Comparative Efficacy of Anti-TNF Therapies For The Prevention of Postoperative Recurrence of Crohn's Disease

A Systematic Review and Network Meta-Analysis of Prospective Trials

Ziad Bakouny, MSc, Fares Yared, MSc,* Elie El Rassy, MD, MSc,† Rita Jabbour,* Rachel Hallit, MD,* Nathalie Khoury, MD,* Khalil Honein, MD,* and Joseph Bou Jaoude, MD**

Introduction: There is a lack of studies on the optimal anti–tumor necrosis factor (anti-TNF) agent for postoperative prophylaxis of Crohn's disease (CD) recurrence. Therefore, we conducted a network meta-analysis (NMA) of prospective trials to compare the efficacy of anti-TNF agents in the prevention of postoperative endoscopic and clinical recurrence of CD following ileocolonic resection.

Methods: We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and recent American gastroenterology association (AGA) meeting abstracts through August 2017. We selected prospective studies comparing anti-TNF agents among each other or to other agents in the setting of postoperative prevention of CD recurrence. We performed a NMA using a frequentist approach with generalized pairwise modeling and inverse variance heterogeneity method.

Results: We identified 9 studies, including 571 patients and 5 treatment agents, among which 2 anti-TNF drugs (adalimumab and infliximab). Compared with infliximab, our NMA yielded the following results for endoscopic recurrence: adalimumab [odds ratio (OR), 0.92; 95% confidence interval (CI), 0.18-4.75], thiopurines (OR, 4.11; 95% CI, 0.68-24.78), placebo (OR, 4.39; 95% CI, 0.70-27.68), and Mesalamine (OR, 37.84; 95% CI, 3.77-379.42). For clinical recurrence: adalimumab (OR, 1.03; 95% CI, 0.17-6.03), thiopurines (OR, 1.40; 95% CI, 0.20-10.02), placebo (OR, 1.77; 95% CI, 1.01-3.10), and mesalamine (OR, 16.54; 95% CI, 1.55-176.24).

Conclusions: On the basis of a NMA combining direct and indirect evidence either adalimumab or infliximab may be used in the postoperative prophylaxis of CD recurrence. There is currently a lack of evidence on the use of other anti-TNF agents in this setting.

Key Words: network meta-analysis, systematic review, anti-TNF, infliximab, adalimumab, Crohn's disease, postoperative, ileocolonic resection, recurrence prevention

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From the Departments of *Gastroenterology; and †Oncology, Hotel Dieu de France University Hospital, Faculty of Medicine, Saint Joseph University, Lebanon.

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The authors declare that they have nothing to disclose.

Address correspondence to: Fares Yared, MSc, Faculty of Medicine, University of Saint Joseph, Ashrafieh, 11-5076, Beirut, Lebanon (e-mail: yaredfares@gmail.com).

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Crohn's disease (CD) is a chronic inflammatory disorder of the bowel that may affect any part of the gastrointestinal tract and can lead to severe tissue damage.[1] CD is responsible for a substantial economic burden, as it frequently occurs in young patients.[2] Up to three-quarters of CD patients require surgical resection for penetrating and stricturing complications,[3] with ileocolonic resection being the most common therapeutic intervention for such complications.[1]

However, surgery is not curative and often CD patients develop clinical and endoscopic recurrence within 5 years of resection in up to 41% and 89%, respectively.[4] Multiple studies have examined the efficacy of traditional drugs in the prevention of postsurgical recurrence of CD, with conflicting results.[5–8]

Because of the efficacy of biological therapy in the induction and maintenance of moderate to severely active CD, multiple studies have been conducted to examine the efficacy of anti–tumor necrosis factor (anti-TNF) agents in preventing postoperative recurrence in CD. Both infliximab and adalimumab were in fact shown to be superior to conventional therapy and placebo in preventing postoperative recurrence.[9–17] Moreover, 3 recent meta-analyses[18–20] have concluded that anti-TNF agents are more effective than conventional treatment in the prevention of postoperative clinical and endoscopic recurrence.

However, there are few studies comparing the efficacy of different anti-TNF agents for the prevention of postoperative recurrence in CD,[14] and there is currently no conclusive evidence of the superiority of either treatment in this setting. Therefore, we conducted a network meta-analysis (NMA) of prospective trials to compare the efficacy of anti-TNF agents in the prevention of postoperative endoscopic and clinical recurrence of CD following ileocolonic resection.

METHODS

This study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. No previously published protocol exists for the current NMA.

Study Selection

Studies included in this NMA met the following criteria: (a) patients: adults aged 18 years or above diagnosed with CD who have had surgical resection of small bowel and/or colon with complete removal of macroscopically visible disease (either as a first-time resection or repeat

resection). (b) Intervention: biological anti-TNF agents including infliximab, adalimumab, certolizumab pegol, golimumab, and etanercept which had been started a maximum of 3 months after surgery. (c) Comparator: any anti-TNF or non–anti-TNF active agent, absence of intervention, or placebo. (d) Outcome: endoscopic and/or clinical recurrence of CD following surgery (with a minimum of 6 mo of follow-up), as well the rate of medication discontinuation due to adverse events. (e) Study design: prospective interventional comparative randomized/nonrandomized trials. The following studies were excluded from this NMA: review, retrospective, noncomparative, or observational studies and studies investigating the treatment of CD postoperative recurrence with anti-TNF agents.

Data Sources

PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and recent American gastroenterology association (AGA) meeting abstracts (from 2015 onwards) were searched for English and non-English reports of studies that investigated the efficacy of anti-TNF biological treatments in the prevention of postoperative recurrence of CD after ileocolonic resection. Databases were searched from inception until the August 4, 2017. The article search was established in order to compare anti-TNF drugs through a NMA. Pubmed search terms were: (inflammatory bowel diseases[MeSH Terms]) OR (inflammatory bowel diseases) OR (crohn disease[MeSH Terms]) OR (crohn disease) AND (surgery) OR (postoperative) OR (recurrence) OR (recur*) AND (infliximab[Supplementary Concept]) OR (infliximab) OR (monoclonal antibody) OR (infliximab[Supplementary Concept]) OR (infliximab) OR (remicade) OR (adalimumab [Supplementary Concept]) OR (adalimumab) OR (certolizumab pegol[Supplementary Concept]) OR (certolizumab pegol) OR (golimumab[Supplementary Concept]) OR (golimumab) OR (TNFR-Fc fusion protein[Supplementary Concept]) OR (TNFR-Fc fusion protein) OR (etanercept) OR (anti-TNF) OR (anti-TNF alpha) AND (Clinical Trial) AND (Clinical Trial[ptyp]) OR (Clinical Trial, Phase I [ptyp]) OR (Clinical Trial, Phase III[ptyp]) OR (Randomized Controlled Trial[ptyp]). The reference lists from retrieved articles and the references included in prior relevant systematic reviews and meta-analyses were also checked to ensure that all studies matching the established criteria were included. When the result of a single study was reported in >1 publication, only the most recent and complete data were included.

Data Extraction and Risk of Bias Assessment

Two reviewers independently reviewed the title and abstract of each article to eliminate duplicates, reviews, case studies, and retrospective studies. Clinical trials and prospective cohorts were included. Excel data forms were used to collect data on patients' characteristics, therapeutic regimens, sample size, trial duration, adverse events, and outcome measures by 2 reviewers independently. Any discordance between reviewers at any stage was resolved by agreement with a third reviewer. Risk of bias of selected studies was assessed at the study level using the Cochrane risk of bias tool.[21]

Outcome Assessment

The primary outcome was the comparison of the rates of endoscopic recurrence following surgical resection between different anti-TNF treatments. The secondary outcome was the comparison of clinical recurrence rates between anti-TNF treatments. A further secondary outcome was the comparison of endoscopic and clinical recurrence rates between the different anti-TNF treatments and non-biological treatments.

A Rutgeerts score of i2-4 was used, whenever possible, to define endoscopic recurrence following surgical resection. When unavailable, the alternative measures of endoscopic recurrence utilized by the authors were used. A CD Activity Index (CDAI) >150 was preferentially used to define clinical recurrence following surgical resection. When unavailable, alternative measures of clinical recurrence were utilized. When data on multiple follow-up times were reported, a length of follow-up of 12 months was preferentially used. Whenever unavailable, the length of follow-up closest to 12 months was used instead. An intention-to-treat analysis was used, whenever possible, whereby all withdrawals before the included follow-up date were considered to have had disease recurrence.

Data Synthesis and Analysis

We constructed 2×2 tables from the raw extracted data on an intention-to-treat basis. We performed a NMA utilizing a frequentist approach with generalized pairwise modeling using MetaXL 5.3 (EpiGear international, Brisbane, Australia). The inverse variance heterogeneity method was used in order to overcome the previously described limitations of the fixed and random effects models.[22] A NMA was computed for each outcome measure. All results were expressed as odds ratios (OR) with their 95% confidence intervals (95% CI). The H consistency index was computed for each NMA in order to assess the consistency of treatment effects with $H=1$ indicating minimum inconsistency, $H<3$ low inconsistency, $3<H<6$ modest inconsistency, and $H>6$ gross inconsistency.[22] Consistency was also evaluated by evaluating the overlap between direct and indirect treatment effect CIs. Network plots were generated in which treatments that were directly compared in studies were connected with lines, the widths of which were proportional to the number of studies comparing the 2 treatments. The sizes of the treatment circles were also proportional to the number of arms in the included studies which corresponded to the treatment. Number of subjects corresponding to each circle and line were displayed. Only 2 treatment arms were included from studies with ≥ 3 arms in order to avoid redundancy. The control treatment was chosen as the anti-TNF treatment most commonly included in a treatment arm as the main therapy, among the included studies. Forrest plots were generated using RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark). Sensitivity analyses were computed in which alternative control treatments were used and alternative treatment arms were excluded from studies with ≥ 3 arms.

RESULTS

Study Selection Process

A flowchart describing the selection process of reports is presented in Figure 1. The electronic search yielded 123 articles from Pubmed, 41 articles from the Cochrane Library, 149 articles from EMBASE and 1 relevant abstract from the AGA meetings. Studies were excluded if the rates of postoperative clinical/endoscopic recurrence or remission were not reported. When reviewing the titles and abstracts, 19 articles (18 full-text articles and 1 abstract) were screened. In total, 10 articles were then excluded,[23–32] leading to a

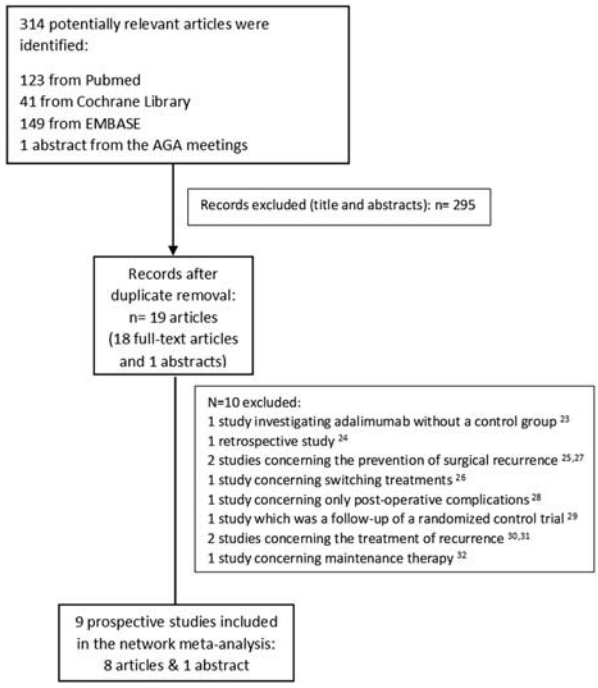

FIGURE 1. Flowchart describing the article selection process. AGA indicates American gastroenterology association.

total of 9 studies. These papers (8 articles and 1 abstract)[9–17] matched the aforementioned criteria and hence were included in the NMA.

In total, in 6 arms of 9 included studies infliximab was the primary treatment,[9,11,12,14–16] adalimumab in 4 arms,[10,13,14,17] thiopurines (azathioprine or 6-mercaptopurine) in 4 arms,[9,10,13,17] placebo (or no treatment) in 3 arms,[11,12,15] and mesalamine in 2 arms.[9,13] No studies investigating anti-TNFs other than infliximab and adalimumab met our inclusion criteria.

Characteristics of Included Studies

Table 1 summarizes the 9 studies included in the present NMA. Overall, the analysis included 571 patients. Of note, all studies included patients with prior ileocolonic resections, except for 1 study which had not specifically reported whether the included patients had undergone prior resections.[17] The network plots representing the meta-analyses with the number of subjects at each node and for each direct comparison are represented in Figure 2. Endoscopic recurrence was defined in all studies as Rutgeerts score ≥ 2 and clinical recurrence was defined as CBAI > 150 in most studies. All studies were 2-arm studies except for Savarino et al' 3-arm study,[13] from which the Azathioprine arm was removed for the purpose of the current NMA.

Risk of Bias Assessment

The results of the study level assessment of bias are reported in Table 2. Seven of the 9 included studies were randomized, 6 had adequate allocation concealment, 3 had adequate blinding of participants and personnel, 3 had adequate blinding of outcome assessment, 5 had no incomplete outcome data or dealt with outcome data adequately, and 7 did not selectively report their results.

Three studies were judged to be at low or moderate risk of bias,[11,12,15] 3 studies at moderate risk of bias[9,13,14] and 3 studies at moderate to high risk of bias.[10,16,17]

Outcome Assessment

Infliximab was chosen as the control treatment for the NMA since, among the included studies:

- Only 2 anti-TNF treatments (adalimumab and infliximab) were included in this NMA. Choosing 1 of these 2 treatments, as the control intervention was necessary to obtain result estimates of combined direct and indirect comparisons between these 2 treatments.
- It was included in the largest number of treatment arms as the main therapy.
- More patients received infliximab than any other treatment.

Forrest plots representing combined direct and indirect treatment effects with infliximab as the control intervention (treatment effect of 1) are represented in Figure 3. Tables 3 and 4 detail all direct and indirect treatment effects (OR) with their 95% CIs, and the sources of data for the indirect comparisons as well as the global estimates of treatment effects for both the endoscopic and clinical recurrence outcomes.

Endoscopic Recurrence

On global estimates of treatment effects, adalimumab was found to have a similar treatment effect to infliximab (OR, 0.92; 95% CI, 0.18-4.75, Fig. 3).

Thiopurines (OR, 4.11; 95% CI, 0.68-24.78), placebo (OR, 4.39; 95% CI, 0.70-27.68), and mesalamine (OR, 37.84; 95% CI, 3.77-379.42) all tended to have increased rates of endoscopic recurrence compared to infliximab, with only mesalamine showing significantly increased rates of endoscopic recurrence (Fig. 3).

Clinical Recurrence

On global estimates of treatment effects, adalimumab was found to have a similar treatment effect to infliximab (OR, 1.03; 95% CI, 0.17-6.03, Fig. 3).

Thiopurines (OR, 1.40; 95% CI, 0.20-10.02), placebo (OR, 1.77; 95% CI, 1.01-3.10), and mesalamine (OR, 16.54; 95% CI, 1.55-176.24) all tended to have increased rates of clinical recurrence compared to infliximab, with only mesalamine showing significantly increased rates of clinical recurrence (Fig. 3).

Adverse Events

Table 5 describes the rates of the most commonly reported adverse events for each the drugs included in this study. A combined withdrawal rate due to adverse events of 26% was found for infliximab, 2.2% for adalimumab, 5% for thiopurines, and 11% for mesalamine. The most common adverse events were: infusion and lupus-like reactions for infliximab (9%), a flu-like syndrome for adalimumab (9%), small bowel obstructions for thiopurines (3%), and arthralgia, flu-like syndrome as well nasopharyngitis (17%) for mesalamine.

Quality of Evidence and Sensitivity Analyses

Comparison of treatment effect CIs between direct and indirect comparisons for all interventions shows a large overlap between intervals, suggesting good consistency between direct and indirect comparisons (Tables 3, 4).

TABLE 1. Characteristics of Included Studies

Study	Drug Regimen	Type of Ileocolonic Resection	Timing of Initiation of Treatment	Patients (N)	Endoscopic Recurrence (%)	Clinical Recurrence (%)	Recurrence Definition	Follow-up (mo)
Sorrentino et al[16]	IFX 5 mg/Kg + MTX 10 mg/wk	Macroscopically diseased bowel resected	2 weeks postresection	7	0 (0)	0 (0)	Clinical: Hanauer score > 2	24
	MES 2.4 g/d			16	12 (75)	4 (25)	Endoscopic: Rutgeerts score ≥ 2	
Regueiro et al[12]	IFX 5 mg/Kg	Macroscopically diseased bowel resected	Within 4 weeks of resection	11	1 (9)	2 (18)	Clinical: CDAI > 150	12
	Placebo			13	11 (85)	6 (46)	Endoscopic: Rutgeerts score ≥ 2	
Yoshida et al[15]	IFX 5 mg/Kg	Macroscopically diseased bowel resected	4 weeks postresection	15	4 (26)	2 (13)	Clinical: CDAI > 150	12
	No treatment			16	13 (81)	4 (25)	Endoscopic: Rutgeerts score ≥ 2	
Armuzzi et al[9]	IFX 5 mg/kg	Curative ileocolonic resection*	2-4 weeks postresection	11	1 (9)	1 (9)	Clinical: HBI ≥ 8	12
	AZA 2.5 mg/Kg/d			11	5 (45)	2 (18)	Endoscopic: Rutgeerts score ≥ 2	
Savarino et al[13]	ADA 40 mg EOW	Macroscopically diseased bowel resected	Within 4 weeks of resection	16	1 (6)	1 (6)	Clinical: CDAI > 150	12
	MES 3 g/d			18	15 (83)	12 (67)	Endoscopic: Rutgeerts score ≥ 2	
	AZA 3 mg/Kg/d			17	11 (65)	13 (76)		
Tursi et al[14]	IFX 5 mg/Kg	Curative ileocolonic resection*	Within 4-6 weeks of resection	10	2 (20)	1 (10)	Clinical: HBI ≥ 8	12
	ADA 40 mg EOW			10	1 (10)	1 (10)	Endoscopic: Rutgeerts score ≥ 2	
De Cruz et al[10]	ADA 40 mg EOW†	Macroscopically diseased bowel resected	Within 1 week of resection	28	6 (21)	10 (36)	Clinical: CDAI > 150	6
	AZA 2 mg/Kg/d or 6 MP 1.5 mg/Kg/d†			73	33 (45)	21 (29)	Endoscopic: Rutgeerts score ≥ 2	
Scapa et al[17] (abstract)	ADA 40 mg EOW	NA	Within 6 weeks of resection	11	1 (9)	NA	Endoscopic: Rutgeerts score ≥ 2	6
	6MP 1.5 mg/Kg/d			8	4 (50)	NA		
Regueiro et al[11]	IFX 5 mg/Kg	Macroscopically diseased bowel resected	Within 6 weeks of resection	147	45 (31)	19 (13)	Clinical: CDAI ≥ 200	19
	Placebo			150	90 (60)	30 (20)	Endoscopic: Rutgeerts score ≥ 2	

*Macroscopically diseased bowel was resected and margins were verified as being free of disease, increasing length of resection when necessary.

†Associated with metronidazole for 6 months.

6 MP indicates 6-mercaptopurine; ADA, adalimumab; AZA, azathioprine; CDAI, Crohn's disease activity index; EOW, every other week; HBI, harvey bradshaw index; IFX, infliximab; MES, mesalamine; MTX, methotrexate; NA, not available.

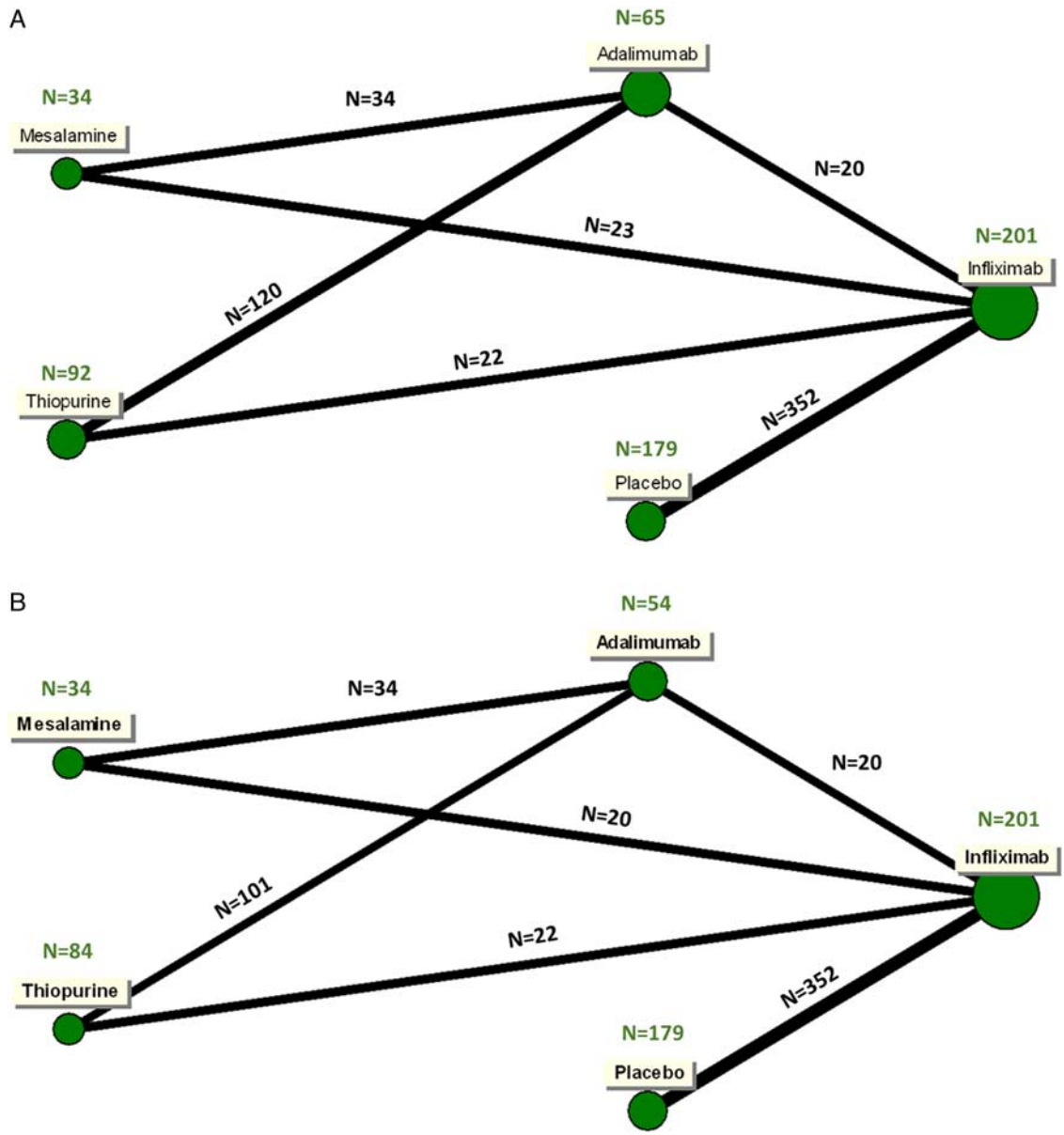

FIGURE 2. Network plots for the network meta-analysis of the endoscopic recurrence outcome (A) and clinical recurrence outcome (B). full color online

Furthermore, an H index of 1.00 was found for each of the 2 NMAs indicating minimum inconsistency. However, the relatively small number of direct comparisons, small numbers of subjects in most of the included studies and the ensuing relatively wide CIs of global estimates of treatment effects limit the precision of the results of this study.

Sensitivity analyses for both of the above NMAs were computed (Supplementary Material, Supplemental Digital Content 1, http://links.lww.com/JCG/A386) with either adalimumab as the control treatment or with the azathioprine arm of Savarino and colleagues study included (instead of the mesalamine arm). Similar results to those reported in the current study were found (Supplementary Material, Supplemental Digital Content 1, http://links.lww.com/JCG/A386). In particular, in all sensitivity analyses, adalimumab and infliximab were found to have similar treatment effects. Furthermore, the various treatment effects reported above were similar to those in the sensitivity analyses.

DISCUSSION

This is the first meta-analysis to compare the efficacy of anti-TNF biological agents in the prevention of endoscopic and clinical recurrence in patients with CD following ileocolonic resection. Only adalimumab and infliximab were examined in this NMA due to the lack of studies, meeting the selection criteria of this review, on other anti-TNF agents in the setting of postoperative recurrence prevention. adalimumab and infliximab were found to have similar efficacy in postoperative endoscopic and clinical recurrence

TABLE 2. Study-level Assessment of Bias According to the Cochrane Risk of Bias Tool

Study	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Armuzzi et al[9]	Random	Open label*	Open label*	Open label*	Adequate	No selective reporting
De Cruz et al[10]	Not random*	Adequate	Open label*	Open label*	Inadequate*	No selective reporting
Scapa et al[17] (abstract)	Random	Unclear†	Unclear†	Unclear†	Inadequate*	Selective reporting*
Regueiro et al[12]	Random	Adequate	Double blind	Adequate	Adequate	No selective reporting
Regueiro et al[11]	Random	Adequate	Double blind	Adequate	Adequate	No selective reporting
Savarino et al[13]	Random	Adequate	Open label*	Open label*	Inadequate*	No selective reporting
Sorrentino et al[16]	Not random*	Inadequate*	Open label*	Open label*	Adequate	No selective reporting
Tursi et al[14]	Random	Adequate	Open label*	Open label*	Adequate	No selective reporting
Yoshida et al[15]	Random	Adequate	Double blind	Adequate	Adequate	Selective reporting*

*High risk of bias.
†Unclear risk of bias.

of CD. Conventional treatments and placebo all tended to have superior recurrence rates to Infliximab, with only mesalamine having a significantly superior rate.

Only 1 prospective study previously compared the efficacy of infliximab and adalimumab in the prevention of postoperative recurrence of CD.[14] This study was included in the current NMA and provided the sole direct comparison between the 2 agents. The conclusions of the current NMA are similar to those of Tursi and colleagues study in that both studies concluded that adalimumab and infliximab have similar treatment effects in the prevention of postoperative CD recurrence. However, the addition of indirect comparisons to Tursi and colleagues results allowed a more precise estimation of treatment effects, which was reflected by the narrower CIs for the endoscopic and clinical recurrence outcomes of the NMA compared with Tursi et al's[14] results (Tables 3, 4).

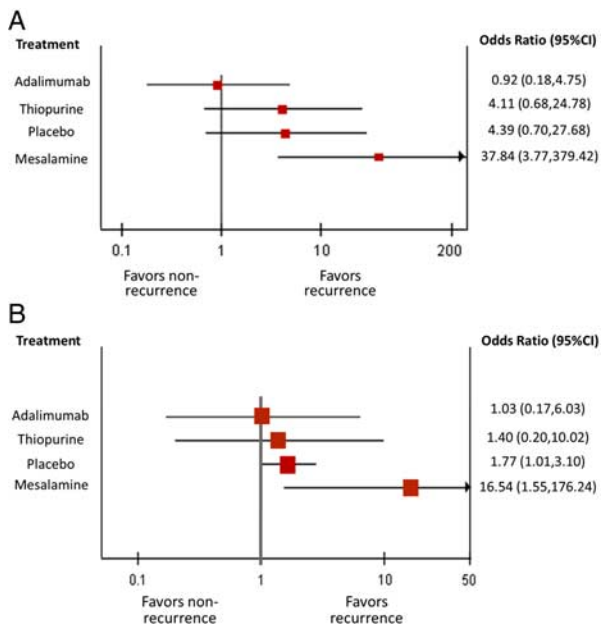

FIGURE 3. Forrest plots for the network meta-analysis of the endoscopic recurrence outcome (A) and clinical recurrence outcome (B). full color online

Conventional treatments and placebo all tended to have superior recurrence rates to infliximab in the prevention of CD recurrence in our NMA. This result is largely in accordance with previous primary studies (among which those included in the current NMAs) and meta-analyses[18–20] that have concluded that biological anti-TNF therapy is more efficacious in the prevention of postoperative CD prevention compared with other treatments.

Considering the scarcity of currently available data on the comparison of various anti-TNF agents in the prevention of postoperative CD recurrence, a strength of the current study is its network design, which allows the combination of both direct and indirect comparisons in order to best estimate treatment effects from currently available data. Furthermore, the use of the inverse variance heterogeneity method instead of the conventionally used fixed and random effect models allowed a more adequate approach to dealing with heterogeneity.[22]

A number of questions were beyond the scope of this NMA due to the lack of primary study data. First, none of the primary studies included combination therapies as treatment arms and therefore the efficacy of combination therapies in the prevention of postoperative recurrence of CD could not be investigated in this NMA. Second, although only studies which administered therapy within 3 months of surgery were included in this NMA, significant variability between studies remained in the timing of treatment administration after surgery (1 to 6 wk postsurgery; Table 1). Because of the scarcity of studies included in this NMA, the effect of the timing of treatment administration on the studied outcomes could not be investigated in the present study. Third, all the studies in this NMA included both patients undergoing first-time resections and patients

TABLE 3. Direct, Indirect, and Overall Estimates of Treatment Effects for Endoscopic Recurrence

ID	Comparison	Active	Control	OR	95% CI
Direct estimates					
1	Tursiet al[14]	Adalimumab	Infliximab	0.44	0.03-5.88
2	Savarino et al[13]	Adalimumab	Mesalamine	0.01	0.00-0.14
3	De Cruz et al[10] and Scapa et al[17] (abstract)	Adalimumab	Thiopurine	0.28	0.11-0.71
4	Sorrentino et al[16]	Infliximab	Mesalamine	0.02	0.00-0.51
5	Regueiro et al,[12] Yoshida et al,[15] and Regueiro et al[11]	Infliximab	Placebo	0.23	0.04-1.44
6	Armuzzi et al[9]	Infliximab	Thiopurine	0.12	0.01-1.29
Indirect estimates (source IDs)					
7	Indirect adalimumab vs. infliximab (2, 4)	Adalimumab	Infliximab	0.56	0.01-26.68
8	Indirect adalimumab vs. infliximab (3, 6)	Adalimumab	Infliximab	2.32	0.18-29.8
9	Indirect mesalamine vs. infliximab (2, 1)	Mesalamine	Infliximab	33.33	1.0-1112.3
10	Indirect thiopurine vs. infliximab (3, 1)	Thiopurine	Infliximab	1.60	0.1-24.9
Overall estimates (source IDs)					
	Adalimumab (1, 7, 8)	Adalimumab	Infliximab	0.92	0.18-4.75
	Mesalamine (4, 9)	Mesalamine	Infliximab	37.84	3.77-379.42
	Thiopurine (6, 10)	Thiopurine	Infliximab	4.11	0.68-24.78
	Placebo (5)	Placebo	Infliximab	4.39	0.7-27.68

H index for consistency = 1.00 (minimum inconsistency).
CI indicates confidence interval; OR, odds ratio.

undergoing repeat resections. Future studies should investigate the efficacy of anti-TNFs in each of these patient populations.

However, a few limitations of the present study merit discussion. First, among anti-TNF agents, only infliximab and adalimumab were compared in this study. This was due to the lack of prospective studies on the efficacy of other anti-TNF agents in the prevention of postoperative prophylaxis of CD recurrence. Furthermore, only 1 prospective study directly comparing infliximab and adalimumab was found by the reviewers and only 2 indirect comparisons between adalimumab and infliximab (Tables 3, 4) were made possible by the other included studies. This lack of primary data led to relatively large 95% CI in the comparison of adalimumab and infliximab treatment effects (Fig. 3). These findings underline the necessity for further studies comparing anti-TNF agents in the setting of CD postoperative prophylaxis. However, the results of the current NMA are currently the best available evidence for such a comparison. Second, the disparity in the reporting between studies and incomplete reporting of adverse events precluded computing NMAs of adverse event rates in the current review. Although, some treatments appeared to have higher rates of adverse events than others, this was possibly due to the disparity in reporting between studies; therefore, performing study-level meta-analyses on such data could have been misleading. This review therefore underlines the importance of fully reporting adverse events in future studies investigating anti-TNF agents, especially considering the importance of adverse event rates when advocating 1 agent over the other. A third limitation of this study, and of all study-level meta-analyses, is that the results can only be interpreted as being observational since the patients had been randomized only at the level of the studies but not between studies. A fourth limitation of this study is the inclusion of an abstract among the sources of data for this NMA.[17] Although an abstract does not provide as much details of study as a full article, the authors attempted to be

TABLE 4. Direct, Indirect, and Overall Estimates of Treatment Effects for Clinical Recurrence

ID	Comparison	Active	Control	OR	95% CI
Direct estimates					
1	Tursi et al[14]	Adalimumab	Infliximab	1.0	0.1-18.6
2	Savarino et al[13]	Adalimumab	Mesalamine	0.0	0.0-0.2
3	De Cruz et al[10]	Adalimumab	Thiopurine	1.4	0.5-3.5
4	Sorrentino et al[16]	Infliximab	Mesalamine	0.1	0.0-2.9
5	Regueiro et al,[12] Yoshida et al,[15] and Regueiro et al[11]	Infliximab	Placebo	0.6	0.3-1.0
6	Armuzzi 2013[9]	Infliximab	Thiopurine	0.5	0.0-5.8
Indirect estimates (source IDs)					
7	Indirect adalimumab vs. infliximab (2, 4)	Adalimumab	Infliximab	0.1	0.0-5.7
8	Indirect adalimumab vs. infliximab (3, 6)	Adalimumab	Infliximab	3.1	0.2-46.7
9	Indirect mesalamine vs. infliximab (2, 1)	Mesalamine	Infliximab	60.0	1.4-2610.4
10	Indirect thiopurine vs. infliximab (3, 1)	Thiopurine	Infliximab	0.7	0.0-15.6
Overall estimates (source IDs)					
	Adalimumab (1, 7, 8)	Adalimumab	Infliximab	1.0	0.2-6.0
	Mesalamine (4, 9)	Mesalamine	Infliximab	16.5	1.6-176.2
	Thiopurine (6, 10)	Thiopurine	Infliximab	1.4	0.2-10.0
	Placebo (5)	Placebo	Infliximab	1.8	1.0-3.1

H index for consistency = 1.00 (minimum inconsistency).
CI indicates confidence interval; OR, odds ratio.

TABLE 5. Description of Adverse Events and Withdrawal due to Adverse Events by Treatment

Drug	No. Subjects	Withdrawal due to Adverse Events	Adverse Events	%
Infliximab[9,11,12,15,16]	189	26%	Lupus-like reaction	9
			Infusion reaction	9
			Bronchitis	3
			Nasopharyngitis	3
			Pyelonephritis	3
			Severe abdominal pain	3
			Abdominal wall abscess	3
Adalimumab[10,13]	44	2.2%	Flu-like syndrome	9
			Small bowel obstruction	7
			Nasopharyngitis	5
			Bronchitis	5
			Lung nodules	2
			Nausea	2
			Arthralgia	2
			Atopic dermatitis	2
			Abdominal pain	2
			Pneumonia	2
			Pyelonephritis	2
			Urolithiasis	2
			Cystitis	2
			Crohn's disease exacerbation	2
			Upper respiratory tract infection	2
			Type 3 hypersensitivity reaction	2
			Uveitis	2
			Perianal fistula	2
Thiopurine[9,10]	101	5%	Small bowel obstruction	3
			Small bowel anastomotic leak	2
			Abdominal pain	2
			Ileus	2
Mesalamine[13]	18	11%	Arthralgia	17
			Flu-like syndrome	17
			Nasopharyngitis	17
			Crohn's disease exacerbation	11
			Bronchitis	6
			Gastroenteritis	6
			Partial small bowel obstruction	6
			Fever	6
			Abdominal wall abscess	6

as exhaustive as possible in their search for prospective trials (which is consistent with standard search practices of systematic reviews[33]).

Implications for Clinical Practice

Despite the recent advances in the medical treatment arsenal of CD, palliative surgical interventions are still inevitable in most patients. However, these surgeries are not curative with as much as 25% of patients requiring further surgical intervention.[34] The postoperative recurrence rate varies depending on the definition of recurrence: clinical, endoscopic, radiologic, or surgical. Rutgeerts[35] has previously shown that the 1-year clinical recurrence rate is 20% to 30% after ileal or ileocolonic resection, with a 10% increase in each subsequent year. The same research group has also shown that the 1-year endoscopic and histologic recurrence rate is as high as 72% after surgical resection.[36] The prevention of postoperative recurrence is therefore a major priority given the morbidity associated with potential recurrences and the long-term risk of short gut syndrome, which may arise from repeated bowel resections. Although previous studies had established that anti-TNFs are superior to conventional medical therapy in the prevention of CD recurrence,[18–20] there is currently no single anti-TNF agent which constitutes the standard of care for the prevention of postoperative recurrences.

On the basis of a combination of direct and indirect comparisons with similar results and the robustness of the results of the NMAs to sensitivity analyses, there is moderate evidence that adalimumab and infliximab have similar efficacy in the prevention of CD recurrence following ileocolonic resection. Unfortunately, no conclusions could be made about other anti-TNF agents due to the lack of primary studies on such agents. Furthermore, the current study yielded similar results to previous meta-analyses by concluding that infliximab tends to be superior to conventional therapy and placebo in postoperative prophylaxis of CD.

The results of the current study therefore primarily underline the scarcity of data comparing different anti-TNF agents in the setting of postoperative prophylaxis of recurrence of CD and lead to the conclusion that, based on currently available data, either adalimumab or infliximab may be used in this setting considering the lack of data on other agents and the absence of a difference in treatment effect between the 2 agents.

In conclusion, this NMA of 9 prospective studies investigating 5 different therapies, among which 2 anti-TNF agents, concluded that either adalimumab or infliximab may be used in the postoperative prophylaxis of CD recurrence. Future randomized-controlled studies directly comparing different anti-TNF agents in the postoperative setting are needed to more accurately determine the optimal anti-TNF agent for postoperative prevention of CD recurrence.

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