Published in final edited form as:

Gastroenterology. 2015 January ; 148(1): 64–76.e2. doi:10.1053/j.gastro.2014.09.031.

Comparative Efficacy of Pharmacological Interventions in Preventing Relapse of Crohn's Disease after Surgery: A Systematic Review and Network Meta-analysis

Siddharth Singh, M.D.¹, Sushil Kumar Garg, M.B.B.S.², Darrell S. Pardi, M.D., M.S.¹, Zhen Wang, Ph.D.³, Mohammad Hassan Murad, M.D., M.P.H.³, and Edward V. Loftus Jr., M.D.¹

¹Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN

²Department of Surgery, University of Minnesota, Minneapolis, MN

³Knowledge and Evaluation Research Unit, Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN

Abstract

Background & Aims—There are several drugs that might decrease the risk of relapse of Crohn's disease (CD) after surgery, but it is unclear whether one is superior to others. We estimated the comparative efficacy of different pharmacologic interventions for post-operative prophylaxis of CD, through a network meta-analysis of randomized controlled trials.

Methods—We conducted a systematic search of the literature through March 2014. We identified randomized, controlled trials that compared the abilities of 5-aminosalicylates (5-ASA),

© 2014 Published by The AGA Institute

Corresponding author: Siddharth Singh, M.D., Instructor of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905, singh.siddharth2@mayo.edu, Phone: (507) 284-2407, Fax: (507) 284-0538.

Disclosures: This study was made possible by support from the Center for the Science of Healthcare Delivery, Mayo Clinic, and a CTSA Grant UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH), as well as the NIH grant EB001981. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. Dr. Loftus has consulted for and has received research support from Janssen Biotech, AbbVie, and UCB Pharma. None of the other authors have relevant financial disclosures.

Author Contributions:

- Study concept and design: SS, EVL
- Acquisition of data: SS, SKG
- Analysis and interpretation of data: SS, ZW, MHM
- Drafting of the manuscript: SS
- Critical revision of the manuscript for important intellectual content: SKG, DSP, ZW, MHM, EVL
- Approval of the final manuscript: SS, SKG, DSP, ZW, MHM, EVL
- Study supervision: EVL
- Obtained funding: SS, MHM

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

antibiotics, budesonide, immunomodulators, anti-tumor necrosis factor α (anti-TNF) (started within 3 months of surgery), and/or placebo or no intervention, to prevent clinical and/or endoscopic relapse of CD in adults after surgical resection. We used Bayesian network meta-analysis to combine direct and indirect evidence and estimate the relative effects of treatment.

Results—We identified 21 trials, comprising 2006 participants comparing 7 treatment strategies. On network meta-analysis, compared with placebo, 5-ASA (relative risk [RR], 0.60; 95% credible interval [CrI], 0.37–0.88), antibiotics (RR, 0.26; 95%CrI, 0.08–0.61), immunomodulator monotherapy (RR, 0.36; 95%CrI, 0.17–0.63), immunomodulators with antibiotics (RR, 0.11; 95%CrI, 0.02–0.51), and anti-TNF monotherapy (RR, 0.04; 95%CrI, 0.00–0.14), but not budesonide (RR, 0.93; 95%CrI, 0.40–1.84), reduced the risk of clinical relapse. Likewise, compared with placebo, antibiotics (RR, 0.41; 95%CrI, 0.15–0.92), immunomodulator monotherapy (RR, 0.33; 95%CrI, 0.13–0.68), immunomodulators with antibiotics (RR, 0.16; 95%CrI, 0.04–0.48), and anti-TNF monotherapy (RR, 0.01; 95%CrI, 0.00–0.05), but neither 5-ASA (RR, 0.67; 95%CrI, 0.39–1.08) nor budesonide (RR, 0.86; 95%CrI, 0.61–1.22), reduced the risk of endoscopic relapse. Anti-TNF monotherapy was the most effective pharmacological intervention for post-operative prophylaxis, with large effect sizes relative to all other strategies (clinical relapse: RR, 0.02–0.20; endoscopic relapse: RR, 0.005–0.04).

Conclusions—Based on Bayesian network meta-analysis combining direct and indirect treatment comparisons, anti-TNF monotherapy appears to be the most effective strategy for post-operative prophylaxis for CD.

Keywords

Comparative effectiveness; Network meta-analysis; Crohn's disease; Postoperative prophylaxis

INTRODUCTION

Crohn's disease (CD) typically evolves from an inflammatory to penetrating and fibrostenotic disease, and often requires surgical intervention.¹ The cumulative risk of surgery in patients with CD at 1, 5 and 10 years is estimated at 16.3%, 33.3% and 46.6%, respectively.² However, surgery is rarely curative, and most patients will develop endoscopic and clinical recurrence on follow-up.³ Endoscopic recurrence is reported in 54% of patients at 5 years in population-based cohorts.⁴ Clinical recurrence follows endoscopic recurrence, and is reported in up to 28–45% of patients by 5 years.

Multiple pharmacological interventions have been studied to decrease the risk of postoperative endoscopic and clinical recurrence of CD. In a pair-wise meta-analysis, Ford and colleagues observed that 5-aminosalicylates (5-ASA) offered a modest benefit as compared to placebo in decreasing the risk of relapse (clinical, endoscopic, radiologic or surgical) after surgery for CD (relative risk [RR], 0.86; 95% confidence interval [CI], 0.74–0.99).⁵ Peyrin-Biroulet and colleagues observed that patients treated with immunomodulators (azathioprine or 6-mercaptopurine) had 8% lower risk of developing clinical recurrence as compared to a control group composed of placebo with or without 5-ASA and antibiotic therapy.⁶ Recently, both placebo-controlled⁷ as well as active-treatment comparison trials⁸ have demonstrated that anti-tumor necrosis factor- α (anti-TNF) therapy is

effective in decreasing the risk of endoscopic and clinical recurrence after surgical resection of CD. However, there are few randomized controlled trials (RCTs) comparing different active treatment strategies, which can inform clinicians and patients regarding the comparative effectiveness of these interventions. Pair-wise meta-analyses provide only partial information in this case, because they can only answer questions about pairs of treatments and, hence, do not optimally inform decision-making.

Network meta-analysis can help assess comparative effectiveness of several interventions and synthesize evidence across a network of RCTs.^{9, 10} This method involves the simultaneous analysis of direct evidence (from RCTs directly comparing treatments of interest) and indirect evidence (from RCTs comparing treatments of interest with a common comparator), to calculate a mixed effect estimate as the weighted average of the two.¹¹ Such a technique can improve the precision of the estimate (compared with direct evidence alone), and also allows estimation of the comparative efficacy of two active treatments, even if no studies directly compare them.¹² Bayesian network analysis combines likelihood with a prior probability distribution, to estimate a posterior probability distribution. For example, through a Bayesian network of 3 agents A, B and C, if we know the relationship between A and B, and B and C, we can infer probabilistic relationship between A and C. This allows us to estimate comparative treatment effects of 2 agents that have not directly been compared against each other but each has been compared against a common comparator (for example, a placebo).^{9, 10}

In this systematic review, we performed a standard pair-wise meta-analysis of direct evidence as well as Bayesian network meta-analysis combining direct and indirect evidence comparing the relative efficacy of all pharmacological interventions (5-ASA, budesonide, antibiotics, immunomodulators, both as monotherapy and in combination with antibiotics, and anti-TNF monotherapy) for the prevention of clinical and endoscopic recurrence after surgical resection for CD, to comprehensively synthesize available evidence for post-operative prophylaxis in patients with CD.

METHODS

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹³ and is conducted following *a priori* established protocol.

Selection Criteria

Studies included in this meta-analysis were RCTs that met the following inclusion criteria: (a) Patients: adults (age >18 years) with established CD, with a history of small bowel and/or colonic resection surgery, with removal of macroscopically visible disease; (b) Intervention: established therapies for management of post-operative prophylaxis for CD including 5-ASA, antibiotics, budesonide, immunomodulators, and anti-TNF agents, started within 3 months of surgery; (c) Comparator: another active agent, placebo, or no intervention; and (d) Outcome: clinical and/or endoscopic relapse with at least 6 months of follow-up after surgery, and rate of medication discontinuation due to adverse events.

We excluded (a) observational studies, (b) trials in which prophylactic medication was started after established endoscopic recurrence of CD or beyond 3 months of surgery (or when timing of initiation was not reported), (c) trials comparing different doses of the same medication, without an alternative intervention/comparator arm, (d) trials of medications not approved for CD therapy (e.g., probiotics), and (e) studies in which sub-clinical relapse was defined only based on imaging, without any endoscopic documentation.

Search Strategy

The search strategy was designed and conducted by an experienced medical librarian with input from study investigators, using controlled vocabulary supplemented with keywords, for RCTs of post-operative prophylaxis in CD. We searched multiple electronic databases, conference proceedings and conducted a recursive search of bibliographies of published systematic reviews on the topic, from inception to March 31, 2014. Details of the search strategy are included in the Supplementary Appendix A. Figure 1 shows the schematic diagram of study selection.

Data Abstraction and Quality Assessment

Data on several study-, patient- and treatment-related characteristics were abstracted onto a standardized form, by two authors independently, details of which are provided in the Supplementary Appendix B. Two study investigators independently assessed the risk of bias in individual studies, using the Cochrane Risk of Bias assessment tool as detailed in the Supplementary Appendix B.¹⁴

Outcomes Assessed

The primary outcome of interest was the relative efficacy of different pharmacological strategies for post-operative prophylaxis, in preventing (a) clinical relapse and (b) endoscopic relapse. In addition, to assess safety of therapy, we also measured relative rates of medication discontinuation due to adverse events.

For assessment of outcomes, a hierarchical approach was used.¹⁵ For clinical relapse, we preferentially used Crohn's Disease Activity Index (CDAI) >150 as evidence of relapse, and when not available, then other CDAI cut-offs, or clinical relapse as defined by authors of individual studies. For endoscopic relapse, we preferentially used i2-4 on Rutgeerts score¹⁶ as evidence of relapse, and, when not available, then i1-i4, other author-defined measure of endoscopic relapse or a combination of endoscopic and/or imaging relapse based on cross-sectional imaging or barium studies, in that order. When outcome was reported at multiple time points, we preferentially used outcomes at 12 months, 18–24 months, 6 months after surgery, or at the last time point reported in trial. When outcomes were reported for multiple doses of medication, we combined data for all doses.

The denominator used in all trials was based on a modified intention-to-treat (mITT) analysis, that is, only data on patients who had at least one endoscopic and/or clinical assessment on follow-up was extracted. This was preferred over true ITT analysis (wherein all dropouts are assumed to be treatment failures) due to high loss to follow-up in some of the trials. A sensitivity analysis using true ITT was performed for the risk of clinical relapse.

Statistical Analysis

We performed direct head-to-head comparisons using a random effects model to estimate pooled RR and 95% confidence intervals (CI) incorporating within- and between-study heterogeneity.¹⁷ We assessed statistical heterogeneity using I^2 statistic, which represents the proportion of heterogeneity that is not due to chance, but rather due to real differences across studies' populations and interventions; I^2 values over 50% indicated substantial heterogeneity.¹⁸ We assessed publication bias by examining funnel plot symmetry and by conducting Egger's regression test.¹⁹ Direct comparisons were performed using Comprehensive Meta-analysis v2 software package (Biostat Inc., Englewood, NJ) and RevMan v5.2 (Cochrane Collaboration, Copenhagen, Denmark).

To incorporate indirect comparisons, we conducted random effects Bayesian network meta-analyses using Markov chain Monte Carlo methods in WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) following methods described by Lu and Ades.¹¹ We modeled the comparative efficacy of any two treatments as a function of each treatment relative to the reference treatment (i.e. placebo in this study). This approach assumes "consistency" of treatment effects across all included trials – that is, the direct and indirect estimates of effect for each pair-wise comparison do not disagree beyond chance. We evaluated inconsistency by comparing the estimates from direct comparisons and those from indirect comparisons for magnitude and direction of the point estimates and extent of overlap of CI. We estimated the posterior distribution of all parameters using non-informative priors to limit inference to data derived from the trials at hand (i.e., we made no assumptions about the efficacy of these drugs from data external to the trials included in this systematic review). We updated Markov chain Monte Carlo model with 100,000 simulated draws after a burn in of 10,000 iterations. We reported the pair-wise RR and 95% credible interval (CrI, or Bayesian CI) and adjusted for multiple arm trials. Besides the Bayesian network meta-analysis, we also conducted a sensitivity analysis using an alternative Lumley's linear mixed model (Supplementary Appendix C).²⁰

We performed multiple post-hoc sensitivity analyses to assess the robustness of our findings for treatment comparisons vs. placebo. These were based on: (a) timing of outcomes assessment (restricting analysis to studies in which primary outcomes was reported at 12 months); (b) blinding (restricting analysis to studies in which patients and physicians were blinded, excluding open-label studies); (c) optimal dosing of azathioprine (restricting analysis to studies in which dose of azathioprine was 2–2.5 mg/kg/day); (d) standard criteria for outcomes assessment (restricting analysis to studies in which clinical relapse was defined based on the CDAI or the Harvey-Bradshaw Index, and endoscopic relapse was defined based on the Rutgeerts score); and (e) high-quality studies (restricting analysis to studies at low-moderate risk of bias).

Additionally, to assess whether the differential placebo response rate in the included RCTs influenced the relative efficacy of active therapy in the network meta-analysis, we performed a meta-regression among placebo-controlled trials, using placebo response rate as a covariate.

RESULTS

From a total of 836 unique studies identified using the search strategy, we included 21 RCTs in the network meta-analysis.^{7, 8, 21–39} Six RCTs of 5-ASA therapy were excluded (because of unclear timing of initiation of post-operative prophylaxis or initiation beyond 3 months of surgery,^{40–42} comparison of different dosing regimens of 5-ASA without a common comparator group,⁴³ short duration of study (3-month outcome assessment),⁴⁴ and comparison with a therapy of unproven benefit (parasite therapy).⁴⁵ One RCT comparing 5-ASA (and probiotics) to rifaximin was also excluded due to unclear timing of initiation of post-operative prophylaxis.⁴⁶ One RCT comparing azathioprine to 5-ASA for prevention of clinical relapse after established endoscopic relapse was also excluded.⁴⁷ Figure 2 demonstrates the available direct comparisons (i.e. two interventions are being compared against each other in a RCT) and the network of trials.

Characteristics and Quality of Included Studies

Table 1 summarizes the RCTs included in the network meta-analysis. Overall, these 21 trials had 2006 participants. In all included studies, post-operative prophylaxis had been initiated within 8 weeks of surgery, typically within 2–4 weeks. Clinical relapse was usually defined based on CDAI scores with cut-offs ranging between 150 and 250; endoscopic relapse was defined based on Rutgeerts score. Of the 21 RCTs, 12 were two-arm controlled trials comparing active intervention (6 RCTs of 5-ASA or sulfasalazine,^{21–26} 2 of budesonide,^{27, 28} 3 of antibiotics,^{29–31} 1 of anti-TNF⁷) to placebo (or no intervention). Two studies had three arms, one comparing anti-TNF to immunomodulator to 5-ASA,⁸ and another comparing immunomodulator to 5-ASA to placebo.³²

Supplementary Appendix D describes the baseline characteristics of patients included in these trials. Nine trials reported adequate allocation concealment and 14 reported blinding of patients and study personnel. The source of funding included for-profit sources in the 6/11 trials where data were available. The proportion of patients lost to follow-up ranged from 0% to 25.2%. Overall, the trials appeared to be at low to moderate risk of bias. Overall and study-level quality assessments are summarized in Supplementary Figures 1A and B, respectively.

Direct Treatment Comparison

Results from standard pair-wise meta-analysis of treatment comparisons for risk of clinical and endoscopic relapse are shown in Figures 3A and B, and in Supplementary Appendix E.

Combined Direct and Indirect Treatment Effects

Clinical relapse—On network meta-analysis combining direct and indirect effect estimates, the overall results were similar to that observed based on direct comparisons alone, with greater precision. As compared with placebo (or no intervention), 5-ASA (RR, 0.60; 95% CrI, 0.37–0.88), antibiotics (RR, 0.26; 95% CrI, 0.08–0.61), immunomodulator monotherapy (RR, 0.36; 95% CrI, 0.17–0.63), immunomodulator with antibiotics (RR, 0.11; 95% CrI, 0.02–0.51), and anti-TNF monotherapy (RR, 0.04; 95% CrI, 0.00–0.14), but not

budesonide (RR, 0.93; 95% CrI, 0.40–1.84), reduced the risk of clinical relapse after surgery for CD. These results are summarized in Table 2.

On comparative-effectiveness of different pharmacological interventions, we observed that anti-TNF monotherapy was superior to immunomodulator monotherapy (RR, 0.11; 95% CrI, 0.01–0.40); on direct head-to-head treatment comparison, this estimate was in the same direction but not statistically significant (Table 2). Anti-TNF monotherapy was also superior to antibiotics, but the effect estimate was based primarily on indirect evidence (RR, 0.20; 95% CrI, 0.01–0.84). On network meta-analysis, we observed that the combination of immunomodulator and antibiotics was not significantly different from immunomodulator monotherapy (RR, 0.34; 95% CrI, 0.05–1.20) and antibiotic monotherapy (RR, 0.48; 95% CrI, 0.08–1.46). Although based primarily on indirect evidence in the absence of head-to-head trials, immunomodulator monotherapy was not superior to antibiotic therapy (RR, 1.92; 95% CrI, 0.93–4.00). Similar results were obtained when we performed the Bayesian analysis using true ITT population and when analysis of the mITT population was repeated using Lumley's linear mixed model (Supplementary Appendix F).

Endoscopic relapse—The estimates for risk of endoscopic relapse with different pharmacological interventions were similar to that observed for clinical relapse. On network meta-analysis combining direct and indirect effect estimates, the overall results were similar to that observed based on direct comparisons alone, with greater precision. As compared with placebo (or no intervention), antibiotics (RR, 0.41; 95% CrI, 0.15–0.92), immunomodulator monotherapy (RR, 0.33; 95% CrI, 0.13–0.68), immunomodulator combined with antibiotics (RR, 0.16; 95% CrI, 0.04–0.48), and anti-TNF monotherapy (RR, 0.01; 95% CrI, 0.00–0.05), but neither 5-ASA (RR, 0.67; 95% CrI, 0.39–1.08) nor budesonide (RR, 0.86; 95% CrI, 0.61–1.22), reduced the risk of endoscopic relapse after surgery for CD. These results are summarized in Table 3.

On comparative-effectiveness of different pharmacological interventions using network meta-analysis, we observed that anti-TNF monotherapy was superior to all other strategies in decreasing the risk of endoscopic relapse, with large effect size estimates – 5-ASA (RR, 0.02; 95% CrI, 0.00–0.07), antibiotics (RR, 0.03; 95% CrI, 0.00–0.15), immunomodulator monotherapy (RR, 0.04; 95% CrI, 0.00–0.14), immunomodulator combined with antibiotics (RR, 0.03; 95% CrI, 0.00–0.49) and budesonide (RR, 0.005; 95% CrI, 0.00–0.08). We observed that the combination of immunomodulator and antibiotics was not significantly different from immunomodulator monotherapy (RR, 0.54; 95% CrI, 0.12–1.59) or antibiotics alone (RR, 0.43; 95% CrI, 0.10–1.19). Likewise, immunomodulator monotherapy was not significantly different from antibiotic monotherapy in reducing the risk of endoscopic relapse (RR, 0.97; 95% CrI, 0.26–2.53). Similar results were obtained when the analysis was repeated using Lumley's linear mixed model (Supplementary Appendix G).

Results from multiple post-hoc sensitivity analyses are reported in Supplementary Appendix H. Overall, the results were unchanged on sensitivity analyses based on (a) timing of outcomes assessment (studies in which primary outcomes was reported at 12 months), (b) blinding (excluding open-label studies), (c) optimal dosing of azathioprine (studies in which azathioprine was used at 2–2.5 mg/kg/day), (d) standard criteria for outcomes assessment

(studies in which clinical relapse was defined based on CDAI or Harvey-Bradshaw Index, and endoscopic relapse was defined based on Rutgeerts score), (e) high quality studies (studies at low-moderate risk of bias). On meta-regression, the placebo response rate in the placebo-controlled trials did not influence the results of the network meta-analysis (Supplementary Appendix H).

Adverse Events

We assessed the relative side effect profile of these medications using network meta-analysis combining direct and indirect effect estimates of medication discontinuation rates due to serious adverse events. Findings from this analysis are summarized in Supplementary Appendix I. The relative risk of medication discontinuation due to adverse events was not significantly different for antibiotics and immunomodulator, alone or in combination, and of anti-TNF monotherapy.

Quality of Evidence

The number of head-to-head comparisons between active interventions to reduce clinical and endoscopic relapse after surgical resection for CD was limited. This undermines the strength of inference associated with the network meta-analysis, introducing a modest degree of imprecision. Importantly, there were no significant discrepancies (inconsistency) between direct and indirect estimates where both were available (Tables 2 and 3), and the two methods had overlapping CI for all interventions. Within direct treatment comparisons, heterogeneity was minimal in most analyses ($I^2 < 50\%$).

We did not find evidence of publication bias (Egger's regression test < 0.05 for all comparisons), although the number of studies included in each comparison was very small, thereby making the available methods for evaluating publication bias unreliable.

DISCUSSION

Endoscopic and clinical relapse are common after surgical resection for CD, and occasionally progress to surgical relapse.³ Multiple different pharmacologic strategies have been studied for post-operative prophylaxis with variable efficacy; however, there is a paucity of comparative effectiveness studies. In this systematic review and network meta-analysis, we combined direct and indirect evidence from 21 RCTs involving 2,006 patients to estimate the relative efficacy of all pharmacological interventions for preventing endoscopic and clinical relapse. We made several key observations: (a) antibiotics and immunomodulator alone or in combination, and anti-TNF monotherapy, but not budesonide, decrease the risk of short-term (~1 year) clinical and endoscopic relapse after surgical resection for CD; (b) 5-ASA decreases the risk of clinical but not endoscopic relapse; (c) anti-TNF monotherapy appears to be the most efficacious pharmacological intervention for post-operative prophylaxis, with large effect sizes relative to all other strategies (clinical relapse: RR, 0.02–0.20; endoscopic relapse: RR, 0.005–0.04); (d) antibiotic monotherapy and immunomodulator monotherapy appear to have similar efficacy, with comparable rates of serious adverse events warranting medication discontinuation. Overall, the strength of inference (quality of evidence) seems to be moderate to high, supporting the efficacy of anti-

TNF monotherapy for reducing the risk of clinical and endoscopic relapse after surgical resection for CD, compared with other pharmacological interventions.

Previous RCTs and standard pair-wise meta-analyses have also demonstrated the efficacy of 5-ASA and immunomodulator monotherapy in preventing relapse after surgically induced remission in CD. Ford and colleagues summarized results from 11 RCTs comparing 5-ASA or sulfasalazine to placebo (or no intervention), and observed a 14% reduction in the risk of relapse (clinical, endoscopic, radiologic or surgical),⁵ somewhat lower than that observed in our direct treatment comparison meta-analysis (RR, 0.75 for clinical relapse; RR, 0.78 for endoscopic relapse), as well as in the network meta-analysis (RR, 0.60 for clinical relapse; RR, 0.67 for endoscopic relapse). Our analysis was limited to studies in which prophylaxis was started within 3 months of surgery, and we used a modified ITT analysis for each study (due to high rate of attrition in individual studies, which precludes appropriate assessment for endoscopic relapse); this resulted in a smaller number of 5-ASA trials being included in our analysis and the observed differences in findings. Peyrin-Biroulet and colleagues performed a pair-wise meta-analysis comparing thiopurine analogs to other interventions (placebo, antibiotics, or 5-ASA) and based on 4 RCTs, observed an 8% decrease in risk of clinical relapse at 1 year with thiopurine use.⁶ We observed a much greater benefit (64% lower risk of clinical and 67% lower risk of endoscopic relapse) with immunomodulator monotherapy in our network meta-analysis. The difference in results from our study may be explained by the heterogenous comparator group in their study, which may have diluted the observed benefit of immunomodulator, given the protective benefit of both 5-ASA and antibiotics relative to placebo.

We also observed that anti-TNF monotherapy was the most efficacious strategy in reducing the risk of clinical and endoscopic relapse, compared to placebo and all other active interventions. While only 3 RCTs compared anti-TNF monotherapy to placebo or other active agents (immunomodulator, 5-ASA),^{7, 8, 35} Bayesian network meta-analysis allowed us to compare anti-TNF therapy with other active agents indirectly when no head-to-head trial existed (antibiotics alone or in combination with immunomodulator, budesonide), and to obtain more precise effect estimates by jointly assessing direct and indirect comparisons for agents where direct evidence was available. Although we preferably used the 1-year risk of recurrence as the endpoint in our analysis, recent studies have shown that the benefit of anti-TNF therapy is more durable. Savarino and colleagues observed that after 2 years of post-surgical prophylactic therapy, the risk of clinical and endoscopic recurrence was considerably lower in adalimumab-treated patients compared to immunomodulator or 5-ASA.⁸ In a long-term, open-label, prospective follow-up of their cohort of patients originally randomized to post-operative infliximab or placebo, Reguiero and colleagues noted that patients who continued on infliximab had a 13.5 times lower risk of endoscopic recurrence compared to patients who chose not to use infliximab at 5 years.⁴⁸

The strengths of our analyses include the comprehensive and simultaneous assessment of the relative efficacy of all available agents for post-operative prophylaxis after surgical resection in CD. Given the limited comparative effectiveness studies, it remains difficult for clinicians to make informed decisions about which medications are most effective for preventing relapse after surgery. However, there are certain limitations, related to both the network

analysis as well as individual studies, which merit further discussion. First, due to a limited number of direct comparative effectiveness studies, estimates based purely on indirect treatment comparisons warrant lower confidence compared to those based on combined direct- and indirect-treatment comparisons, and the strength of inference is low to moderate for these estimates.¹⁰ Where both direct and indirect evidence was available, we observed that CrI of all pooled RRs from network meta-analysis included CIs of corresponding RRs from direct comparisons by pairwise meta-analysis, and the point estimates of RRs were also similar between the direct and network meta-analyses, supporting that there was no significant inconsistency between direct and indirect comparisons. Second, a network meta-analysis assumes that patients enrolled in the studies could have been sampled from the same theoretical population and that similar comparators between different trials have a consistent risk-benefit ratio.⁹ This may not be accurate, with inherent differences in risk of post-operative recurrence based on trial design and patient characteristics in included trials (smoking, disease location, CD phenotype, number of surgeries, etc.). At a meta-analysis level, we tried to minimize this conceptual heterogeneity by including only studies in which post-operative prophylaxis was started within 3 months of surgery and using a hierarchy of outcomes (timing of assessment, definition of clinical and endoscopic recurrence) to allow consistency as best possible, and using a modified ITT analysis. We also conducted multiple sensitivity analyses as well as meta-regression analysis to account for the differential placebo response rates across RCTs; the overall findings were unchanged, suggesting robustness of the primary analysis. Third, our study was not designed to address cost-effectiveness of these strategies. Finally, our analysis was done with study-level data, rather than individual patient data, which would be the preferred methodology. As mentioned above, we preferentially used outcomes at 1 year after surgery, and so it is difficult to estimate whether some of the short-term prophylactic medications (like antibiotics) would have long-term effects on risk of CD recurrence.

There were similar limitations in the individual studies, which also undermine the strength of the meta-analysis. Most of the studies defined clinical relapse based on CDAI; however, CDAI is a poor predictor of clinical recurrence based on the subjectivity of the score after a patient has undergone surgery. Likewise, most studies used Rutgeerts score to assess endoscopic relapse; while this index is frequently used in RCTs of postoperative pharmacological prophylaxis to score endoscopic recurrence as an efficacy endpoint, it has not been prospectively validated for this outcome. Additionally, there were limited data in individual studies to define endoscopic relapse as presence and absence of any inflammation (i.e., i0 vs. i1-4), and hence, our analysis focused on the standard definition of endoscopic relapse (i2-4).

Implications for Clinical Practice

Based on a combination of direct and indirect treatment comparisons with consistent evidence across both, and with relatively narrow CIs in most cases, there is moderate to high-quality evidence supporting the efficacy of anti-TNF monotherapy over other strategies for postoperative prophylaxis after surgical resection for CD. Consequently, in patients deemed at highest risk of recurrence (young individuals, smokers, with a history of penetrating and perianal CD and a history of prior surgeries), it may be prudent to

recommend anti-TNF therapy for postoperative prophylaxis. In patients deemed at high-risk of recurrence, but with contraindications to anti-TNF therapy (or if anti-TNF therapy is cost-prohibitive), the combination of immunomodulator with short-duration of antibiotics (3–6 months in included trials), immunomodulator monotherapy or antibiotic monotherapy were not significantly different, although the evidence supporting this is weak and merits further evaluation. There are no studies on combination anti-TNF and immunomodulator therapy for post-operative prophylaxis.

In patients at moderate risk of recurrence (patients not deemed to be high risk, with intermediate duration inflammatory CD), immunomodulator monotherapy or antibiotic monotherapy may be comparable options; patients in whom there is concern for side effects from immunomodulator therapy, antibiotics alone may be considered; however, the evidence supporting this is based primarily on indirect treatment comparisons, and only for short-term risk of recurrence. Finally, in patients at low-risk of recurrence after surgical resection (older individuals, with long-standing CD and first surgery for a short stricture), antibiotics or perhaps 5-ASA antibiotics may be considered, the former perhaps more effective (indirect evidence); alternatively, an option of watchful monitoring may also be offered.

In conclusion, using a Bayesian network meta-analysis involving 21 RCTs comparing 7 different pharmacological interventions, we observed that anti-TNF monotherapy appears to be the most effective strategy compared to all other strategies in decreasing the risk of endoscopic and clinical relapse after surgical resection of CD. Large RCTs are warranted to establish the comparative efficacy of different strategies for postoperative CD. Cost-utility analyses are also warranted to more definitively individualize a strategy for post-operative prophylaxis depending on risk of recurrence after surgical resection of CD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We wish to thank Ms. Patricia Erwin, Medical Librarian at the Mayo Clinic Library for helping in the literature search for this systematic review and meta-analysis.

References

1. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet*. 2012; 380:1590–605. [PubMed: 22914295]
2. Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology*. 2013; 145:996–1006. [PubMed: 23896172]
3. Sorrentino D. State-of-the-art medical prevention of postoperative recurrence of Crohn's disease. *Nat Rev Gastroenterol Hepatol*. 2013; 10:413–22. [PubMed: 23648935]
4. Buisson A, Chevaux JB, Allen PB, et al. Review article: the natural history of postoperative Crohn's disease recurrence. *Aliment Pharmacol Ther*. 2012; 35:625–33. [PubMed: 22313322]
5. Ford AC, Khan KJ, Talley NJ, et al. 5-aminosalicylates prevent relapse of Crohn's disease after surgically induced remission: systematic review and meta-analysis. *Am J Gastroenterol*. 2011; 106:413–20. [PubMed: 20717106]

6. Peyrin-Biroulet L, Deltenre P, Ardizzone S, et al. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. *Am J Gastroenterol*. 2009; 104:2089–96. [PubMed: 19568226]
7. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology*. 2009; 136:441–50. [PubMed: 19109962]
8. Savarino E, Bodini G, Dulbecco P, et al. Adalimumab is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial. *Am J Gastroenterol*. 2013; 108:1731–42. [PubMed: 24019080]
9. Cipriani A, Higgins JP, Geddes JR, et al. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med*. 2013; 159:130–7. [PubMed: 23856683]
10. Mills EJ, Ioannidis JP, Thorlund K, et al. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA*. 2012; 308:1246–53. [PubMed: 23011714]
11. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004; 23:3105–24. [PubMed: 15449338]
12. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997; 50:683–91. [PubMed: 9250266]
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009; 339:b2700. [PubMed: 19622552]
14. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011; 343:d5928. [PubMed: 22008217]
15. Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011; 106:644–59. [PubMed: 21407183]
16. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990; 99:956–63. [PubMed: 2394349]
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7:177–88. [PubMed: 3802833]
18. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327:557–60. [PubMed: 12958120]
19. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315:629–34. [PubMed: 9310563]
20. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med*. 2002; 21:2313–24. [PubMed: 12210616]
21. Brignola C, Cottone M, Pera A, et al. Mesalamine in the prevention of endoscopic recurrence after intestinal resection for Crohn's disease. Italian Cooperative Study Group. *Gastroenterology*. 1995; 108:345–9. [PubMed: 7835575]
22. Caprilli R, Andreoli A, Capurso L, et al. Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post-operative recurrence of Crohn's disease. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). *Aliment Pharmacol Ther*. 1994; 8:35–43. [PubMed: 8186345]
23. Ewe K, Herfarth C, Malchow H, et al. Postoperative recurrence of Crohn's disease in relation to radicality of operation and sulfasalazine prophylaxis: a multicenter trial. *Digestion*. 1989; 42:224–32. [PubMed: 2572495]
24. Lochs H, Mayer M, Fleig WE, et al. Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI. *Gastroenterology*. 2000; 118:264–73. [PubMed: 10648454]
25. McLeod RS, Wolff BG, Steinhart AH, et al. Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. *Gastroenterology*. 1995; 109:404–13. [PubMed: 7615189]
26. Wenckert A, Kristensen M, Eklund AE, et al. The long-term prophylactic effect of salazosulphapyridine (Salazopyrin) in primarily resected patients with Crohn's disease. A controlled double-blind trial. *Scand J Gastroenterol*. 1978; 13:161–7. [PubMed: 24891]

27. Ewe K, Bottger T, Buhr HJ, et al. Low-dose budesonide treatment for prevention of postoperative recurrence of Crohn's disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group. *Eur J Gastroenterol Hepatol*. 1999; 11:277–82. [PubMed: 10333200]
28. Hellers G, Cortot A, Jewell D, et al. Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. *Gastroenterology*. 1999; 116:294–300. [PubMed: 9922309]
29. Herfarth HH, Katz JA, Hanauer SB, et al. Ciprofloxacin for the prevention of postoperative recurrence in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis*. 2013; 19:1073–9. [PubMed: 23511031]
30. Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology*. 1995; 108:1617–21. [PubMed: 7768364]
31. Rutgeerts P, Van Assche G, Vermeire S, et al. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. *Gastroenterology*. 2005; 128:856–61. [PubMed: 15825069]
32. Hanauer SB, Korelitz BI, Rutgeerts P, et al. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology*. 2004; 127:723–9. [PubMed: 15362027]
33. Ardzzone S, Maconi G, Sampietro GM, et al. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. *Gastroenterology*. 2004; 127:730–40. [PubMed: 15362028]
34. Nos P, Hinojosa J, Aguilera V, et al. Azathioprine and 5-ASA in the prevention of postoperative recurrence of Crohn's disease. *Gastroenterol Hepatol*. 2000; 23:374–8. [PubMed: 11227650]
35. Armuzzi A, Felice C, Papa A, et al. Prevention of postoperative recurrence with azathioprine or infliximab in patients with Crohn's disease: An open-label pilot study. *J Crohns Colitis*. 2013; 7:e623–9. [PubMed: 23810678]
36. D'Haens GR, Vermeire S, Van Assche G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. *Gastroenterology*. 2008; 135:1123–9. [PubMed: 18727929]
37. Herfarth H, Tjaden C, Lukas M, et al. Adverse events in clinical trials with azathioprine and mesalamine for prevention of postoperative recurrence of Crohn's disease. *Gut*. 2006; 55:1525–6. [PubMed: 16966711]
38. Manosa M, Cabre E, Bernal I, et al. Addition of metronidazole to azathioprine for the prevention of postoperative recurrence of Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Inflamm Bowel Dis*. 2013; 19:1889–95. [PubMed: 23689809]
39. Yoshida K, Fukunaga K, Ikeuchi H, et al. Scheduled infliximab monotherapy to prevent recurrence of Crohn's disease following ileocolic or ileal resection: a 3-year prospective randomized open trial. *Inflamm Bowel Dis*. 2012; 18:1617–23. [PubMed: 22081474]
40. Sutherland LR, Martin F, Bailey RJ, et al. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. *Gastroenterology*. 1997; 112:1069–1077. [PubMed: 9097988]
41. Lennard-Jones JE. Sulphasalazine in asymptomatic Crohn's disease. A multicentre trial. *Gut*. 1977; 18:69–72. [PubMed: 14057]
42. Summers RW, Switz DM, Sessions JT Jr, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology*. 1979; 77:847–69. [PubMed: 38176]
43. Caprilli R, Cottone M, Tonelli F, et al. Two mesalazine regimens in the prevention of the post-operative recurrence of Crohn's disease: a pragmatic, double-blind, randomized controlled trial. *Aliment Pharmacol Ther*. 2003; 17:517–23. [PubMed: 12622760]
44. Florent C, Cortot A, Quandale P, et al. Placebo-controlled clinical trial of mesalazine in the prevention of early endoscopic recurrences after resection for Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Eur J Gastroenterol Hepatol*. 1996; 8:229–33. [PubMed: 8724022]

45. Ren J, Wu X, Liao N, et al. Prevention of postoperative recurrence of Crohn's disease: Tripterygium wilfordii polyglycoside versus mesalazine. *J Int Med Res.* 2013; 41:176–87. [PubMed: 23569144]
46. Campieri M, Rizzello F, Venturi A, et al. Combination of antibiotic and probiotic treatment is efficacious in prophylaxis of post-operative recurrence of Crohn's disease: A randomized controlled study vs mesalamine. *Gastroenterology.* 2000; 118:A781.
47. Reinisch W, Angelberger S, Petritsch W, et al. Azathioprine versus mesalazine for prevention of postoperative clinical recurrence in patients with Crohn's disease with endoscopic recurrence: efficacy and safety results of a randomised, double-blind, double-dummy, multicentre trial. *Gut.* 2010; 59:752–9. [PubMed: 20551460]
48. Regueiro M, Kip KE, Baidoo L, et al. Postoperative Therapy with Infliximab Prevents Long-Term Crohn's Disease Recurrence. *Clin Gastroenterol Hepatol.* 201410.1016/j.cgh.2013.12.035

Figure 1.
Flow sheet summarizing study identification and selection.

Figure 2.

Evidence network of different pharmacological intervention for post-operative prophylaxis against clinical relapse of Crohn's disease included in the network meta-analysis. Please note that two of the included RCTs were three-arm trials. The numbers (and numbers in brackets) refers to the number of trials (and number of combined number of participants in these trials), and the thickness of the connecting line corresponds to the number of trials between comparators.

Table 1

Characteristics of included randomized controlled trials comparing different pharmacological interventions for post-operative prophylaxis after surgical resection in Crohn's disease.

Study, Year of Publication	Study Design	Location; Time period	Timing of intervention after surgery and outcome assessment	Intervention (ITT/mITT)	Control (ITT/mITT)	Outcomes	
						Clinical	Endoscopic
Mesalamine/Sulfasalazine v. Placebo/No intervention							
Brignola, ²¹ 1995	MC, DB, PC	Italy; 1990–91	<4 weeks; 12 months	Pentasa 3 g/day, for 12 months; N=44 (ITT), 43 (mITT)	Placebo, for 12 months; N=43 (ITT), 42 (mITT)	Increase of CDAI by 100 points, with score >150	i2-4, Rutgeerts score
Caprilli, ²² 1994	MC, OL, no placebo group	Italy; 1990–92	<2 weeks; 12 months	Asacol 2.4 g/day, for 12 months; N=55 (ITT), 47 (mITT)	No intervention; N=55 (ITT), 48 (mITT)	Increase of CDAI by 100 points, with score >150	i2-4, Rutgeerts score
Lochs, ²⁴ 2000	MC, DB, PC	Europe; 1992–96	<10 days; 18 months	Pentasa 4 g/day, for 18 months; N=152 (ITT), 143 (mITT)	Placebo, for 18 months; N=166 (ITT), 161 (mITT)	Increase of CDAI by 60 points, with score >150	i2-4, Rutgeerts score
McCleod, ²⁵ 1995	MC, DB, PC	Canada; 1986–93	<8 weeks; mean follow-up 29–36 months	Mesalamine 3 g/day, for mean 35 months; N=87 (ITT), 87 (mITT)	Placebo, for mean 29 months; N=76 (ITT), 76 (mITT)	Clinician diagnosed	Non-validated, binary score
Wenckert, ²⁶ 1978	MC, DB, PC	Europe; NR	<4 weeks; 12 months	Sulfasalazine 3 g/day, for 18 months; N=32 (ITT)	Placebo, for 18 months; N=34 (ITT)	Clinician diagnosed	NR
Ewe, ²³ 1989	MC, DB, PC	Germany; NR	During index hospitalization; 12 months	Sulfasalazine 3 g/day, for 36 months; N=111 (ITT)	Placebo, for 36 months; N=121 (ITT)	NR	Not defined
Immunomodulators v. mesalamine (v. placebo)							
Arizzone, ³³ 2004	SC, OL	Italy; NR	<2 weeks; 24 months	Azathioprine 2 mg/kg/day, for 24 months; N=69 (ITT), 65 (mITT)	Mesalamine 3 g/day, for 24 months; N=69 (ITT), 65 (mITT)	CDAI>200, warranting corticosteroid therapy	NR
Herfarth, ³⁷ 2006	MC, DB	Germany; NR	<2 weeks; 12 months	Azathioprine 2–2.5 mg/kg/day, for 12 months; N=37 (ITT), 19 (mITT)	Mesalamine 4 g/day, for 12 months; N=42 (ITT), 18 (mITT)	Not defined	Not defined
Nos, ³⁴ 2000	SC, OL	Spain; NR	<4 weeks; 12 months	Azathioprine 50 mg/day, for 24 months; N=21 (ITT), 19 (mITT)	Mesalamine 3 g/day, for 24 months; N=18 (ITT), 15 (mITT)	CDAI>200	i2-4, Rutgeerts score
Hanauer, ³² 2004	MC, DB, PC, triple-arm trial	USA, Belgium; 1992–96	During index hospitalization; 24 months	6-mercaptopurine 50 mg/day, for 24 months; N=47 (ITT), 32 (mITT)	1 Pentasa 3 g/day, for 24 months; N=40 (ITT),	Non-validated, 4-point severity scale	i2-4, Rutgeerts score

Study, Year of Publication	Study Design	Location; Time period	Timing of intervention after surgery and outcome assessment	Intervention (ITT/mITT)	Control (ITT/mITT)	Outcomes	
						Clinical	Endoscopic
Antibiotics v. Placebo/No intervention							
Rutgeerts, ³⁰ 1995	MC, DB, PC	Belgium; 1988–91	<1 week; 12 months (clinical), 36 months (endoscopic)	Metronidazole 20 mg/kg/day, for 3 months; N=30 (ITT), 29 (mITT)	Placebo, for 3 months; N=30 (ITT), 28 (mITT)	Clinician diagnosed	i3-4, Rutgeerts score
Rutgeerts, ³¹ 2005	MC, DB, PC	Belgium; NR	<2 weeks; 12 months	Ornidazole 500 mg BID, for 12 months; N=38 (ITT), 38 (mITT)	Placebo, for 12 months; N=40 (ITT), 40 (mITT)	CDAI>250	i2-4, Rutgeerts score
Herfarth, ²⁹ 2013	MC, DB, PC	USA; 2008–11	<2 weeks; 6 months	Ciprofloxacin 500 mg BID, for 6 months; N=17 (ITT), 9 (mITT)	Placebo, for 6 months; N=16 (ITT), 10 (mITT)	HBI score >5, or 3-point increase from baseline	i2-4, Rutgeerts score
Immunomodulators + Antibiotics v. Antibiotics							
D'Haens, ³⁶ 2008	MC, DB, PC	Belgium; 1999–2005	<2 weeks; 12 months	Azathioprine 100 mg (wt<60 kg) or 150 mg (wt>60 kg), for 12 months AND metronidazole 250 mg TID for 3 months; N=40 (ITT), 32 (mITT)	Metronidazole 250 mg TID, for 3 months AND placebo, for 3 months; N=41 (ITT), 29 (mITT)	CDAI>250	i2-4, Rutgeerts score
Immunomodulators + Antibiotics v. Immunomodulators							
Manosa, ³⁸ 2013	MC, DB, PC	Spain; 2004–10	During index hospitalization; 12 months	Azathioprine 2–2.5 mg/kg/day, for 12 months AND metronidazole 15–20 mg/kg/day for 3 months; N=25 (ITT), 23 (mITT)	Azathioprine 2–2.5 mg/kg/day, for 12 months AND placebo, for 3 months; N=25 (ITT), 22 (mITT)	HBI score >7	i2-4, Rutgeerts score
Budesonide v. Placebo/No intervention							
Hellers, ²⁸ 1999	MC, DB, PC	Europe; NR	<2 weeks; 12 months	Budesonide 6 mg/day, for 12 months; N=63 (ITT)	Placebo, for 12 months; N=66 (ITT)	CDAI>200	i2-4, Rutgeerts score
Ewe, ²⁷ 1999	MC, DB, PC	Germany; 1992–94	<2 weeks; 12 months	Budesonide 3 mg/day, for 12 months; N=43 (ITT), 29 (mITT)	Placebo, for 12 months; N=40 (ITT), 23 (mITT)	CDAI>200	i2-4, Rutgeerts score
Anti-TNF v. Placebo/No intervention							
Regueiro, ⁷ 2009	SC, DB, PC	USA; 2005–07	<4 weeks; 12 months	Infliximab 5 mg/kg at 0, 2 and 6 weeks, followed by 8 weeks, for 54 weeks (+/- concomitant mesalamine, 30.8% or placebo, 30.8%)	Placebo, for 54 weeks (+/- concomitant mesalamine, 30.8% or placebo, 30.8%)	CDAI>200	i2-4, Rutgeerts score

Study, Year of Publication	Study Design	Location; Time period	Timing of intervention after surgery and outcome assessment	Intervention (ITT/mITT)	Control (ITT/mITT)	Outcomes	
						Clinical	Endoscopic
				– concomitant mesalamine, 9.1% or immunomodulator, 36.4%; N=11 (ITT), 11 (mITT)	– concomitant mesalamine, 53.8%; N=13 (ITT), 13 (mITT)		
Anti-TNF v. Immunomodulator (v. Mesalamine)							
Armuzzi, ³⁵ 2013	SC, OL	Italy; 2007–11	<4 weeks; 12 months	Infliximab 5 mg/kg at 0, 2 and 6 weeks, followed by q8 weeks, for 12 months; N=11 (ITT), 11 (mITT)	Azathioprine 2–2.5 mg/kg/day, for 12 months; N=11 (ITT), 10 (mITT)	HBI score >7	i2-4, Rutgeerts score
Savarino, ⁸ 2013	SC, OL, triple-arm trial	Italy; 2008–10	<4 weeks; 12 months	Adalimumab 160 mg at week 0, 80 mg at week 2, followed by 40 mg q2 weeks, for 24 months; N=16 (ITT), 16 (mITT)	1 Azathioprine 2 mg/kg/day, for 24 months; N=17 (ITT), 17 (mITT) 2 Pentasa 3 g/day, for 24 months; N=18 (ITT), 18 (mITT)	CDAI >200 or using non-validated, 4-point severity scale	i2-4, Rutgeerts score
Anti-TNF + Mesalamine v. Mesalamine							
Yoshida, ³⁹ 2012	SC, OL, no placebo group	China; 2007–11	<4 weeks; 12 months	Infliximab 5 mg/kg q8 weeks, for 36 months AND mesalamine 1.5 g/day, for 36 months; N=16 (ITT), 15 (mITT)	Mesalamine 1.5 g/day, for 36 months; N=16 (ITT), 16 (mITT)	CDAI >150	i2-4, Rutgeerts score

CDAI, Crohn's Disease Activity Index; DB, double-blind; HBI, Harvey-Bradshaw index; ITT, intention-to-treat; mITT, modified intention-to-treat; MC, multicenter; NR, not reported; PC, placebo-controlled; OL, open-label; RCT, randomized controlled trial; SC, single center; TNF, tumor necrosis factor

Table 2

Pooled relative risk of **clinical relapse** based on combined direct and indirect evidence from Bayesian network meta-analysis (first row) and from direct evidence from standard pair-wise meta-analysis (second row) with different pharmacological interventions in patients after surgical resection for Crohn's disease. The column treatment is compared with the row treatment (i.e., row treatment is reference for each comparison). Numbers in parentheses indicate 95% credible interval (for Bayesian network meta-analysis) and 95% confidence interval (for standard pair-wise meta-analysis).

Placebo	0.93 (0.40, 1.84) 0.92 (0.60, 1.42)	0.60 (0.37, 0.88) 0.75 (0.62, 0.91)	0.26 (0.08, 0.61) 0.32 (0.14, 0.75)	0.36 (0.17, 0.63) 0.68 (0.49, 0.94)	0.11 (0.02, 0.41) -	0.04 (0.00, 0.14) 0.12 (0.01, 1.87)	0.43 (0.02, 1.94) -
Budesonide		0.61 (0.28, 1.61) -	0.21 (0.07, 0.92) -	0.35 (0.14, 1.05) -	0.15 (0.02, 0.56) -	0.02 (0.00, 0.19) -	0.54 (0.03, 2.58) -
		5-ASA	0.45 (0.13, 1.15) -	0.61 (0.33, 1.02) 0.83 (0.54, 1.30)	0.20 (0.01, 0.84) -	0.07 (0.01, 0.23) 0.13 (0.02, 0.88)	0.72 (0.04, 3.07) -
			Antibiotics	1.82 (0.47, 4.80) -	0.48 (0.08, 1.46) 0.39 (0.11, 1.36)	0.20 (0.01, 0.84) -	2.17 (0.09, 10.98) -
			Immunomodulator monotherapy		0.34 (0.05, 1.20) 0.50 (0.05, 5.17)	0.11 (0.01, 0.40) 0.24 (0.02, 2.40)	1.28 (0.07, 5.86) -
					Immunomodulator + Antibiotics	0.14 (0.02, 3.57) -	7.07 (0.18, 38.21) -
						Anti-TNF monotherapy	26.18 (0.57, 175.40) 0.53 (0.11, 2.50)
							Anti-TNF + 5-ASA

5-ASA, 5-aminosalicylate; TNF, tumor necrosis factor.

Table 3

Pooled relative risk of **endoscopic relapse** based on combined direct and indirect evidence from Bayesian network meta-analysis (first row) and from direct evidence from standard pair-wise meta-analysis (second row) with different pharmacological interventions in patients after surgical resection for Crohn's disease. The column treatment is compared with the row treatment (i.e., row treatment is reference for each comparison). Numbers in parentheses indicate 95% credible interval (for Bayesian network meta-analysis) and 95% confidence interval (for standard pair-wise meta-analysis).

Placebo	0.79 (0.26, 1.81) 0.87 (0.68, 1.11)	0.67 (0.39, 1.08) 0.78 (0.57, 1.06)	0.41 (0.15, 0.92) 0.37 (0.18, 0.77)	0.33 (0.13, 0.68) 0.67 (0.45, 1.00)	0.16 (0.04, 0.48) -	0.01 (0.00, 0.05) 0.11 (0.02, 0.71)	0.08 (0.00, 0.34) -
Budesonide	0.79 (0.31, 2.78) -	0.79 (0.31, 2.78) -	0.42 (0.14, 2.00) -	0.35 (0.12, 1.54) -	0.27 (0.04, 0.96) -	0.005 (0.00, 0.08) -	0.13 (0.01, 0.61) -
	5-ASA	5-ASA	0.66 (0.21, 1.59) -	0.51 (0.22, 0.99) 0.77 (0.55, 1.08)	0.26 (0.05, 0.77) -	0.02 (0.00, 0.07) 0.04 (0.00, 0.60)	0.12 (0.01, 0.50) 0.33 (0.14, 0.78)
			Antibiotics	0.97 (0.26, 2.53) -	0.43 (0.10, 1.19) 0.63 (0.40, 1.01)	0.03 (0.00, 0.15) -	0.23 (0.01, 1.12) -
			Immunomodulator monotherapy	Immunomodulator monotherapy	0.54 (0.12, 1.59) 0.60 (0.23, 1.55)	0.04 (0.00, 0.14) 0.13 (0.03, 0.66)	0.27 (0.01, 1.23) -
					Immunomodulator + Antibiotics	0.03 (0.00, 0.49) -	0.74 (0.03, 3.72) -
						Anti-TNF monotherapy	18.53 (0.34, 107.20) -
							Anti-TNF + 5-ASA

5-ASA, 5-aminosalicylate; TNF, tumor necrosis factor.