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Original Article

Anti-TNF agents prevent endoscopic and clinical recurrence of Crohn's disease after surgical resection: a systematic review and a meta-analysis

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Abstract: Anti-TNF Agents Prevent Endoscopic and Clinical Recurrence of Crohn's Disease after Surgical Resection: A Systematic Review and A Meta-Analysis Background and Aim: Recent studies suggest that anti-TNF agents can prevent Crohn's disease (CD) recurrence after surgical resection. The objective of this study was to perform a systematic review of the literature and a meta-analysis of randomized trials that compared anti-TNF agents with other treatment modalities for prophylaxis of post-operative CD recurrence. Methods: Electronic database including PubMed, Scopus, and ScienceDirect were searched for relevant studies. The random effect model was used to pool the effect size across studies and presented as risk ratio (RR) of experiencing endoscopic or clinical recurrence while on an anti-TNF agent compared to not. Results: Four studies met the inclusion criteria: 3 with infliximab (IFX) and 1 with adalimumab, including patients in total (53 patients treated with an anti-TNF and 74 controls). The pooled RR of endoscopic recurrence among patients treated with an anti-TNF agent compared with other conventional therapies was 0.179 (95% confidence interval [CI]: 0.084-0.383, $p \leq 0.001$, risk difference was 0.624, number needed to treat [NNT] 1-2). The pooled RR of clinical recurrence among patients treated with an anti-TNF agent was 0.374 (95% CI: 0.172-0.784, p=0.013), risk difference was 0.22 (95% CI: 0.354-0.107) and an NNT of 4-5. Conclusions: Post-operative use of either infliximab or adalimumab is associated with a significant decrease in endoscopic and clinical recurrence rates after resection surgery and is more effective than other conventional therapies, including AZA and/or 5-ASA. The published studies suffer some limitations, including design limitations in some and small sample size.

Keywords: Anti-TNF, post-operative Crohn's, meta-analysis

Introduction

Despite the many advances in the medical and endoscopic therapy of Crohn's disease, resection surgery remains inevitable in up to 50% of patients within 10 years of diagnosis [1, 2]. Surgery rates for Crohn's disease have been declining, likely as a result of the increased use of more aggressive medical therapies [1]. Although surgery signifies a more severe or complex (predominantly stricturing or fistulizing) disease, it does not necessarily indicate medical therapy failure. Rather, surgery complements medical therapy and plays an integrated role in the management of Crohn's disease and its complications [3]. Resection surgery with "clear margins" can induce remission, but endoscopic, clinical disease can recur in a significant proportion of patients [4-6]. Endoscopic recurrence at the site of anastomosis can occur a few weeks postoperatively and may herald clinical recurrence [7]. Using postoperative medications to prevent or at least delay recurrence has been the aim of numerous studies and reviews in the past three decades. Medications included 5-aminosalicylic acid (5-ASA), metronidazole and immunomodulators, such as AZA or 6-mercaptopurine (6MP) [8-10]. However, the efficacy of these medications in long-term prevention or delayed recurrence remains debatable, with an estimated 8-10 patients needed to treat to prevent one recurrence at one year post-surgery [9, 11].

Since their introduction, anti-TNF agents have become the mainstay for the treatment of moderate to severe Crohn's disease. Anti-TNF agents are effective in treating all phenotypes, improving quality of life and possibly decreasing the need for surgery [9, 12]. More recently, their efficacy in preventing postoperative recurrence has been investigated in a few small size comparative studies [13-18]. Only half of these studies reported superior efficacy of anti-TNF agents in preventing endoscopic recurrence and/or clinical recurrence. This was, in part, due to small sample size and variable designs.

Our aim was to perform a systematic review and a meta-analysis of randomized trials that evaluated the efficacy of anti-TNF agents for the prevention of post-operative endoscopic or clinical recurrence in Crohn's disease patients who underwent ileal or ileocolic resection.

Methods

Literature search

A comprehensive literature search was performed to identify all reports on the use of IFX, adalimumab and certolizumab in postoperative Crohn's disease. The searched electronic database included MEDLINE (PubMed), Scopus, and ScienceDirect with no restrictions on the date, publication type or language as of January 31st, 2014. In addition, we searched the abstracts presented at Digestive Disease Week or the Advances in Inflammatory Bowel Disease meetings, those submitted to the American College of Gastroenterology annual meeting between 2004 and 2013 and abstracts presented at the Congress of European Crohn's and Colitis Organization between 2011 and 2013. The keywords and terms searched included anti-TNF, IFX, adalimumab, certolizumab and biologics in combination with one or more of the following: surgery, postoperative, post-surgery and recurrence. Searches were performed within the title, abstract and keywords.

Inclusion and exclusion criteria

Studies that specifically addressed the use of anti-TNF agents for the prevention of endoscopic and/or clinical Crohn's disease recurrence in their abstracts were included in the systematic review. We excluded the studies that were updated and included in a later publication by the same authors and that were duplicated (including abstracts presented at multiple meetings). Only randomized trials that used widely accepted and well-defined outcomes were included in the meta-analysis (Supplemental Figure 1).

Study selection

The first two authors (HM & AG) independently searched the literature and identified studies for the review. The abstracts of studies selected by either author were then scanned by both authors to determine their eligibility for the systematic review and the meta-analysis. Disagreements were resolved by reaching a consensus among the authors and after discussion with the other authors (LS and TB).

Data extraction, quality and risk of bias assessment

The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19] (Supplemental Figure 1). The following data were collected: the absolute numbers of patients in the study, the identity of each group and each outcome, the method of patient selection, the start time of anti-TNF agent postoperatively, evaluation points for outcomes, treatments in the comparison groups, the clinical and endoscopic outcome assessment methods and whether the outcome was primary or secondary, a priori or post-hoc analysis. The study quality and risk of bias assessments were performed according to the Cochrane Collaboration's tool (Supplemental Table 1) [20].

Data synthesis and statistical analysis

We used a conservative approach in the meta-analysis to account for the small number of studies with small sample sizes and varied study designs, follow-up lengths and comparison groups' treatments. We used a random effect model (DerSimonian Laird method) to pool and calculated the risk ratios (RRs) and 95% confidence intervals (CIs) of recurrence while receiving anti-TNF agent. The analysis was based on the intention to treat. When there were more than two comparison groups, the analysis was based on receiving versus not receiving the anti-TNF agent. Some studies used multiple clinical indices and/or different

Table 1. Summary of Findings of the studies reviewed but were not included in the meta-analysis

Study [reference #]	Year	Design (number of pts)	Intervention	Duration/ assessment time	Outcome assessed	findings	Reason for exclusion
Sorrentino et al [13]	2007	Prospective cohort (23)	Infliximab + MTX (7) vs mesalamine (16)	12mos	Endoscopic (Rutgeerts) and clinical (Hanauer scale) recurrence	Clinical recurrence 2 yrs: 0% vs 31.3% Endoscopic recurrence 2 yrs: 0% vs 75%	Not randomized trial; cohort
Yoshimura et al [21]	2008 (a)	Retrospective analysis	Infliximab within 1 year	12 mos (mean)	Clinical (CDAI)	Clinical remission: 64.7%	Retrospective, comparison made with pts who did not have surgery, unclear if surgical remission achieved.
Fernandez-Blanco et al [22]	2010 (a)	Prospective case series (20)	Adalimumab within 2 weeks	12 mos	Endoscopic (Rutgeerts), clinical (NR) and histological	Endoscopic recurrence: 10% Histological recurrence: 45% Clinical recurrence: 0%	Case series, no comparison group
Sorrentino et al [23]	2010	Prospective case series (12)	Low dose infliximab (3 mg/kg)	36 mos	Endoscopic (Rutgeerts) and clinical (Hanauer)	Approximately 83% exhibited endoscopic recurrence 4 months after stopping infliximab	Case series, main aim to assess impact of stopping Rx
Terkegan et al [24]	2011 (a)	Retrospective (236)	Biologics (B) vs Immunomodulators (I) vs B+I vs no treatment	24.8 mos (mean)	Endoscopic (Rutgeerts)	Biologic Rx associated with lower Rutgeerts' scores (OR 2.88)	Retrospective
Aguas et al [25]	2012	Prospective case series (29)	Adalimumab within 2 weeks	12 mos (mean)	Endoscopic (Rutgeerts), radiological (MRI) and clinical (symptoms)	Endoscopic recurrence: 20.7% Radiologic recurrence: 36.8 Clinical recurrence: 13.7%	Case series, no comparison group
De Cruz et al [15]	2012 (a)	Prospective cohort (61)	Adalimumab within 2 weeks vs AZA	6 mos	Endoscopic (Rutgeerts)	Endoscopic remission: 93.8 vs 62%	Not randomized trial; cohort
Esaki et al [26]	2012 (a)	Retrospective cohort (37)	Infliximab vs unclear/not reported	26.9 mos (mean)	Endoscopic (Rutgeerts) or radiologic	Recurrence: 15.8% vs 77.8%	Retrospective/
Papamichael et al [27]	2012	Prospective cohort (23) two steps (after 6 mos, pts in the comparison group with endoscopic recurrence were treated with adalimumab)	Adalimumab vs AZA or infliximab or 5ASA	6 & 24 mos	clinical (HBI) and Endoscopic (Rutgeerts)	Endoscopic recurrence at 6 mos: 12.5% of adalimumab-treated vs 100% in comparison group. Clinical recurrence at 6 mos: 0% of adalimumab-treated vs 60% in comparison group	Anti-TNF agent (infliximab) was used in 3/15 in the comparison group
Sakuraba et al [28]	2012	Prospective case series (11)	Infliximab within 2-4 weeks of surgery	24 mos	Clinical (CDAI increase by >50) endoscopic (NR), radiological (NR)	Clinical remission: 60% Endoscopic or radiologic remission: 40%	Case series, no comparison group
Savarino et al [29]	2012	Case series (6)	Adalimumab within 2 weeks	36 mos	Endoscopic (Rutgeerts) and clinical (Hanauer)	0% clinical and endoscopic recurrence	Case series, no comparison group
Araki et al [30]	2013	Case controlled (200)	Infliximab within 8 weeks of surgery	36 mos	Surgical recurrence (reoperation)	Infliximab associated with decreased recurrence (3% vs 34%); HR 0.22	retrospective
Kotze et al [31]	2013 (a)	Retrospective case series (56)	Infliximab (28 pts) or adalimumab (28 pts)	12.8 mos (mean)	Endoscopic (Rutgeerts)	Infliximab endoscopic recurrence: 32.14%. Adalimumab endoscopic recurrence (28.57%)	Retrospective case series, comparison made between infliximab and adalimumab
Shinzaki et al [32]	2013 (a)	Retrospective cohort (36)	Nutritional Rx (Elental) + infliximab vs Nutritional Rx	24 mos	Serologic (CRP) and endoscopic (Rutgeerts)	Serologic remission: 63% vs 60% (ns) Endoscopic remission 50% in both	Retrospective

Sorrentino et al [3]	2013 (a)	Subgroup analysis/case control (11)	Low-dose infliximab (3 mg/kg) vs standard dose (5 mg/kg)	30 mos	ATI formation, clinical (CDAI) and endoscopic (Rutgeerts)	No difference in clinical or endoscopic recurrence between the two doses; 0% recurrence after 30 months	Subgroup analysis with no comparison group
Regueiro et al [34]	2014	Prospective cohort/long term observation and f/u of a previous RCT pts (24)	Infliximab within 4 weeks in initial RCT in 11 pts and after one year in 10 pts	>48 mos	Endoscopic (Rutgeerts) and surgical (reoperation)	Among initial RCT patients treated with infliximab (12), endoscopic recurrence was 58.3% and surgical recurrence was 33.3% after stopping infliximab. Among initial RCT pts who received placebo (12), 10 were started on infliximab: surgical recurrence was 30% while on infliximab and 16.7% after stopping infliximab; 100% endoscopic recurrence.	No separate comparison group, main aim to assess impact of stopping infliximab; data from RCT included in meta-analysis

a=abstract.

Table 2. Summary of Findings of the studies included in the meta-analysis

Study [reference #]	Year	Design	Anti-TNF used/ start time	Total n	Evaluation point	Treatment arms (n)	Concomitant Rx	Prior anti-TNF	Primary outcome	Secondary outcome(s)	Reported results
Regueiro et al [14]	2009	RCT, double blind placebo	Infliximab 5 mg/kg with induction/within 4 weeks	24	12 mos	Infliximab (11) vs placebo (13)	4 I & 1 5ASA vs 7 I and 4 5ASA	3 vs 5	Endoscopic recurrence (Rutgeerts)	Clinical (CDAI), histological, CRP & ESR	Endoscopic recurrence: 9.1% vs 84.6% Clinical remission: 80% vs 53.8% (ns) Clinical recurrence: 0% vs 38.5% Histologic recurrence: 27.3% vs 84.6%
Yoshida et al [16]	2012	RCT	Infliximab 5 mg/kg q 8 wks with induction/within 4 weeks	31	12 & 36 mos	Infliximab (15) vs No infliximab (16)	7 ED & 15 5ASA vs 13 ED & 16 5ASA	0 vs 1	Clinical remission (CDAI & IOIBD) at 12 ms	Clinical remission (IOIBD) at 36 mos. Endoscopic recurrence (Rutgeerts) and serologic recurrence (CRP)	Clinical remission (IOIBD) 12 mos: 100% vs 68.8% .Clinical remission (CDAI) 12 mos: 86.7% vs 75% (ns). Clinical remission (IOIBD) 36 mos: 93.3% vs 56.3. Clinical remission (CDAI) 36 mos: 80% vs 75% (ns). Endoscopic Remission 12 mos: 73.3% vs 18.8%
Armuzzi et al [17]	2013	RCT	Infliximab 5 mg/kg q 8 wks with no induction/ within 4 weeks	22	12 mos	Infliximab (11) vs AZA (11)	None/NR	6 vs 4	Endoscopic (Rutgeerts), clinical (HBI) and histological recurrence	Serologic recurrence (CRP) and histologic recurrence	Clinical recurrence 2 yrs: 9% vs 10% Endoscopic recurrence: 9% vs 40% Histologic recurrence: 18% vs 80%
Savarino et al [18]	2013	RCT, single blind	Adalimumab 40 mg qow with induction/within 4 weeks	51	24 mos	Adalimumab (16), AZA (17), 5ASA (18)	None/NR	5 vs 4 vs 1	Endoscopic (Rutgeerts) and clinical (CDAI, Hanauer scale) recurrence	QOL	Endoscopic recurrence: 6.3% vs 64.7% vs 83.3% Clinical recurrence: 12.5% vs 64.7% vs 50%. QOL: 202 vs 90 vs 98

Table 3. Efficacy of anti-TNF treatment in preventing post-operative endoscopic recurrence

Study [reference #]	Final evaluation time	Anti-TNF prior to surgery	Endoscopic recurrence rate: anti-TNF vs comparator	Statistical significance
Regueiro et al [14]	12 mos	30% vs 39%	9.1% vs 84.6%	p=0.006
Yoshida et al [16]	12 mos	0% vs 6%	21.4% vs 81.3%	p=0.004
Armuzzi et al [17]	12 mos	54% vs 36%	9% vs 40%	p=0.14
Savarino et al [18]				
Adalimumab vs AZA	24 mos	31% vs 24%	6.3% vs 64.7%	OR 0.036 (0.004-0.347)*
Adalimumab vs mesalamine		31% vs 6%	6.3% vs 83.3%	OR (0.001-0.143)*

*95% CI.

Table 4. Efficacy of anti-TNF treatment in preventing post-operative clinical recurrence

Study [reference #]	Final evaluation time	Scoring system(s) used	Clinical recurrence rates: Anti-TNF treated vs not (p)	Clinical remission rates: Anti-TNF treated vs not (p)
Regueiro et al [14]	12 mos	CDAI	0% vs 38.5% (p=0.46)	80% vs 53.8% (p=0.38)
Yoshida et al [16]	12 mos	CDAI	13.3% vs 25% (p=0.696)	86.7% vs 75% (p=0.696)
		IOIBD	0% vs 32% (p=0.020)	100% vs 68% (p=0.020)
	36 mos	CDAI	20% vs 25% (p=0.696)	80% vs 75% (p=0.696)
		IOIBD	6.7% vs 43.7% (p=0.008)	93.3% vs 56.3% (p=0.008)
Armuzzi et al [1]	12 mos	HBI	9% vs 10% (p=0.14)	91% vs 90% (p=0.14)
Savarino et al [18]				
Adalimumab vs AZA vs mesalamine	24 mos	CDAI	6.3% vs 70.6% vs 50% (p=0.0085)	93.8% vs 23.5% vs 33.3% (p=0.0037)
		Hanauer	12.5% vs 64.7% vs 50% (P=0.0188)	87.5% vs 35.3% vs 50% (p=0.0188)

Clinical recurrence: CDAI >150 in Yoshida study and >200 in Regueiro and Savarino studies, HBI ≥8, Clinical recurrence score (Hanauer) ≥2 Clinical remission: CDAI ≤150, HBI <8, Hanauer <2.

Crohn's Disease Activity Index (CDAI) cutoffs for defining clinical remission and/or clinical recurrence. In our analysis, the most conservative results among patients treated with anti-TNF agent were used. For example, if a study reported higher recurrence rates (or lower remission rates) based on CDAI scores than on another scale, the higher recurrence (or lower remission) rates were used in the analysis. We performed sensitivity analysis based on the "one study removed" method to assess the robustness of the pooled effect size. We also tested for heterogeneity using the Q test and reported a tau-squared (τ^2) and I^2 with p values for the percentage of heterogeneity observed. A funnel plot was used to assess the possibility of a publication bias in either endoscopic or clinical recurrence data, and a meta-regression was conducted to assess the impact of the study duration as a moderator of the overall results. Statistical analysis was performed using Comprehensive Meta Analysis (CMA) software version 2.2.064, 2011 New York City, NY, USA.

Results

Study characteristics

Table 1 includes the Summary of Findings (SoF) of the studies that were reviewed but were not included in the meta-analysis with the reasons for exclusion [13, 15, 21-34]. The reasons for exclusion from the meta-analysis were as follows: retrospective design, prospective non-randomized or case series design with no comparison groups and unclear outcomes measurements. In general, these studies reported a wide range of clinical, endoscopic, histological or surgical postoperative Crohn's disease recurrence rates. Clinical and endoscopic recurrence rates ranged from 0-40% and 0-60%, respectively, depending on length of study and/or follow-up time and concomitant therapies.

Table 2 summarizes the studies that met the inclusion criteria for the meta-analysis [14, 16-18]. All four studies used the Rutgeerts scoring criteria to define endoscopic recurrence and remission. Endoscopic remission (or recurrence) was one of the primary outcomes measured in all of the studies. All studies clearly reported that the surgeon inverted the resection ends to assure macroscopically intact mucosa before performing side-to-side anastomosis. Despite having the only randomized double-blind placebo-controlled design, Regueiro et al reported significantly higher baseline erythrocyte sedimentation rate (ESR) and

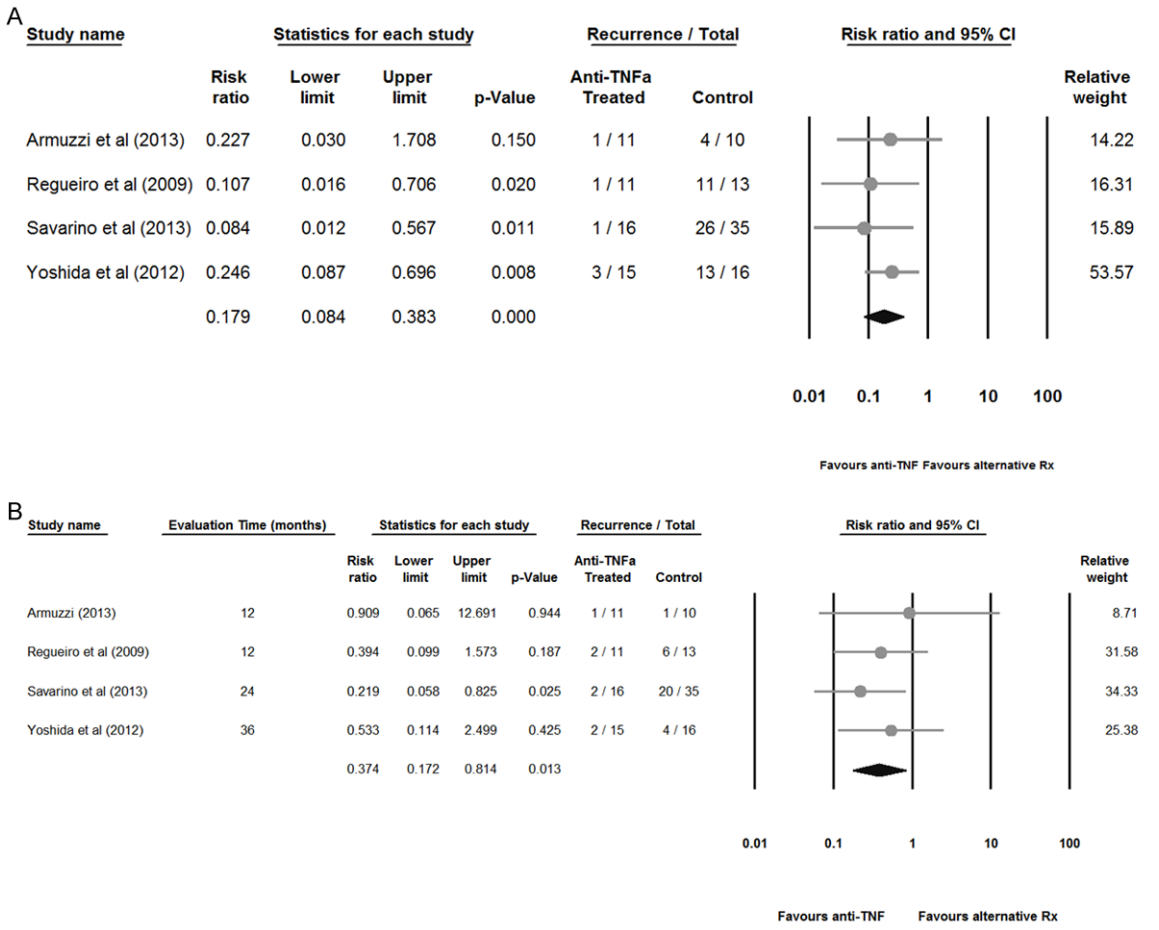

Figure 1. Pooled Risk Ratio (RR) of endoscopic recurrence (A/top) and clinical recurrence (B/bottom) in anti-TNF treated vs non-treated patients.

C-reactive protein (CRP) levels among the patients treated with IFX compared to placebo (ESR 40 vs 11, p=0.0004 & CRP 0.5 vs 0.1, p=0.049, respectively) and a much higher proportion of active smokers in the IFX arm (45.5% vs 7.7%, p=0.06). All other studies reported no significant differences in baseline characteristics. The study by Armuzzi et al reported the use of metronidazole post-operatively in all patients for 2 weeks [17]. In total, 53 patients were treated with either IFX or adalimumab post-operatively, and 74 received other therapies, mainly AZA or mesalamine.

The use of anti-TNF agents and post-operative endoscopic recurrence

The study by Armuzzi et al was the only study that reported no significant difference in endoscopic recurrence rates between IFX-treated and AZA treated patients (9% vs 40%, p=0.14). However, more than half of the patients in the IFX arm (6/11) were treated with IFX prior to surgery whereas the patients in Yoshida et al [16] study were naïve to IFX. Regueiro et al and Savarino et al [14, 18] studied patient groups with prior anti-TNF treatment rates of approximately 30%. The reported endoscopic recurrence rates are summarized in **Table 3**.

The aggregate endoscopic recurrence rate among the patients treated with an anti-TNF agent was 5/53 (9.4%) compared with 54/74 (73%) in the non-treated patients (p<0001) at a median follow-up time of 18 months across the studies. The RR of experiencing endoscopic recurrence while on anti-TNF agent post-operatively was 0.179 (95% CI: 0.084-0.383; p<0.001) (**Figure 1A**). The risk difference was 0.624 (95% CI: 0.781-0.467), and the number needed to treat (NNT) to prevent one endoscopic recurrence was 1-2 patients (95% CI: 1-3).

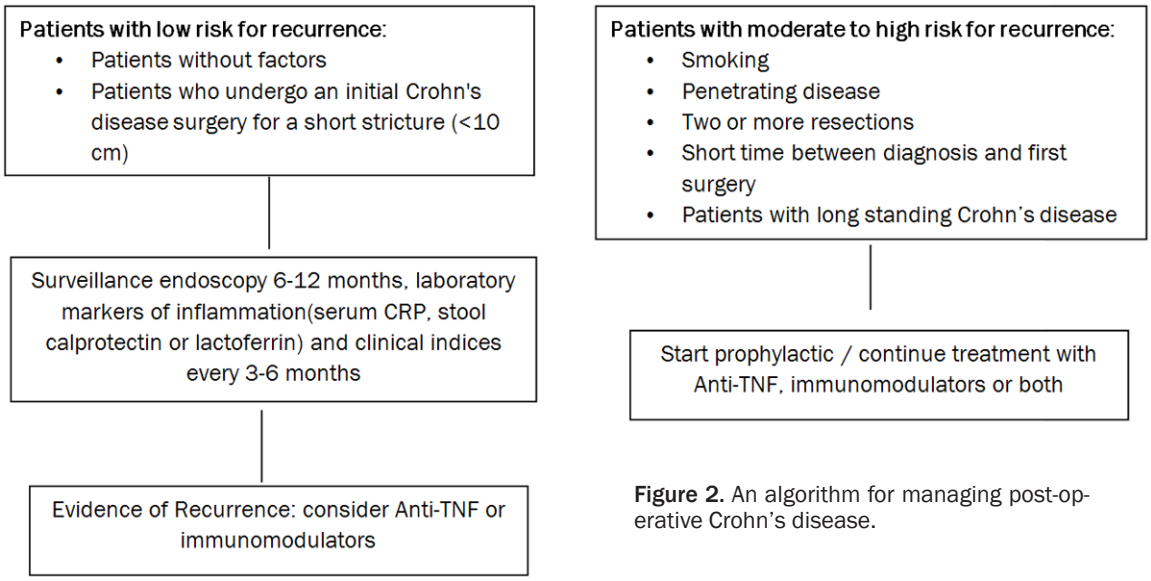

Figure 2. An algorithm for managing post-operative Crohn's disease.

Anti-TNF agent use and post-operative clinical recurrence

There was more heterogeneity in how clinical remission and recurrence were measured and defined (**Table 4**). Three studies used more than one scoring system to measure and define clinical remission and recurrence (CDAI and either the International Organization for the Study of Inflammatory Bowel Diseases [IOIBD] criteria or the clinical recurrence grading scale proposed by Hanauer). In some studies, there were inconsistencies in the clinical remission rates between the scoring systems used in the same study. Specifically, in the study by Yoshida et al and based on CDAI scores, the respective remission rates were 86.7% and 80% at 12 and 36 months in the IFX-treated patients compared with 75% and 75% in the non-treated patients, a difference that was not statistically significant. In contrast, based on the IOIBD score, 100% and 93.3% of the patients treated with IFX were in clinical remission compared with 68% and 56.3% in the non-treated arm (p=0.02 & 0.008, respectively).

In addition, both Regueiro et al and Savarino et al used two different CDAI score cutoffs to define remission (<150) and recurrence (>200), whereas Yoshida et al used a cutoff of <150 to define remission and >150 to define clinical recurrence. In the studies by Regueiro et al and Savarino et al, CDAI <150 was consistent with clinical remission, but clinical recurrence was defined as a score of >200. This is in contrast to the study by Yoshida et al, in which a single CDAI cutoff of 150 was used to define remission and recurrence.

In the pooled analysis, if a patient was not in clinical remission based on any of the scoring systems used, we included the event as a "recurrence" event.

The aggregate clinical recurrence rates were 7/53 (13.7%) for the anti-TNF-treated patients compared with 31/74 (41.9%) for the patients treated with other modalities (p=0.001). The pooled RR of experiencing clinical recurrence post-operatively was 0.374 (95% CI: 0.172-0.784, p=0.013), with an absolute risk difference of 0.22 (95% CI: 0.354-0.107) and an NNT of 4-5 (95% CI: 3-10) (**Figure 1B**). Overall, the studies included in the analysis were comparable in several components making comparisons valid.

Other outcomes reported

Some studies reported on other secondary outcomes. Regueiro et al and Armuzzi et al reported on histological recurrence rates in their studies, and both used same scoring system. The authors reported significantly lower histologic recurrence rates among IFX-treated patients with a pooled RR of 0.331 (95% CI: 0.163-0.673, p=0.002) (Supplemental Figure 2).

All four studies reported on CRP levels at the end of the study. Two of the studies reported significant difference in CRP levels between the anti-TNF treated and the non-treated patients. Two studies reported mean values; one study reported median values, and one study reported the proportions of patients above and below the CRP cutoff value of 0.3. The pooled analysis of the two studies that reported mean values revealed a significant difference in means between the anti-TNF-treated and non-treated groups, favoring anti-TNF treatment (-0.199, p=0.002) (Supplemental Figure 3).

Sensitivity analysis, heterogeneity testing and publication bias assessment

Sensitivity analysis was performed using a "one study removed" method and its effect on the overall effect size estimate of the use of anti-TNF agents on endoscopic and clinical recurrence. No significant changes in the endoscopic recurrence estimates were observed, indicating robust overall estimates. However, in the clinical recurrence estimates, the effect size changed and rendered the p values for the overall effect without that study 0.08 (RR without the study 0.447; 95% CI: 0.181-1.108).

Heterogeneity testing confirmed the absence of significant heterogeneity among studies with regard to endoscopic recurrence data (τ^2 and I^2 <1%, p=ns in both) and mild heterogeneity for clinical recurrence data (τ^2 0.026= and I^2 57%, p=0.09). Due to the small number of studies included in the analysis, funnel plot or other publication bias assessment could not be performed adequately. A meta-regression revealed no significant impact of the study duration on the results of either endoscopic or clinical meta-analysis estimates.

Discussion

Historically, post-operative recurrence of Crohn's disease after resection surgery occurs in up to 50% of patients within the first year [4-7]. Endoscopic recurrence occurs early and may predict clinical recurrence and its severity and timing [7]. Multiple systematic reviews and meta-analyses have been published on the topic of post-operative prevention of Crohn's disease recurrence. Those include a Cochrane Database systemic review and American College of Gastroenterology systematic review and evidence-based recommendations. However, due to the paucity of the reports that specifically investigated the use of anti-TNF agents to prevent postoperative Crohn's disease recurrence at the time of publication of the aforementioned reviews, there were no specific robust conclusions on the use of anti-TNF therapy to prevent post-operative recurrence. To our knowledge, this report is the first and only meta-analysis on the use of anti-TNF agents in the prevention of postoperative Crohn's disease recurrence after resection surgery. There has been several studies on the use of nitroimidazole antibiotics, mesalamine and AZA/6 MP. These agents were reported to be superior to placebo in preventing post-operative recurrence. Their efficacy appears to be comparable and at best a modest with an NNT of 8-10 (mesalamine and AZA) or associated with significant intolerance due to side effects (e.g., high-dose metronidazole and ornidazole). In addition, the efficacy of some of these medications in the treatment of Crohn's disease in general has been questioned, and recommendations regarding their use in pre-operative active disease and post-operative prevention of disease recurrence are inconsistent or contradictory [9, 11, 12]. A 2011 ACG evidence-based systematic review specifically states that 5-ASA therapies and antibiotics are not recommended for inducing or maintaining remission in Crohn's disease [12]. It is somewhat counterintuitive that a medicine that may not be effective in treating pre-operative Crohn's disease may be effective in the post-operative setting, given that surgery in general signifies a more severe and complex form of the disease that requires more effective treatment.

Although anti-TNF alone or in combination with immunomodulators is effective in treating all phenotypes of moderate to severe Crohn's disease, and although many anti-TNF agents are being used empirically post-operatively, the evidence for their use in this setting has been limited until recently [9, 12].

In our meta-analysis, IFX and adalimumab were superior to placebo, mesalamine and/or AZA for the prevention of endoscopic and clinical recurrence after surgical resection in Crohn's disease patients. Nevertheless, it is important to acknowledge and discuss several observations and limitations in our analysis and in the studies included.

Except for the study by Regueiro et al, the risk of bias due to the lack of a placebo arm and blinding to the treatment is substantial and may affect the internal validity of the studies included (Supplemental Table 1). Double blinding, the use of a placebo arm and allocation concealment are particularly important in the conditions known to have high rates of placebo response rates. Fortunately, all studies included the more objective endoscopic evaluation as one of the primary outcome(s), and the rates of endoscopic recurrence were highly consistent across studies, regardless of their design.

Pre- and post-operative Crohn's disease patients can be a very heterogeneous group of patients with multiple risk factors that can both be difficult to control and increase the risk of requiring surgery. These factors include disease behavior, response to previous treatments and smoking status. Treatment with an anti-TNF agent prior to surgery varied substantially across the studies. The underutilization of effective medical therapy may have led to the need for surgery in some patients who otherwise would have avoided it. Conversely, a patient who requires surgery despite vigorous medical therapy (including anti-TNF) may indicate a more aggressive disease and/or failed medical therapy. These discrepancies may have been behind the negative results reported by Armuzzi et al, where more than 50% of patients were treated with IFX and more than 30% were treated with both IFX and AZA prior to surgery compared with 0% of patients in the study by Yoshida et al In addition, post-operative treatment was not standardized across studies. Two studies used metronidazole in all patients post-operatively, the study by Yoshida et al included elemental diet in the majority of patients post-operatively.

There was discrepancy between the reported endoscopic and clinical recurrence rates which has been reported in many other studies. It is possible that the clinical indices used, as important as they are, have substantial limitations in the post-operative setting due to the confounding structural effects of ileal resection. For example, many patients experience diarrhea after ileal resection depending on the length of the resected segment. Thus, diarrhea after surgery may not indicate recurrence of Crohn's disease. By including diarrhea as an indicator of clinical activity, authors may have over-estimated the frequency of Crohn's recurrence [35].

We used a conservative approach in our analysis of clinical recurrence. If a patient in the anti-TNF group was not in remission by any criteria, that patient was counted as a "failure" or clinical recurrence. Had we changed our analysis to count recurrence as CDAI >200 or to adopt the lower recurrence rates when two scores were used, the clinical recurrence data would have been substantially more robust and would not have changed with sensitivity analysis when the study by Savarino was removed (data not included).

The studies by Regueiro et al and Savarino et al had very similar designs with a few exceptions, including the use of adalimumab instead of IFX for 24 instead of 12 months. However, the study by Savarino et al was the only study that reported a significant and positive effect of adalimumab on all primary and secondary outcomes and parameters measured, including quality of life, CRP and ESR. We analyzed the data based on the assumption that adalimumab and IFX exhibit similar efficacy and tolerance profiles. Although there is no (and likely will never be) a head-to-head direct comparison between the two medicines in this setting, we feel there is no evidence to indicate that a significant difference in efficacy exists between the two agents. Although not all experts in the field agree with this statement, a very recent (in-press) population-based study by Oserman et al supports the relatively equal efficacies of IFX and adalimumab (indirect comparison) [36, 37].

One other limitation of the analysis, is that the overall quality of evidence is reduced due to imprecision (small number of events, very wide 95% CI of the individual studies potentially masking heterogeneity).

Despite the above limitations, the efficacy of IFX or adalimumab in preventing endoscopic and clinical recurrence appears to be significantly superior to other interventions currently available, with a relatively large and consistent effect size across studies and very small number needed to treat. The efficacy of the anti-TNF agents is further supported by long-term follow-up data and the outcome of withholding treatment. Recent reports have demonstrated very

substantial rates of endoscopic, clinical and even surgical disease recurrence shortly (within 4-6 months) after treatment when an anti-TNF agent was stopped [23, 30, 34].

There is at least one large dedicated multicenter randomized trial that is being conducted to provide higher quality evidence on the efficacy of infliximab for the prevention of clinical and endoscopic recurrence. The primary outcome in this study will be both clinical and endoscopic recurrence at week 76 and will enroll 299 patients. It is expected to be completed by mid-2016 [38]. In addition, a few more studies are being conducted, and adalimumab with smaller numbers and are expected to be completed around the same time. Until results from these studies become available, the best available evidence for the use of anti-TNF agents for the prevention of endoscopic and clinical recurrence of Crohn's disease is compiled in our meta-analysis.

One final question remains to be answered: should every patient with Crohn's disease who undergoes respective surgery be started on anti-TNF therapy? The answer to this question, in our opinion, is probably no. Anti-TNF therapy remains costly and carries increased risk of infection and malignancy. Therefore, the risk of recurrence after surgery should be determined and patients at moderate or high risk for recurrence should be considered for prophylactic anti-TNF therapy immediately after surgery. Although no predictive model exists, risk factors for postoperative recurrence include smoking, penetrating disease, having two or more resections, and short time between diagnosis and first surgery [39, 40]. Patients without these risk factors or with long-standing Crohn's disease or who undergo an initial Crohn's disease surgery for a short stricture (<10 cm) are considered to be at low risk for postoperative recurrence. These patient may be managed by surveillance endoscopy, laboratory markers of inflammation (serum CRP, stool calprotectin or lactoferrin) and clinical indices [40, 41]. Once evidence of recurrence is present, treatment with anti-TNF is probably indicated (**Figure 2**).

Furthermore, Crohn's disease patients requiring surgery can be broadly grouped into three categories that may dictate post-operative approach to recurrence prophylaxis:

1. Patients with benign non-inflamed stricture: these patients can be managed expectantly with surveillance endoscopies (initially every 6 months with increasing intervals if remain in remission). If disease recur endoscopically or clinically, treatment might be indicated with immunomodulators or anti-TNF agents.

2. Patients with slow smoldering disease resulting in the need for resection: these patients will likely need prophylaxis immediately post-operatively with immunomodulators or anti-TNF agents.

3. Patients with crescendo/aggressive disease progressing to resection: these patients will likely require a combination of immunomodulators and anti-TNF agent [40].

This paradigm is being validated and hopefully results will become available soon. (Personal communication with Miguel Regueiro, MD).

Disclosure of conflict of interest

None of the authors has any conflict of interest relevant to the manuscript.

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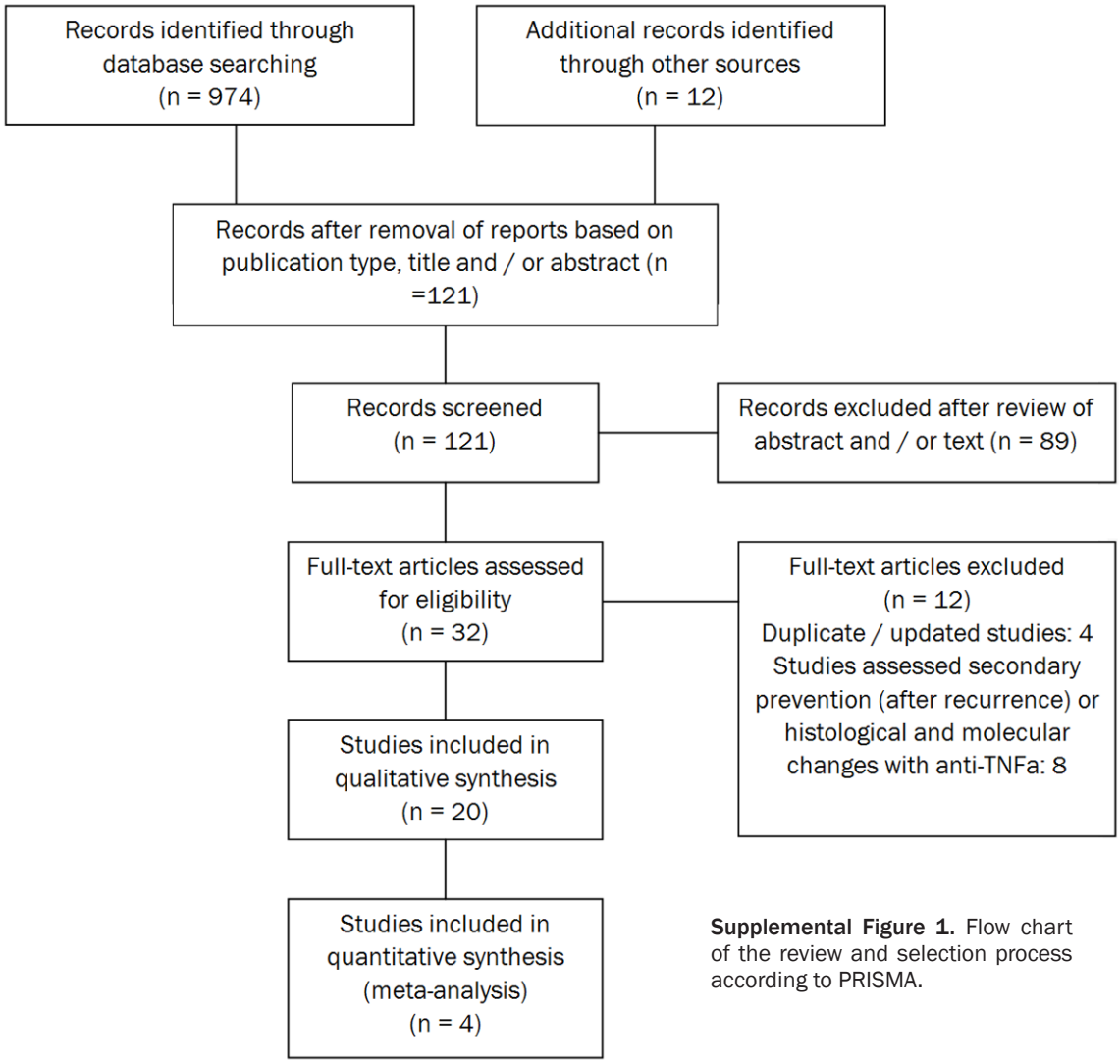
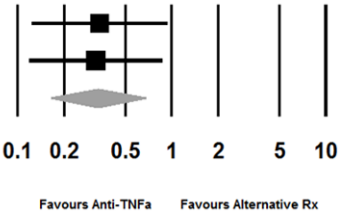


Supplemental Figure 1. Flow chart of the review and selection process according to PRISMA.

Supplemental Table 1. The Cochrane Collaboration's tool for risk of bias assessment

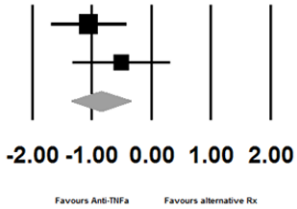
Study	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Regueiro et al	Yes	Yes	Yes	Yes	Yes	Yes
Yoshida et al	unclear	No	No	Yes	Yes	Yes
Armuzzi et al	unclear	No	No	Yes	unclear	No
Sorrentino et al	Yes	Yes	No	Yes	Yes	Yes

Study name	Risk ratio	Lower limit	Upper limit	p-Value	Anti-TNFa Treated	Control
Armuzzi et al (2013)	0.341	0.124	0.939	0.037	3 / 11	8 / 10
Regueiro et al (2009)	0.322	0.119	0.870	0.025	3 / 11	11 / 13
	0.331	0.163	0.673	0.002		



Supplemental Figure 2. Pooled Risk Ratio (RR) of histologic recurrence (anti-TNF treated vs. non-treated).

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	p-Value
Savarino et al	-1.056	0.319	0.102	-1.682	-0.430	0.001
Regueiro et al	-0.506	0.416	0.173	-1.321	0.310	0.224
	-0.852	0.253	0.064	-1.349	-0.356	0.001



Supplemental Figure 3. Pooled CRP differences in means (anti-TNF treated vs. non-treated).