids; low SOE	*Week 17*: Favors steroids; low SOE	Insufficient	Insufficient	Insufficient	*Week 17*: Favors steroids; low SOE	Insufficient
Thiopurines vs. ASA 30 weeks	Favors ASA; low SOE	Favors neither; low SOE	*Week 17*: Favors neither; l ow SOE *Week 30*: Favors 6-MP; low SOE	Insufficient	Insufficient	Insufficient	*Week 17*: Favors neither; low SOE	Insufficient
Thiopurines (IV, then oral) vs. thiopurines (oral) 16 weeks	Insufficient	Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table C. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 2–4	Disease Activity Measure: Weeks 12–16	Disease Activity Measure: After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Thiopurines + steroids vs. steroids 28 weeks	Insufficient	Favors thiopurines + steroids; low SOE	*Week 28*: Favors thiopurines + steroids; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Thiopurines + steroids vs. methotrexate (IV, then oral) + steroids 26 weeks	Insufficient	Favors neither; low SOE	*Week 26*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	*Week 26*: Favors methotrexate + steroids; low SOE	Insufficient
Methotrexate (oral) vs. placebo 38 weeks	Favors neither; low SOE	Favors neither; low SOE	*Week 38*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Methotrexate (oral) vs. ASA 30 weeks	Insufficient	Insufficient	*Week 30*: Favors methotrexate; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Methotrexate (IM) + prednisone vs. prednisone 16 weeks	Insufficient	Favors methotrexate; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 16*: Favors neither; moderate SOE
Budesonide vs. placebo 16 weeks	*≥9 mg daily*: Favors budesonide; moderate SOE *<9 mg daily*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 8*: No difference; low SOE
6-methyl-prednisolone or prednisone vs. placebo 104 weeks	*6-methyl-prednisolone*: Favors 6-methyl-prednisolone; low SOE *Prednisone* Favors neither; low SOE	Favors steroids; low SOE	*Week 104*: Favors steroids; low SOE	Insufficient	Insufficient	Insufficient	*Week 17*: Favors steroids; low SOE	Insufficient

Table C. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to induce remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 2–4	Disease Activity Measure: Weeks 12–16	Disease Activity Measure: After 16 Weeks	Mucosal Healing	Hospitalizations and Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Budesonide vs. other steroids 10 weeks	Favors neither; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 8* Favors neither; moderate SOE
Steroids vs. ASA 104 weeks	Favors steroids; low SOE	Favors steroids; low SOE	*Week 104*: Favors steroids; low SOE	Insufficient	Insufficient	Insufficient	*Week 17*: Favors neither; low SOE	*Week 2*: Favors steroids; high SOE§ *Week 12*: Favors neither; moderate SOE§
6-methyl-prednisolone + sulfasalazine vs. placebo 104 weeks	Favors 6-methyl-prednisolone + sulfasalazine; low SOE	Favors 6-methyl-prednisolone + sulfasalazine; low SOE	*Week 104*: Favors 6-methyl-prednisolone + sulfasalazine; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. steroids 104 weeks	Favors neither; low SOE	Favors neither; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. sulfasalazine 104 weeks	Favors steroids + sulfasalazine; low SOE	Favors steroids + sulfasalazine; low SOE	*Week 104*: Favors steroids + sulfasalazine; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Mesalamine vs. placebo 17 weeks	Favors neither; low SOE	*≥3.2 g daily*: Favors mesalamine; low SOE *<3.2 g daily*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Sulfasalazine vs. placebo 104 weeks	Favors neither; low SOE	Favors sulfasalazine; low SOE	*Week 104*: Favors sulfasalazine; low SOE	Insufficient	Insufficient	Insufficient	*Week 17*: Favors sulfasalazine; low SOE	Insufficient

6-MP = 6-mercaptopurine; ASA = aminosalicylates; CP = certolizumab pegol; IM = intramuscular; IV = intravenous; SC = subcutaneous; SOE = strength of evidence; steroids = corticosteroids

Note: The strength of the evidence was defined as follows: high = high confidence that the evidence reflects the true effect; moderate = moderate confidence that the evidence reflects the true effect; low = low confidence that the evidence reflects the true effect; insufficient = evidence is unavailable.

*All other potential comparisons of therapies and outcomes were graded as insufficient because there were no eligible trials. The evidence for the last reported measure is provided for disease activity after 16 weeks, mucosal healing, hospitalizations and surgeries, reduction of steroids, fistula respons, and patient-reported outcomes.

†Patient-reported outcomes were measured by the Inflammatory Bowel Disease Questionnaire except where indicated by a footnote.

‡Outcome based on “feeling better” in 2 trials.

§Used McMaster University Quality of Life scale.

Table D. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to maintain remission*

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 48–54	Disease Activity Measure: After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Natalizumab vs. placebo 48 weeks	Favors natalizumab; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	*Week 48*: Favors natalizumab; moderate SOE	Insufficient	*Week 48*: Favors natalizumab; moderate SOE
Adalimumab vs. placebo 52 weeks	Favors adalimumab; low SOE	Insufficient	Insufficient	*Week 52*: Favors adalimumab for all-cause hospitalizations; favors neither for CD-related hospitalizations; moderate SOE	*Week 52*: Favors neither; moderate SOE	*Week 52*: Favors adalimumab; low SOE	Insufficient	*Week 52*: Favors neither; low SOE
CP vs. placebo 18 weeks	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 18*: Favors neither; low SOE
Infliximab vs. placebo 52 weeks	Favors neither among all randomized; favors infliximab among responders; low SOE	Insufficient	*Week 52*: Favors infliximab; low SOE	*Week 52*: Favors infliximab; moderate SOE	*Week 52*: Favors neither among patients with fistulizing disease; moderate SOE	*Week 52*: Favors infliximab; low SOE	*Week 40*: Favors infliximab; low SOE	*Week 52*: Favors infliximab; low SOE
Infliximab + azathioprine vs. infliximab 104 weeks	Insufficient	*Week 104*: Favors neither; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	*Week 104*: Favors neither; low SOE
Infliximab + azathioprine vs. infliximab + hydrocortisone 104 weeks	Favors neither; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table D. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 48–54	Disease Activity Measure: After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Azathioprine vs. placebo 104 weeks	*≥1.7 mg/kg/day*: Favors azathioprine; low SOE *<1 mg/kg/day*: Favors neither; low SOE	*Week 104*: Favors azathioprine at ≥1.7 mg/kg/day; low SOE Favors neither at <1 mg/kg/day; low SOE	Insufficient	Insufficient	Insufficient	*Week 26*: Favors azathioprine; low SOE	Insufficient	Insufficient
Azathioprine vs. budesonide 52 weeks	Favors azathioprine; low SOE	Insufficient	*Week 52*: Favors azathioprine; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Azathioprine vs. prednisone 104 weeks	Favors azathioprine; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Azathioprine vs. sulfasalazine 104 weeks	Favors neither; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Methotrexate (IM) vs. placebo 40 weeks	*Week 40*: Favors methotrexate; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Budesonide vs. placebo 52 weeks	Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 52*: Favors neither; low SOE
Prednisone vs. placebo 104 weeks	Favors neither; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
6-methyl-prednisolone vs. placebo 104 weeks	Favors 6-methyl-prednisolone; low SOE	*Week 104*: Favors 6-methyl-prednisolone; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

Table D. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 48–54	Disease Activity Measure: After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Budesonide vs. mesalamine 52 weeks	Favors budesonide; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 52*: Favors budesonide; moderate SOE
Steroids (6-methyl-prednisolone or prednisone) vs. sulfasalazine 104 weeks	Favors neither; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
6-methyl-prednisolone + sulfasalazine vs. placebo 104 weeks	Favors neither; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. steroids 104 weeks	Favors neither; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Steroids + sulfasalazine vs. sulfasalazine 104 weeks	Favors neither; low SOE	*Week 104*: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Mesalamine (controlled release) vs. placebo 52 weeks	Favors mesalamine; low SOE	*Week 104*: Favors neither; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	*Week 48*: Favors neither; low SOE

Table D. Key findings and strength of evidence: comparing pharmacologic therapies for the management of Crohn's disease to maintain remission* (continued)

Comparison Maximum Trial Duration	Disease Activity Measure: Weeks 48–54	Disease Activity Measure: After 54 Weeks	Mucosal Healing	Hospitalizations	Surgeries	Reduction of Steroids	Fistula Response	Inflammatory Bowel Disease Questionnaire†
Mesalamine (pH release) vs. placebo 208 weeks	Favors mesalamine; low SOE	Week 104: Favors placebo; low SOE Week 208: Favors mesalamine; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Olsalazine vs. placebo 52 weeks	Favors neither; moderate SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Sulfasalazine vs. placebo 104 weeks	Favors neither; low SOE	Week 104: Favors neither; low SOE	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

CD = Crohn's disease; CP = certolizumab pegol; IM = intramuscular; SOE = strength of evidence; steroids = corticosteroids

Note: The strength of the evidence was defined as follows: high = high confidence that the evidence reflects the true effect; moderate = moderate confidence that the evidence reflects the true effect; low = low confidence that the evidence reflects the true effect; insufficient = evidence is unavailable.

*All other comparisons and outcomes were graded as insufficient because there were no eligible trials.

†Patient-reported outcomes were measured by the Inflammatory Bowel Disease Questionnaire except where indicated by a footnote. Total scores for the Inflammatory Bowel Disease Questionnaire range from 32 to 224, with higher scores indicating better quality of life.[29]

Key Question 3. Safety

Study Characteristics of RCTs

Of 64 RCTs, 45 (70 percent) reported a safety outcome of interest according to treatment group. The only information on safety assessment for nearly all RCTs was that researchers ascertained unspecified safety outcomes at study visits. These RCTs made no mention of the ascertainment method (questionnaire, patient-initiated report) or blinding.

Study Characteristics of Observational Studies

Seven prospective cohort (n=26,973), 26 retrospective cohort (n=53,856), 11 case-control (n=40,040), 1 cross-sectional (n=207),[30] and 1 observational study of unclear study design (n=573)[31] reported safety outcomes. All of the prospective and case-control studies stated a specific safety outcome of interest. All of the retrospective studies aimed to assess safety, but about half of them did not specify the exact safety outcomes of interest. No observational study mentioned active ascertainment or blinded assessment of safety outcomes.

Most observational studies occurred at single study centers. Most single-center or multicenter studies took place in the United States, Europe, Canada, or Australia, with one study in Africa and no studies in Asia.

Population Characteristics of Observational Studies

The age distribution was very inclusive, with some studies including patients of all ages (from children up to 90 years). Twenty-eight studies reported results for inflammatory bowel disease patients without separately reporting results for Crohn's disease patients.

In contrast to the RCTs, most of the observational studies reporting safety included all activity levels and severities of Crohn's disease. Most of the observational studies had no restrictions on previous medication use.

Sixteen studies included only patients who had used infliximab. These 16 studies compared the safety of infliximab alone or in combination with other medications. Two retrospective studies required azathioprine use because researchers designed the studies to compare the effectiveness of azathioprine with or without concomitant aminosalicylate.[32,33]

Safety Results

We did not perform meta-analyses because very few safety outcomes had more than three studies that contributed to any monotherapy or combination therapy comparison. Also, when more than three studies were available, the inclusion criteria and study duration were too heterogeneous. We summarized the safety results in Table E.

There was no obvious trend that any medication was more or less safe across the safety outcomes of interest. The ability to examine such trends was limited, as the strength of evidence (SOE) for nearly every comparison was insufficient or low. A few findings indicated effects with some confidence according to the SOE grading, although each finding was based on a single RCT. Two safety comparisons were graded as high SOE: one comparison favored oral azathioprine with placebo infusion over intravenous infliximab, and a second comparison favored placebo over intravenous azathioprine. Two safety comparisons were graded as moderate SOE: one comparison favored a combination of prednisone and sulfasalazine over prednisone alone for infections, and a second comparison did not favor either budesonide or prednisolone for the development of bone fractures.

Subgroup Analyses

No study reported a statistical interaction test for a subgroup of interest for the safety outcomes.

Table E. Summary of the comparative safety of pharmacologic therapies for the management of Crohn's disease

Outcome (Incidence)	Strength of Evidence	Conclusion
Mortality (<1% in most observed comparisons)	Low	The only comparison for which mortality differed between groups was treatment with corticosteroids compared with treatment without corticosteroids. The RRs in observational studies ranged from 1.0 to 2.5 favoring no corticosteroids, with followup ranging from 6 weeks to 7 years.
Mortality (<1% in most observed comparisons)	Low	In comparisons not involving corticosteroids, mortality did not differ among groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, aminosalicylates, or combinations of these drugs. The RRs in observational studies compared with no treatment or another treatment ranged from 0.8 to 1.0 for TNF-alpha inhibitors, 0.7 to 1.3 for immunomodulators, and 0.7 for aminosalicylates, with followup ranging from 4 weeks to 12 years.
HSTCL (insufficient data to estimate incidence)	Insufficient	We identified 37 unique cases of HSTCL associated with treatment of Crohn's disease from research reports, case series, and the AERS. Of these cases, 95% used a thiopurine and 76% used at least 1 biologic, but we could not establish a causal relationship because of limitations in the available information.
Lymphoma (<1% in most observed comparisons)	Low	The risk of lymphoma did not differ among groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, corticosteroids, aminosalicylates, or combinations of these drugs. The observational RRs compared with no treatment or another treatment were 0.6 to 1.7 for TNF-alpha inhibitors, 0.3 to 5.3 for immunomodulators, 1.0 for corticosteroids, and 1.0 for aminosalicylates, with followup ranging from 4 weeks to 12 years.
Lymphoma (<1% in most observed comparisons)	Insufficient	RCTs of immunomodulators, corticosteroids, or aminosalicylates did not report lymphoma as an outcome.
Cervical cancer (insufficient data to estimate incidence)	Low	The risk of cervical cancer did not differ among groups that received TNF-alpha inhibitors, immunomodulators, corticosteroids, aminosalicylates, or combinations of these drugs, with followup ranging from 26 weeks to 3 years.
Cervical cancer (insufficient data to estimate incidence)	Insufficient	None of the studies of natalizumab reported on cervical cancer.
All cancers (insufficient data to estimate incidence)	Low	The risk of nonmelanoma skin cancer was higher with TNF-alpha inhibitors alone or with immunomodulators used recently (within 90 days) or persistently (within 90 days and greater than 365 days) than with no TNF-alpha inhibitors or no immunomodulators. The ORs in observational studies ranged from 2.1 to 6.8.
All cancers (insufficient data to estimate incidence)	Low	The risk of nonmelanoma skin cancer was higher with thiopurines used recently (within 90 days) or persistently (within 90 days and greater than 365 days) than with no thiopurines. The ORs in observational studies ranged from 3.8 to 4.3.
All cancers (insufficient data to estimate incidence)	Low	The risk of adenocarcinoma of the small bowel was higher with 6-mercaptopurine than with no 6-mercaptopurine. The OR in an observational study was 10.8; the study did not report length of followup.
All cancers (insufficient data to estimate incidence)	Low	The risk of other cancers did not differ between treatment groups. The RRs compared with no treatment or another treatment from observational studies ranged from 0 to 10.8, with followup ranging from 4 weeks to 12 years.
Infections (<5% in most trials for serious infections; <5 out of every 100 person-years for opportunistic infections; 5 to 20% in most trials)	Low	The risk of infection did not differ among groups that received natalizumab, TNF-alpha inhibitors, immunomodulators, or aminosalicylates. The RRs, HRs, or ORs from RCTs and observational studies, compared with no treatment or another treatment, were 0.3 to 1.3 for natalizumab, 0.3 to 11.1 for TNF-alpha inhibitors, 0.3 to 5.4 for immunomodulators, 0.4 to 3.4 for corticosteroids, and 0.9 to 1.8 for aminosalicylates, with followup ranging from 4 weeks to 9 years.

Table E. Summary of the comparative safety of pharmacologic therapies for the management of Crohn's disease (continued)

Outcome (Incidence)	Strength of Evidence	Conclusion
Infections (<5% in most trials for serious infections; <5 out of every 100 person-years for opportunistic infections; 5 to 20% in most trials)	Moderate	The risk of infection was lower with prednisone and sulfasalazine than with prednisone alone. The RR from one RCT was 0.3, with 8 weeks of followup.
Tuberculosis (insufficient data to estimate incidence)	Low	The risk of developing tuberculosis did not differ between treatment groups in 5 RCTs comparing TNF-alpha inhibitors with placebo, 1 RCT comparing a combination of infliximab and immunomodulators with infliximab, and 1 RCT comparing a combination of infliximab and immunomodulators with immunomodulators. The followup ranged from 4 to 52 weeks.
Infusion-site reactions (0 to 40% in most trials of biologics)	Low	The rate of infusion reactions did not differ between treatment groups in most comparisons. The RRs, HRs, or ORs from RCTs and observational studies were: natalizumab vs. placebo, RR ranged from 0.8 to 1.5; certolizumab pegol vs. placebo, RR ranged from 0.2 to 1.7; combinations with infliximab vs. infliximab alone, RR ranged from 0.3 to 1.5; infliximab combined with thiopurine vs. infliximab combined with methotrexate, RR ranged from 0.8 to 1.4.
Infusion-site reactions (0 to 40% in most trials of biologics)	Low	The rate of infusion reactions was higher with infliximab and adalimumab than with placebo. The RRs from RCTs ranged from 1.1 to 3.2.
Infusion-site reactions (0 to 40% in most trials of biologics)	High	The rate of infusion reactions was higher with infliximab than with azathioprine. The RR from one RCT was 3.0, with 1 year of followup.
Bone fractures (insufficient data to estimate incidence)	Moderate	The risk of bone fracture did not differ between treatment groups that received budesonide or prednisolone. The RR from one RCT with 2 years of followup was 1.0.
Bone fractures (insufficient data to estimate incidence)	Low	The risk of bone fracture did not differ between corticosteroid users and corticosteroid nonusers. The RR from observational studies ranged from 0 to 2.5, with 2 years of followup.

AERS = Adverse Event Reporting System; HR = hazard ratio; HSTCL = hepatosplenic T-cell lymphoma; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; TNF = tumor necrosis factor

Key Question 4. Patient-Reported Outcomes After Surgery

We identified only one study that met the inclusion criteria for KQ4. This RCT compared azathioprine with mesalamine and reported on the IBDQ among patients who had undergone ileocolonic anastomosis within 6 to 24 months prior to randomization. The strength of the evidence was high for no difference in the effect on the IBDQ between azathioprine and mesalamine.

Key Questions 1–4 for Pediatrics

Study Characteristics

Five studies were RCTs,[34-38] two were prospective cohort studies,[39,40] and three were retrospective cohort studies.[41-43] Studies were conducted in various countries, and five studies were multicentered. The length of followup ranged from 8 weeks to 18 months for RCTs and up to 3.6 years in an observational study.

Population Characteristics

The mean age of patients ranged from 12 to 14 years. In the RCTs, 55 to 69 percent of patients were male, more than 90 percent of patients were White, and mean disease duration ranged from 7 to 36 months. Individual studies restricted their patients in terms of disease location, disease duration, and/or medications allowed prior to and during the study.

Pediatric Results

Few studies examined the efficacy and safety of Crohn's disease treatments in the pediatric population (younger than 18 years old). Four RCTs compared the efficacy of therapies, alone or in combination, in inducing or maintaining remission in children with Crohn's disease. Eight studies reported the comparative safety of therapies, alone or in combination, in children with Crohn's disease. Of these eight studies, most used height or weight change as their primary outcomes of interest. No study reported patient-reported outcomes after surgical resection.

The SOE was graded as insufficient or low for all but two comparisons in the pediatric population. The SOE was graded as moderate for no difference in the effectiveness of budesonide versus prednisolone in inducing remission. The SOE was also graded as moderate that patients treated with prednisolone had fewer infections than patients treated with budesonide.

Discussion

Key Findings

We found that a number of medications were effective in inducing and maintaining remission in Crohn's disease, but no single medication or class of medications stood out as being most effective while also providing the highest quality of life and the best safety profile. Consistency of effect was based on a medication comparison having the same direction of effect for both disease activity (across evaluable time points) and at least one other outcome.

For KQ1, on induction of remission, infliximab was found to have the greatest consistency across the outcomes of disease activity, mucosal healing, fistula healing, and IBDQ when compared with placebo (based on two trials). It was also the only comparison that included a high SOE for a given outcome (fistula healing).

Other consistent comparisons that included at least one outcome with a moderate SOE included the following: infliximab was favored over azathioprine for disease activity and mucosal healing (based on one trial); the combination of infliximab and azathioprine was favored over azathioprine alone for disease activity and mucosal healing (based on two trials); and the combination of infliximab and azathioprine was favored over infliximab alone for disease activity and mucosal healing (based on one trial). In all three of these comparisons, IBDQ was not different between treatment arms.

Several placebo-controlled trials were also found to be consistent across outcomes. However, all the individual outcomes were rated as low SOE. The following interventions were favored over placebo: prednisone/6-methyl-prednisolone for disease activity and fistula healing (based on two trials); sulfasalazine for disease activity and fistula healing (based on two trials); and thiopurine for disease activity and fistula healing (based on one trial). Thiopurines and placebo did not differ in corticosteroid reduction and IBDQ.

For head-to-head trails, the following comparisons were consistent across outcomes, with all individual outcomes rated as low SOE: combination of infliximab and methotrexate favored over infliximab alone for disease activity, steroid reduction, and IBDQ (based on one trial); and corticosteroids favored over thiopurines for disease activity and fistula healing (based on one trial).

For KQ2, on maintenance of remission, infliximab was found to have the greatest consistency across outcomes when compared with placebo for disease activity, mucosal healing, hospitalization, surgery, corticosteroid reduction, fistula healing, and IBDQ (based on three

trials). Adalimumab was also favored over placebo for the outcomes of disease activity, hospitalization, surgery, and corticosteroid reduction (based on two trials); however, adalimumab was not favored over placebo for IBDQ.

Other consistent comparisons with at least one outcome rated as moderate SOE included: natalizumab favored over placebo for disease activity, steroid reduction, and IBDQ (based on one trial); azathioprine over budesonide for disease activity and mucosal healing (based on one trial); and budesonide over aminosalicylates for disease activity and IBDQ (based on one trial). Thiopurines were consistently favored over placebo for disease activity and corticosteroid reduction (based on four trials); however, all the outcomes were rated as low SOE.

For KQ3, on safety, the SOE for nearly every comparison was graded as insufficient or low for safety-related outcomes.

Applicability of Remission Results for Adults

Older populations and non-Whites were underrepresented. Additionally, the relevance of the study findings beyond the clinical trial setting may be limited due to the lack of routine reporting on outcomes other than the CDAI, which is not used in clinical practice. The applicability to newly diagnosed patients and comparisons of step-up versus top-down treatment were limited because almost all of the trials included patients with at least 10 years of Crohn's disease prior to randomization and no trial compared patients receiving their first treatment after diagnosis. Finally, very few trials had endpoints beyond a 1-year duration.

Applicability of Safety Results for Adults

Because they had fewer inclusion and exclusion criteria than RCTs, the observational studies likely apply to Crohn's disease patients of all disease activity and severity levels. Very few observational studies required disease activity or prior medication use for study entry. Despite the differences in inclusion and exclusion criteria between the RCTs and observational studies, we did not see meaningful differences in safety signals between the RCTs and observational studies. The studies that included all inflammatory bowel disease patients had safety findings similar to those of studies that included only Crohn's disease patients or that reported results for both Crohn's disease and all inflammatory bowel disease patients.

Pediatric Applicability

The applicability of the pediatric studies was limited because of the small number of studies, with few participants per study. Also, very few medications were compared. The longest RCT had only 18 months of followup, and the longest prospective study had less than 4 years of followup.

Limitations

The identified body of evidence had several limitations that restricted the ability to draw conclusions about the effectiveness of medications to treat Crohn's disease. Head-to-head studies were limited, especially with regard to maintenance of remission. Although much attention has been given to top-down therapy (starting TNF-alpha inhibitors and/or thiopurines early in the disease course), few studies have compared this strategy with more traditional step-up therapy (escalating therapy after treatment with aminosalicylates or corticosteroids fails) in an RCT setting. Additionally, data were lacking on measures of remission other than the CDAI, such as patient-reported outcomes, mucosal healing, steroid reduction, fistula healing, hospitalization, and surgical rates. Comparisons for safety outcomes almost always had low or insufficient SOE due to lack of details on their assessment in RCTs and poor control for confounding in nonrandomized studies. The scope of studies in pediatric patients was very limited, as there are no double-blind RCTs among this population. None of the studies directly addressed safety concerns relevant to children, who may have longer lifetime exposures to these medications. Safety concerns of particular interest are the risk of hepatosplenic T-cell lymphoma, which affects boys and young men more than other demographic groups.

Findings in Relation to What Is Known

The major difference in findings between this review and previous reviews[4,44-57] pertains to infliximab. Other reviews found that all TNF-alpha inhibitors are efficacious at inducing and maintaining remission. When the clinically meaningful threshold for a difference in treatment effects is considered for consistency of efficacy across the different outcomes of interest, infliximab is the only TNF-alpha inhibitor that is consistently favored over placebo at multiple time points and for multiple outcomes. Consistency was not found for adalimumab or certolizumab pegol because of inconsistency of efficacy between outcomes and absence of outcome information other than the CDAI.

Research Gaps

Multiple gaps in the literature on medical therapy for Crohn's disease were isolated:

- Studies underrepresented non-White patients, pediatric patients, and newly diagnosed populations.
- Few studies made direct comparisons of medications.
- Trials were not powered to compare safety, and observational studies did not account for confounders when comparing adverse events.
- Few studies evaluated outcomes other than the CDAI, such as mucosal healing, rates of hospitalization and surgery, fistula healing, and patient-reported outcomes.
- Maintenance therapy outcomes in RCTs have rarely extended beyond 1 year, while observational studies have been insufficiently long to capture adverse events that may not manifest for years.

Conclusions

Infliximab was the only medication that was found to be consistently effective compared with placebo across a number of outcomes for both induction and maintenance of remission. There was little consistency across outcomes for head-to-head trials. For most medication comparisons, data were lacking on outcomes other than disease activity indexes. In children, the evidence was insufficient to permit assessment of the consistency of medication efficacy across outcomes. The quality of the safety evidence was poor due to poor reporting of the methods in trials and poor confounding control in observational studies. No strong or previously unidentified signals of harm were identified. Comparing Crohn's disease medications directly using pragmatic clinical trials will help to understand the effectiveness of medications in clinical practice using outcomes other than the Crohn's Disease Activity Index.

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