



Original Article

Systematic Review and Network Meta-Analysis of Medical Therapies to Prevent Recurrence of Post-Operative Crohn's Disease

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Abstract

Background and Aims: Surgery is an important treatment for Crohn's disease [CD], but recurrence occurs in up to 80% of individuals post-operatively. The efficacy of several drugs to prevent post-operative recurrence has been studied in previous meta-analyses, but a number of randomized controlled trials [RCTs] have recently been published. We therefore performed an updated systematic review and network meta-analysis to investigate this issue.

Methods: We performed a comprehensive literature search through to July 2018 to identify RCTs investigating the endoscopic and clinical recurrence of CD at 12 months post-operatively. We performed a random-effects network meta-analysis to produce a pooled relative risk [RR] with 95% confidence intervals [CIs]. We ranked the treatments according to their P-score.

Results: We included 10 RCTs, containing 751 patients, in our primary analysis of endoscopic recurrence of CD at 12 months. Anti-tumour necrosis factor [TNF]- α therapies were significantly better than placebo, either alone [P-score 0.98, RR 0.13; 95% CI 0.04–0.39] or in combination with 5-aminosalicylates [5-ASAs] [P-score 0.81, RR 0.30; 95% CI 0.12–0.75], or 5-nitroimidazoles [P-score 0.75, RR 0.40; 95% CI 0.23–0.69]. Combination therapy with a thiopurine and 5-nitroimidazole was also more effective than placebo [P-score 0.59, RR 0.56; 95% CI 0.40–0.80], as was thiopurine monotherapy [P-score 0.31, RR 0.84; 95% CI 0.74–0.94]. However, neither 5-nitroimidazoles nor 5-ASAs alone were superior to placebo.

Conclusions: In network meta-analysis, anti-TNF- α therapies alone, or in combination, appear to be the best medications for preventing endoscopic post-operative recurrence of CD.

Key Words: Anti-TNF- α ; Crohn's disease; recurrence; prophylaxis

Abbreviations: ASA, aminosalicylic acid; CI, confidence interval; CD, Crohn's disease; GI, gastrointestinal; MeSH, medical subject heading; RCT, randomized controlled trial; RR, relative risk; TNF, tumour necrosis factor.

1. Introduction

Up to 80% of patients with Crohn's disease [CD] will require surgery at some point in their lives, and it is estimated that as many as 40% may need several surgeries.^{1,2} Indications for surgery include symptoms refractory to medical treatment, bowel obstruction, and fistula or abscess formation. The most common surgical procedure is intestinal resection. Although in many cases surgery may provide a prolonged period of disease control, it is unlikely to be curative, and the recurrence rate is high.³ Among patients who have undergone ileocaecal resection, which is the most common operation performed in CD, endoscopic recurrence rates are as high as 73% at 1 year and 85% at 3 years post-surgery.⁴ The risk of clinical recurrence defined as symptomatic disease is estimated to be 20–25% per year.⁵ There is a requirement for surgical re-intervention in up to 40% of individuals after 15 years.⁶

The efficacy of a number of drugs has been studied, as medical prophylaxis to reduce the rate of endoscopic and clinical recurrence following intestinal resection. These include 5-aminosalicylates [5-ASAs], thiopurines like azathioprine and mercaptopurine, anti-tumour necrosis factor [TNF]- α therapies, and 5-nitroimidazole antibiotics.^{7–9} Several previous meta-analyses of randomized controlled trials [RCTs] have estimated their relative efficacy in this situation, with three studies reporting a superiority for anti-TNF- α therapies over immunomodulators.^{10–12}

However, this particular patient cohort has inherent complexity, and the majority of patients coming to surgery will have either experienced intolerance to, or failure of, at least one drug regimen. Previous meta-analyses have focused on comparing one therapy with another,^{9,10} but in real-world clinical practice the choice is rarely as simple as immunomodulator therapy vs anti-TNF therapy in treatment-naïve populations. Network meta-analysis allows comparison of indirect evidence from clinical studies where head-to-head evidence is not available, or is inconclusive.¹³ It also allows ranking of treatments in order of efficacy.¹⁴ Previous network meta-analyses have been conducted examining this issue,¹⁵ but a number of important studies examining post-surgical prophylaxis have been published in the intervening years since these were conducted. For these reasons, we performed a contemporaneous systematic review and network meta-analysis to determine the effect of medical therapies in the prevention of the post-surgical recurrence of Crohn's disease.

2. Materials and Methods

The study was reported according to the extension to the Preferred Reporting Items for Systematic reviews and Meta-Analyses [PRISMA] guidelines update for network meta-analysis.¹⁶

2.1. Search strategy and study selection

A comprehensive search of the literature was performed to July 2018. Full details of the search are included in the [Supplementary Data](#).

Studies included in this meta-analysis were RCTs recruiting adults [age \geq 16 years] with established CD, and with a history of intestinal resection. The intervention had to be an established drug, or a combination of established drugs, for the management of post-operative prophylaxis of CD, including 5-ASAs, antibiotics, immunomodulators, anti-TNF- α therapies, or any combination thereof, started within 3 months of surgery. The comparator could be another established drug, or placebo. Our primary outcome of interest was endoscopic recurrence of CD at 12 months after the initial resection.

A Rutgeerts score of \geq i2 was used to define endoscopic recurrence, as this has been shown to be associated with an increased need for subsequent surgery or an escalation of medical therapy.² Clinical recurrence, as defined by study investigators, was used as a secondary outcome measure. There are a variety of different clinical scores available, but these may not be an accurate assessment of mucosal inflammation.¹⁷ In addition we also performed an analysis to assess the overall safety of each medication by pooling the adverse events that necessitated ceasing the study medication.

We excluded RCTs in which prophylactic medication was commenced after endoscopic recurrence of CD had already been established, or beyond 12 months post-surgery; trials comparing different doses of the same medication, without an alternative intervention or comparator arm; and trials in which subclinical relapse was defined based only on radiological evidence.

2.2. Assessment of risk of bias

Risk of bias was assessed as described in the Cochrane handbook.¹⁸ Data extraction and bias assessments were performed independently by two investigators, with any disagreement being resolved by consensus with the research team.

2.3. Data analysis

We produced a network plot to summarize the treatments and RCTs included, and visually inspected the geometry and symmetry of the evidence. We then performed a network meta-analysis using a frequentist setting, and a random effects model as a conservative estimate. A network meta-analysis combines direct evidence in head-to-head studies with indirect evidence linking treatments that may not have been directly compared.¹³ We ranked the treatments in order of the probability of being the most effective treatment with a P-score, using the R package Netmeta.¹⁴ The P-score is a value between 0 and 1, with a higher score indicating a greater probability of the treatment being ranked as best.¹⁴ We produced forest plots of the active treatments versus placebo, displaying the relative risk [RR] and 95% confidence intervals [CIs] for our primary and secondary outcome measures. We then produced league tables to display the combined direct and indirect evidence from each treatment comparison in the network meta-analysis. Global statistical heterogeneity was assessed using the I^2 statistic. The I^2 measure ranges between 0% and 100%. Values of 25–49%, 50–74%, and \geq 75% are typically considered low, moderate, and high levels of heterogeneity, respectively.¹⁹ We assessed inconsistency in the network analysis by comparing direct and indirect evidence, where available, by producing a network heat plot.^{20,21} These plots have grey squares that represent the size of the contribution of the direct estimate in columns compared with the network estimate in rows.²¹ The coloured squares, around these, represent the degree of inconsistency, with red squares indicating 'hotspots' of inconsistency. In order to investigate sources of potential inconsistency, we planned to remove studies that introduced any red 'hotspots,' and repeat the analyses. We produced a comparison adjusted funnel plot to explore publication bias for all available comparisons, versus placebo, using Stata version 14 [Stata Corp., College Station, TX, USA]. Symmetry around the effect estimate line indicates the absence of publication bias, or small study effects.²²

2.4. Sensitivity analyses

We performed a series of pre-specified sensitivity analyses. First, we repeated the primary analysis for clinical and endoscopic recurrence

using the per-protocol results from each study, where available. Second, we excluded those studies with a high risk of bias. Third, we included only studies performed after the year 2000, in order to try and account for potential changes in disease management, patient-related behaviours, and phenotypes of CD over time. We repeated our primary analyses using a Bayesian model using WinBUGS and the visual basic Microsoft Excel package NetMetaXL.²³ Again, we used a random effects model and ranked the treatments, in this model using the surface under the cumulative ranking curve [SUCRA] value, which is equivalent to the P-score used in the frequentist model.¹⁴

3. Results

The search strategy generated 2753 citations, of which, 124 were deemed relevant to the systematic review. Following further review of abstracts and papers, 15 RCTs were included in the network meta-analysis (Table 1).^{24–37} Details of the study selection are shown in Figure 1. One study was only published in letter form.²⁹ We excluded several trials that did not report recurrence at 12 months.^{7,38,39} Risk of bias of each included study is shown in Supplementary Figures 1 and 2. Seven studies were at low risk of bias.^{26,28,30,31,34–36}

3.1. Endoscopic recurrence at 12 months post-operation according to a Rutgeerts score of ≥ 2

We included 10 studies reporting on 751 patients in our primary analysis [Supplementary Table 1].^{26,28,30–37} The network plot illustrating the number of randomized subjects allocated to each treatment, and the studies investigating each treatment comparison, are shown in Figure 2. Placebo and thiopurine monotherapy had both the most patients, and study comparisons in the network. Anti-TNF- α combination therapies with either 5-ASA or 5-nitroimidazole were the least connected treatments, with only one study each.^{32,37} There was no global statistical heterogeneity [$I^2 = 0\%$]. The network heat plot had no red 'hotspots' of inconsistency [Supplementary Figure 3]. The comparison adjusted funnel plot only included five placebo-controlled trials, so we could not exclude publication bias, or other small study effects [Supplementary Figure 4].

Anti-TNF- α monotherapy was ranked as the most effective treatment [P-score 0.98] [Figure 3], and was significantly more effective than placebo [RR 0.13; 95% CI 0.04–0.39], 5-ASA monotherapy [RR 0.14; 95% CI 0.04–0.43], thiopurine monotherapy [RR 0.15; 95% CI 0.05–0.46], 5-nitroimidazole monotherapy [RR 0.15; 95% CI 0.05–0.49], and thiopurine and 5-nitroimidazole combination therapy [RR 0.22; 95% CI 0.07–0.72] [Table 2]. Anti-TNF- α in combination with 5-ASAs [P-score 0.81; RR 0.30; 95% CI 0.12–0.75], anti-TNF- α in combination with a 5-nitroimidazole [P-score 0.75; RR 0.40; 95% CI 0.23–0.69], a thiopurine in combination with a 5-nitroimidazole [P-score 0.59; RR 0.56; 95% CI 0.40–0.80], and thiopurine monotherapy [P-score 0.31; RR 0.84; 95% CI 0.74–0.94] were also more effective than placebo. 5-nitroimidazole and 5-ASA monotherapy were no more effective than placebo. On indirect comparison, anti-TNF- α monotherapy was more effective than all other medications, apart from combination therapy with either 5-ASA or 5-nitroimidazole. Combination therapy with anti-TNF- α and 5-ASA, anti-TNF- α , and 5-nitroimidazole, and combination therapy with thiopurines and 5-nitroimidazole were significantly better than monotherapy with 5-nitroimidazole, thiopurines, or 5-ASA [Table 2].

We explored the modified intention-to-treat data from each study, where available, due to high proportions of individuals not

attending for subsequent colonoscopic evaluation. This analysis included 10 studies reporting on 589 patients.^{26,28,30–37} There was no global statistical heterogeneity [$I^2 = 0\%$]. Anti-TNF- α monotherapy was again ranked as the best treatment [P-score 0.98], and was significantly more effective than placebo. Anti-TNF- α in combination with a 5-ASA or a 5-nitroimidazole, thiopurine monotherapy, and a thiopurine in combination with a 5-nitroimidazole were also more effective than placebo. Again 5-nitroimidazole and 5-ASA monotherapy were not significantly better than placebo, with 5-ASA being the worst performing drug [P-score 0.20] [Supplementary Figure 5]. Following indirect comparison, anti-TNF- α monotherapy was significantly more effective than a thiopurine and a 5-nitroimidazole combined, 5-nitroimidazole monotherapy, thiopurine monotherapy, and 5-ASA monotherapy.

After excluding studies with a high risk of bias, there were seven studies reporting on 614 patients.^{7,26,28,30,34–36} There was no global statistical heterogeneity [$I^2 = 0\%$]. Anti-TNF- α monotherapy was ranked as the best treatment [P-score = 1.00]. Thiopurine monotherapy, or in combination with 5-nitroimidazole, was also significantly better than placebo [Supplementary Figure 6]. When excluding studies performed since the year 2000, there were nine studies involving 665 patients,^{7,28,30,32–37} and no global statistical heterogeneity [$I^2 = 0\%$]. Anti-TNF- α monotherapy was again ranked as the most effective treatment [P-score 0.98] and, when in combination with either a 5-nitroimidazole or a 5-ASA, was also more effective than placebo. Thiopurines, either in combination with a 5-nitroimidazole, or as monotherapy were also more effective than placebo [Supplementary Figure 7].

We repeated the primary analysis using a Bayesian model. The results were similar, using the SUCRA instead of the P-score from the frequentist model. Anti-TNF- α remained ranked first, with combinations including anti-TNF- α remaining in the first three positions [Supplementary Table 1].

3.2. Clinical recurrence at 12 months post-operation

We included 13 studies, reporting on 898 randomized patients, in this analysis [Supplementary Table 2].^{24–33,35–37} The network plot illustrating the number of studies and comparisons is provided in Supplementary Figure 8. Global statistical heterogeneity was low [$I^2 = 42\%$]. The network heat plot showed no red 'hotspots' of inconsistency [Supplementary Figure 9]. Combination therapy with anti-TNF- α and a 5-nitroimidazole was ranked as the most effective treatment [P-score 0.97], and was significantly more effective than placebo [RR 0.06; 95% CI 0.01–0.42]. Thiopurine and 5-nitroimidazole combination therapy, anti-TNF- α monotherapy, and 5-nitroimidazole monotherapy were also more effective than placebo [Supplementary Figure 10]. The results of the indirect comparisons are shown in Table 3.

3.3. Pooled adverse events

We included 14 studies, reporting on 831 randomized patients in this analysis.^{24,26–33,35–37} Global statistical heterogeneity was low [$I^2 = 29\%$]. Only 5-nitroimidazole monotherapy was significantly worse than placebo, with all other interventions having confidence intervals that crossed the line of no effect [Supplementary Figure 11].

4. Discussion

This systematic review and network meta-analysis has shown that anti-TNF- α agents used alone, or in combination with a 5-nitroimidazole

Table 1. Characteristics of included studies.

Study	Geographical location	Patient group studied	Number of patients [% female]	Drug, dosage, schedule, and duration of therapy	Criteria used to define Endoscopic relapse	Criteria used to define clinical relapse
Lennard-Jones, 1977 ²⁴	UK	CD patients after ileum and/or colonic resection. Unselected.	35 [not reported]	Sulfasalazine 1g t.i.d. versus placebo	Rutgeerts ≥ 2 not reported	Clinician-determined
Wenckert 1978 ²⁵	Europe	CD patients after ileum and/or colonic resection. Unselected.	66 [50]	Salazosulphapyridine 3 g per day versus placebo	Rutgeerts ≥ 2 not reported	Clinician-determined
Brignola, 1995 ²⁶	Italy	CD patients after terminal ileal or ileocaecal resection. Unselected.	87 [48]	Mesalazine [Pentasa] 1g t.i.d. or placebo	Rutgeerts score of ≥ 2	Either an increase in CDAI by 100, or total score >150
Rutgeerts, 1995 ²⁷	Belgium	CD patients after terminal ileal or ileocaecal resection. Unselected.	60 [not reported]	Metronidazole 1 g o.d. extra 250 mg per 10 kg weight increase [3 months] versus placebo.	Rutgeerts ≥ 2 not reported	Clinician-determined
Herfarth, 2006 ²⁹	Germany	CD patients. Unspecified disease location. Unselected.	37 [not reported]	Azathioprine 2–2.5 mg/kg/day versus mesalazine 4 g o.d.	Rutgeerts ≥ 2 not reported	Clinical recurrence, not defined
Rutgeerts, 2005 ²⁸	Belgium	CD patients after terminal ileal or ileocaecal resection. Unselected.	80 [54]	Ornidazole 500 mg b.i.d. versus placebo for 54 weeks	Rutgeerts score of ≥ 2	CDAI >250
D'Haens, 2008 ³⁰	Belgium	CD patients after terminal ileal or ileocaecal resection. Unselected.	81 [46]	Azathioprine 100 mg [<60 kg] or 150 mg [>60 kg] o.d. and metronidazole 750 mg o.d. [for 3 months] versus placebo and metronidazole 750 mg [for 3 months]	Rutgeerts score of ≥ 2	CDAI >250
Regueiro, 2009 ³¹	USA	CD patients after terminal ileal or ileocaecal resection. Unselected.	24 [46]	Infliximab 5 mg/kg at 0, 2, 6 and then 8-weekly versus identical placebo infusions for 54 weeks.	Rutgeerts score of ≥ 2	CDAI >200
Yoshida, 2012 ³²	Japan	CD patients after terminal ileal or ileocaecal resection. Unselected.	31 [26]	Infliximab 5 mg/kg at 0, 2, 6, and then 8-weekly and mesalazine [Pentasa] 2.25 g/day versus mesalazine [Pentasa] 2250 mg/day	Rutgeerts score of ≥ 2	CDAI >150
Armuzzi, 2013 ³³	Italy	CD patients after ileocolonic resection	22 [50]	Infliximab 5 mg/kg at 0, 2, 6, and then 8-weekly versus azathioprine 2.5 mg/kg. Both groups received metronidazole 500 mg b.i.d. [for 2 weeks].	Rutgeerts score of ≥ 2	Harvey–Bradshaw index score >7
Savarino, 2013 ³⁵	Italy	CD patients after terminal ileal or ileocaecal resection. Unselected.	51 [49]	Adalimumab 160/80 mg at 0 and 2 weeks, then 40 mg fortnightly, versus azathioprine 2 mg/kg/day versus mesalazine 3 g o.d.	Rutgeerts score of ≥ 2	CDAI >200 .
Manosa, 2013 ³⁴	Spain	CD patients after terminal ileal or ileocaecal resection. Unselected.	50 [not reported]	Azathioprine 2–2.5 mg/kg/day and metronidazole 15–20 mg/kg [for 3 months], azathioprine 2–2.5 mg/kg/day and placebo [for 3 months]	Rutgeerts score of ≥ 2	Not applicable
Mowat, 2016 ³⁶	Multinational	CD patients with ileocolic or small bowel resection.	240 [60]	6-mercaptopurine 1 mg/kg/day versus placebo	Rutgeerts score of ≥ 2	CDAI >150 and at least a 100 point increase from baseline
Lopez-Sanroman, 2017 ³⁷	Spain	CD patients after ileocolonic resection	85 [50]	Adalimumab 160 mg at 0 weeks, 80 mg at 2 weeks, and then 40 mg fortnightly versus azathioprine 2.5 mg/kg/day	Rutgeerts score of ≥ 2	CDAI >200

CD, Crohn's disease; CDAI, Crohn's disease activity index.

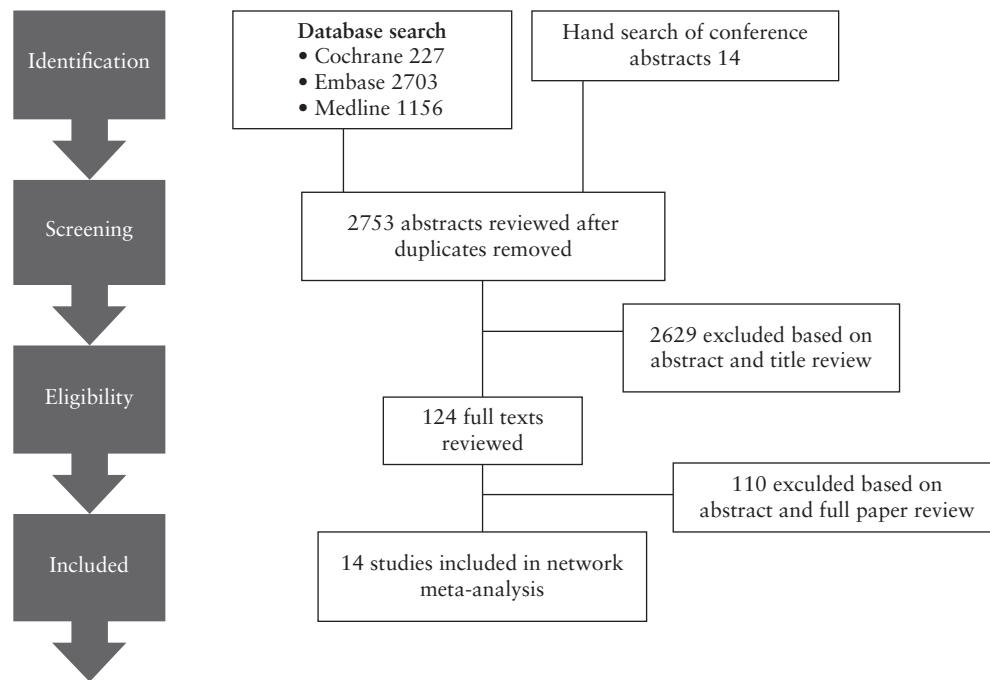


Figure 1. Flow diagram of search strategy and included studies.

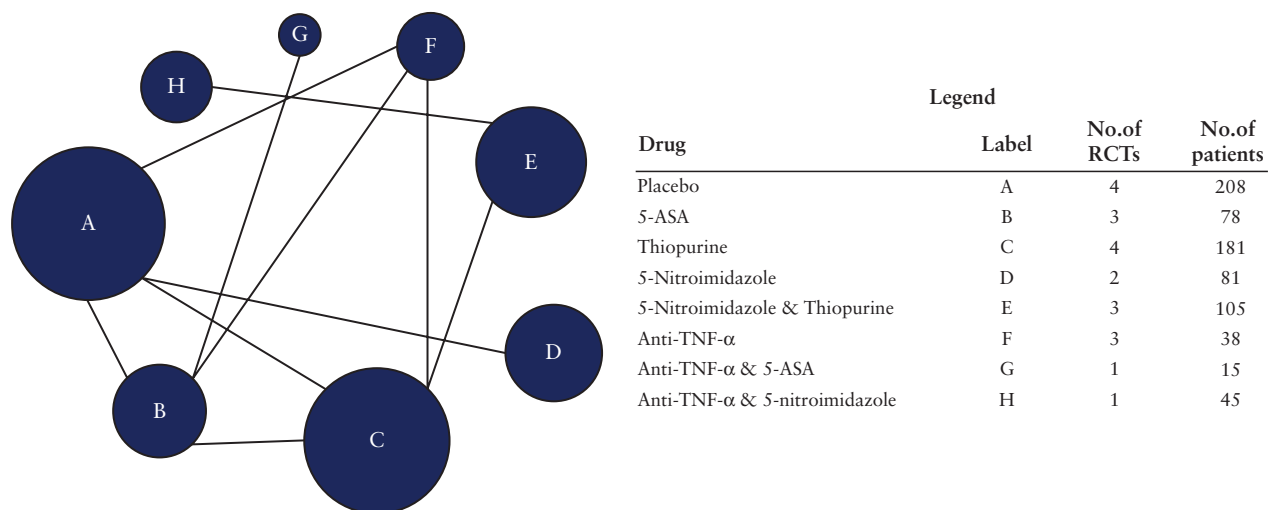


Figure 2. Network plot of studies included in the primary analysis. The nodes correspond to the number of patients included in the network, and the thickness of the connecting lines corresponds to the number of trials between comparators.

or 5-ASA medication are the most effective in preventing endoscopic recurrence of CD post-operatively. Thiopurine medications used alone, or in combination with 5-nitroimidazoles were also more effective than placebo, but did not rank highly on our indirect comparisons of the available therapies. Anti-TNF- α therapy, either alone or in combination with a 5-ASA, were consistently ranked as the most effective therapies in sensitivity analyses based on our primary end point, and was also significantly more effective than placebo, thiopurines, or 5-ASA for our secondary outcome of clinical recurrence at 12 months post-surgery. 5-nitroimidazole or 5-ASA monotherapies were no better than placebo. Finally, adverse events, necessitating the withdrawal of therapy, were only significantly more frequent with 5-nitroimidazole monotherapy compared with placebo.

We performed an extensive review of the available evidence in order to identify 14 RCTs investigating the prevention of endoscopic, or clinical, recurrence of CD at 12 months post-operatively. Our primary end point was endoscopic recurrence at the surgical anastomosis, as this is robust and reproducible. Previous analyses have concentrated on clinical recurrence. However, although this may lead to increased health-care utilization, it does not correlate well with disease activity,¹⁷ and would not necessarily warrant escalation in therapy alone. We used strict inclusion criteria, as it is important to maintain transitivity within a network analysis, only combining data with clinical and methodological homogeneity.⁴⁰ We used a rigorous study end point, including only those studies that reported a Rutgeerts score of ≥ 2 at 12 months, in order to allow

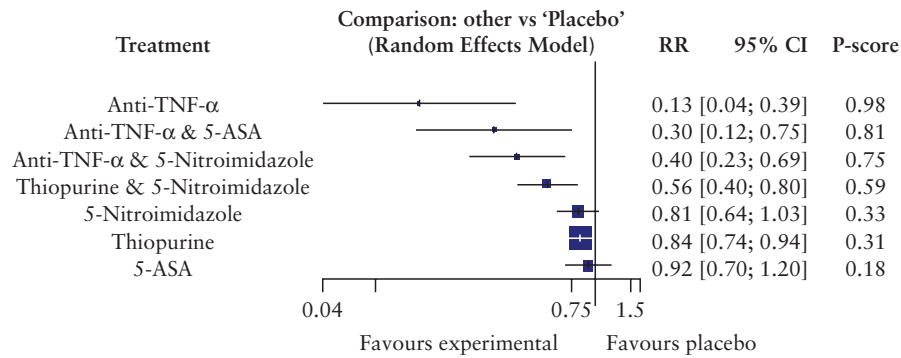


Figure 3. Forest plot displaying the network meta-analysis results of treatments versus placebo for prevention of endoscopic recurrence of Crohn's disease 12 months post-operation. The P-score [between 0 and 1, the higher the better] is the probability of the treatment being ranked 'best' in the network meta-analysis.

Table 2. League table showing the efficacy of treatments for prevention of endoscopic recurrence of Crohn's disease at 12 months post-operation, defined as a Rutgeerts score of ≥ 2 .

Anti-TNF-α											
0.42 [0.10; 1.74]	Anti-TNF-α and 5-ASA										
0.32 [0.09; 1.10]	0.76 [0.26; 2.19]	Anti-TNF-α and 5-Nitroimidazole									
0.22 [0.07; 0.72]	0.53 [0.20; 1.41]	0.70 [0.46; 1.08]	Thiopurine and 5-Nitroimidazole								
0.15 [0.05; 0.49]	0.37 [0.14; 0.95]	0.49 [0.29; 0.82]	0.70 [0.52; 0.93]	5-Nitroimidazole							
0.15 [0.05; 0.46]	0.36 [0.14; 0.90]	0.47 [0.27; 0.83]	0.67 [0.47; 0.96]	0.97 [0.74; 1.26]	Thiopurine						
0.14 [0.04; 0.43]	0.33 [0.14; 0.78]	0.43 [0.24; 0.79]	0.62 [0.40; 0.95]	0.88 [0.62; 1.26]	0.91 [0.70; 1.19]	5-ASA					
0.13 [0.04; 0.39]	0.30 [0.12; 0.75]	0.40 [0.23; 0.69]	0.56 [0.40; 0.80]	0.81 [0.64; 1.03]	0.84 [0.74; 0.94]	0.92 [0.70; 1.20]	Placebo				

Note: Combined direct and indirect evidence. The treatments are shown in relative ranking of efficacy. The treatment in the top-left position is considered 'best', and shaded boxes represent statistically significant comparisons. The comparisons should be read from left to right.

like-for-like comparisons in our analyses. We feel that it is essential that when studies are combined in a network meta-analysis they should have identical end points and duration to minimize bias. This meant that the 2016 study by Regueiro et al.⁷ comparing infliximab and placebo was excluded, as recurrence at 19 months was reported. This study reported similar results to our primary analysis with significant benefit for anti-TNF-α [infliximab] compared with placebo for the prevention of endoscopic recurrence.

We could not assess for evidence of publication bias via our comparison-adjusted funnel plots, but there were no 'hotspots' of inconsistency between direct and indirect evidence from our heat plots. All studies were randomized trials, included patients after a primary resection for Crohn's disease, and had comparable characteristics at baseline, justifying their synthesis in a network meta-analysis. Statistical heterogeneity was low for our primary and secondary analyses.

There were several limitations of this study. Although we included 751 patients in our primary analysis, there was only one study, randomizing 15 patients, investigating the efficacy of anti-TNF-α and 5-ASA combination therapy.³² Similarly there was only one treatment node for combination treatment with anti-TNF-α and 5-nitroimidazole. This made the network sparse. There were only 38 patients, randomized in three trials, investigating anti-TNF-α monotherapy therapies.^{31,33,35} The relatively small number of patients in each treatment arm resulted in wide confidence intervals in some instances, notably for our secondary outcome measure of clinical recurrence. All of the studies were conducted in secondary care, although patients will almost certainly be managed in this setting after a resection.

Combination therapy with an anti-TNF-α and a thiopurine is better than with either medication alone in both inducing and maintaining remission in moderate to severe CD.⁴¹ It is therefore surprising that no RCT, to date, has used this combination therapy in a post-operative cohort. There is some evidence from retrospective studies that combination therapy with anti-TNF-α therapy and immunomodulator medication led to significantly better prevention of post-operative recurrence.^{4,42} We did not identify any eligible trials comparing different anti-TNF-α medications that met our inclusion criteria. There has been one study comparing infliximab and adalimumab, but this included a highly selected patient group, and was excluded from our meta-analysis.⁴³ In this RCT, both intervention groups were given a short, 2-week course of metronidazole, and participants were selected to be those at high risk of recurrence with the presence of two known risk factors for CD recurrence. There was no significant difference in rates of endoscopic recurrence at 12 months [$p = 0.10$], with 3 out of 20 patients overall receiving either drug reaching this end point. Further evidence is therefore needed to guide selection of a specific anti-TNF-α therapy in this situation, and we suggest prescription according to local policies when considering which anti-TNF-α to commence post-operatively as part of conventional care.

We found no significant benefit of 5-ASA or 5-nitroimidazole for preventing endoscopic recurrence at 12 months. This is an important finding as current European Crohn's and Colitis Organisation⁴⁴ and American College of Gastroenterology guidelines advocate both treatments for low-risk patients, albeit as a conditional recommendation with a low level of evidence.⁴⁵ A previous meta-analysis

Table 3. League table showing the efficacy of treatments for prevention of clinical recurrence of Crohn's disease at 12 months post-operation.

Anti-TNF- α and 5-Nitroimidazole 0.41 [0.15; 1.15]	Thiopurine and 5-Nitroimidazole 0.22 [0.02; 2.20]	Anti-TNF- α 0.18 [0.03; 1.06]	5-Nitroimidazole 0.09 [0.01; 1.26]	Anti-TNF- α and 5-ASA 0.06 [0.01; 0.42]	Placebo 0.05 [0.01; 0.41]	Thiopurine 0.05 [0.01; 0.37]	5-ASA 0.14 [0.03; 0.76]	0.27 [0.08; 0.89]	0.32 [0.13; 0.80]	0.65 [0.11; 3.78]	0.90 [0.52; 1.58]	0.91 [0.56; 1.46]
		0.44 [0.10; 1.84]	0.21 [0.02; 2.47]	0.24 [0.08; 0.76]	0.29 [0.10; 0.84]	0.22 [0.07; 0.71]	0.26 [0.09; 0.75]	0.53 [0.10; 2.84]	0.82 [0.48; 1.41]			

Note: Combined direct and indirect evidence. The treatments are shown in relative ranking of efficacy. The treatment in the top-left position is considered 'best' and shaded boxes represent statistically significant comparisons. The comparisons should be read from left to right. Clinical recurrence was defined as per the individual study criteria.

found a significant benefit of 5-ASA preparations versus placebo [RR 0.86; 95% CI 0.74–0.99], but this study did not use identical end points in each of the included trials, which may explain the difference in the efficacy of 5-ASAs in our analyses.⁹

It is important to try and individualize treatment for those with CD, and there will be a proportion of patients who do not experience a relapse post-operatively, despite not being on any prophylaxis therapy. The placebo response rate for the prevention of endoscopic recurrence in the RCTs included in this meta-analysis ranged from 13%³⁶ to 46%.³¹ It was beyond the remit of this meta-analysis, and the individual trials included within it, to try to determine aetiological factors that may predict relapse. Risk factors for relapse reported in previous observational studies include young age at presentation, penetrating phenotype, smoking,^{46,47} and the presence of adherent *Escherichia coli* bacteria at the resection margins.⁴⁸ A recent prospective cohort study found that penetrating disease behaviour was an independent predictor of recurrence, and post-operative anti-TNF- α agents were significantly more likely to prevent endoscopic [$p < 0.001$] and clinical [$p = 0.018$] relapse.⁴⁹ A sub-group analysis from the TOPPIC trial,³⁶ which was included in this meta-analysis, found that thiopurine therapy only appeared to be significantly more effective than placebo in smokers.

This issue is an important one. In clinical practice most gastroenterologists adopt a pragmatic approach, weighing the benefits of prophylaxis against the risks of adverse events from, and the costs of, therapy.⁵⁰ A cost-effectiveness analysis reported that thiopurine drugs had the most favorable incremental cost-effectiveness ratio [ICER] in the prevention of clinical recurrence up to 1 year post-surgery, and mesalazine the most favorable ICER at 5 years.⁵¹ Anti-TNF- α agents, which we have shown in this study to be the most efficacious, in terms of their ability to reduce endoscopic recurrence at 12 months, were the least cost-effective, with an ICER per quality-adjusted life-year of \$1.9 million. Published guidelines from major professional societies have been inconsistent in their recommendations concerning postoperative prophylaxis. The American College of Gastroenterology recommends prophylactic treatment after small intestinal resection in patients with risk factors for recurrence, and specifically that anti-TNF agents should be started within 4 weeks of surgery in high-risk patients, combined with an immunomodulator to decrease immunogenicity and decrease loss of response, although the lack of data to support combination therapy is acknowledged.⁴⁵ The European Crohn's and Colitis Organisation recommends prophylactic treatment after small intestinal resection, and favours thiopurines over both 5-ASAs and 5-nitroimidazole

antibiotics,⁴⁴ but the British Society of Gastroenterology does not endorse this view.⁵² The guidelines are, however, consistent on advising close follow-up, with endoscopic evaluation recommended within 1 year of surgery. Beyond this time frame, there are a range of possible approaches for monitoring disease activity, including repeated endoscopic evaluation, wireless capsule endoscopy, or via biomarkers, with some evidence that faecal calprotectin performs better than C-reactive protein in this setting.⁵³ Future trials should address the benefits of planned prophylactic therapy against a more reactive algorithm, based on the results of planned endoscopic assessments. Data on longer term follow-up beyond a year is also required, because it remains unclear how long prophylactic therapy is required for.

We have shown that anti-TNF- α therapy provided the greatest protection against post-operative recurrence of CD. Despite this, we would not advocate universal treatment, and medical therapy needs to be targeted at those most at risk. Information from large-scale prospective studies or robust large-scale retrospective analyses is urgently required to identify those patients with Crohn's disease at highest risk of recurrence post-surgery.

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Conflict of Interest

Nicholas E. Burr: Has received speaker fees and travel grants from Abbvie. Barry Hall: Has received speaker fees from Abbvie. John Hamlin: Has received speaker or advisory board fees from AbbVie, Merck Sharp Dome, Ferring, Janssen, Otsuka, Tillots, and Schering Plough. Christian P Selinger: Has received speaker or advisory board fees from Warner Chilcott, AbbVie, Dr FALK Pharma, Janssen, Merck Sharp Dome, and Takeda. Alexander C. Ford: Has received speaker fees from Merck Sharp Dome and Shire. Anthony O'Connor: None.

Author Contributions

NEB, AOC, and ACF conceived the study. NEB, BH and AOC extracted and analysed the data. All authors commented on drafts of the manuscript and approved the final version.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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