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Comparing adalimumab and infliximab in the prevention of postoperative recurrence of Crohn's disease: a systematic review and meta-analysis

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Abstract

Background Crohn's disease is a relapsing disease that often requires operative management. Prevention of postoperative recurrence (POR) is critical to maintain remissions. Biologic agents have proven to be most successful in remission maintenance. We made a direct head-to-head comparison of the 2 anti-tumor necrosis factor agents, infliximab (IFX) and adalimumab (ADA), to compare endoscopic and clinical POR of Crohn's disease.

Methods We conducted a comprehensive literature search in 7 databases, including Medline, Embase, Cochrane Central Register of Controlled Trials, Web of Science Core Collection, KCI-Korean Journal Index, SciELO, and Global Index Medicus. Odds ratios (OR) were calculated with 95% confidence intervals (CI) and P-values (<0.05 considered significant). We evaluated the total rates of endoscopic recurrence, endoscopic recurrence at 1 year, and clinical recurrence rates of IFX and ADA in a direct head-to-head comparison.

Results The search strategy yielded a total of 393 articles. Three studies with a total of 268 participants were included. Our meta-analysis showed no statistically significant difference in total endoscopic recurrence rate between ADA and IFX (27.1% vs. 32.3%, OR 0.696, 95%CI 0.403-1.201; P=0.193; I^2=0%). Nor was there any significant difference between the drugs in endoscopic recurrence rate at 1 year (OR 0.799, 95%CI 0.329-1.940; P=0.620) or clinical recurrence rate (OR 0.477, 95%CI 0.477-1.712; P=0.755).

Conclusions ADA and IFX show comparable efficacy in preventing POR endoscopically and clinically. The clinical decision should be based on cost, side-effects, tolerability, and patient preferences. Additional studies, particularly randomized controlled trials, are needed to determine generalizability.

Keywords Postoperative recurrence, Crohn's disease, adalimumab, infliximab, biologics

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Conflict of Interest: None

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Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) with a relapsing and remitting nature and a disabling progression with complications such as intestinal strictures, enteric fistulae, inflammatory masses, or abscesses [1]. Although rates of surgical management are declining over the years, as newer biological therapies emerge, surgical management is still warranted in a significant proportion of patients within 10 years of diagnosis [2]. Considering the disease process, postoperative recurrence (POR) remains high, with clinical recurrence rates at around 30-60% within 3-5 years, and a significant percentage of patients may require a second resection within 5 years [3]. Endoscopic recurrence with mucosal lesions can be up to 70%

occurring within 1 year of surgery, and histologic recurrence can occur as early as 1 week after surgery. The rates of POR are even higher in high-risk patients such as smokers, cases of early diagnosis, or those with a history of perianal disease or prior intestinal resection [4]. Endoscopic POR severity correlates fairly well with the likelihood of developing clinical POR in the near future and can serve as a surrogate marker for the risk of clinical POR to drive therapeutic decisions in clinical practice [2].

There have been a variety of therapeutic agents evaluated to prevent POR endoscopically and clinically to induce and maintain remission, though with inconsistent results. Postoperative prophylaxis with anti-tumor necrosis factor (TNF) agents or thiopurines (azathioprine, 6-mercaptopurine) has been shown in the literature to reduce the risk of POR [5]. Anti-TNF agents, such as adalimumab (ADA), a self-injected, fully humanized recombinant monoclonal antibody, and infliximab (IFX), a chimeric immunoglobulin G human (75%)/murine (25%) administered by intravenous infusion, have been shown to be effective in preventing endoscopic and clinical POR [3,6]. According to a recent meta-analysis, anti-TNF therapy outperformed other therapeutic strategies, including thiopurines, but the study did not include a direct comparison between anti-TNF therapies [7].

Considering the better outcomes of biologics compared to other therapeutic strategies, as seen in various studies, we aimed to make a head-to-head direct comparison between the most commonly used biologics, ADA and IFX, to evaluate their efficacy in preventing POR endoscopically and clinically, with a view to optimizing therapeutic management strategies.

Materials and methods

Search strategy

The "Meta-analysis of observational studies (MOOSE)" guidelines for systematic reviews were used to plan the study; we adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines; no language restriction was applied [8,9]. A comprehensive literature search from inception through September 9th 2022 was conducted using the Medline (PubMed, NCBI), Embase (Embase.com, Elsevier), Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley), Web of Science Core Collection, KCI-Korean Journal Index, SciELO (Web of Science, Clarivate), and Global Index Medicus (World Health Organization) databases. An experienced librarian (WLS) assisted with the search methodology. The core concepts of "Crohn's disease", "infliximab", "adalimumab", "recurrence or remission" and the postoperative period, and their corresponding subject heading terms, were searched in the above databases (Supplementary Table 1). We added manual searching and cross-referencing to the computerized literature search. Results were exported to EndNote 20 (Clarivate, Philadelphia, Pennsylvania, United States) and duplicates were removed by successive algorithmic deduplication and manual inspection.

Inclusion and exclusion criteria

We limited the screening to include randomized controlled trials (RCTs) and observational studies with head-to-head comparisons between ADA and IFX. Outcomes assessed included clinical recurrence rate, endoscopic recurrence at 1 year and overall endoscopic recurrence. Abstracts were included in the search strategy, as we anticipated a lower number of full-text studies overall. We excluded case reports, case series (<10 patients), editorials, guidelines and review articles.

Study definitions

Study definitions, including endoscopic recurrence and clinical recurrence of each study, are described in Supplementary Table 2.

Screening and data extraction

Two independent investigators (FP and DSD) conducted the screening and data extraction. Conflict resolution was achieved through mutual discussion. Initially, titles and abstracts were screened, followed by full texts. Data pertaining to technical and clinical success rates, adverse events, length of hospital stay, and procedure time were recorded using Microsoft Excel (Microsoft, Redmond, Washington, United States).

Data synthesis and statistical analysis

Statistical analysis was performed using Open Meta-Analyst (CEBM, University of Oxford, Oxford, United Kingdom). We calculated the pooled rates of each outcome. Dichotomous variables were compared using the odds ratio (OR) with a 95% confidence interval (CI) and P-value (<0.05 was considered statistically significant). We used the random effects model and DerSimonian-Laird method for pooling data [10]. Study heterogeneity was calculated with the I^2 statistic, in which

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Table 1 Baseline characteristics of included studies

Author [ref.]	Year	Type of study	Duration of study (years)	Patient population	ADA/IFX	Subset	Age	Female (n/N)	Male (n/N)
Kotze [14]	2015	Retrospective	5	96	ADA	37	33.6±12.1	16/37 (43.2)	21/37 (56.8)
					IFX	59	31.1±10.9	21/59 (35.6)	38/59 (64.4)
Tursi [13]	2014	Prospective randomized	2.5	20	ADA	10	34.5	6/10 (60)	4/10 (40)
					IFX	10	30.5	5/10 (50)	5/10 (50)
Cañete [1]	2019	Retrospective	1.5	152	ADA	97	40.3±13.5	47/97 (48.5)	50/97 (51.5)
					IFX	55	41.0±14.8	20/55 (36.4)	35/55 (63.6)

ADA, adalimumab; IFX, infliximab

values of 0%, 25%, 50%, and 75% indicate absent, low, moderate and high heterogeneity, respectively.

Bias assessment

A risk-of-bias assessment for the observational studies was performed using the Newcastle-Ottawa scale. One study was a randomized control trial and the risk of bias for RCTs was assessed using the Cochrane risk-of-bias tool [11,12]. Funnel plots were used for the qualitative and Egger regression tests for the quantitative analysis of publication bias; a P-value of <0.05 was considered significant for the latter.

Results

Baseline study characteristics

The search strategy yielded a total of 393 articles. From these, 286 studies were screened by title and abstract, leaving 116 studies for full text screening after removal of duplicates. Three studies with 268 participants [1,13,14], 144 in the ADA group and 124 in the IFX group, were selected for final inclusion after strict inclusion and exclusion criteria had been applied (Fig. 1). No abstracts met the inclusion criteria to be included in final analysis. The studies were published between 2014 and 2019. The mean age of participants ranged from 30.5-41.1 years; 115 (42.9%) of the subjects were female (69 in ADA and 46 in IFX group) and 153 (57.1%) were male (75 in ADA and 78 in IFX group), as described in Table 1. The duration of disease ranged from 48-84 months; 19.7% participants had a history of smoking, 41.5% had prior resections, 68.3% had previous biologic use, and 30.2% subjects had history of perianal disease (Table 2).

Outcomes

Our meta-analysis showed no difference in the total endoscopic recurrence rate between ADA and IFX (27.1% vs. 32.3%, OR 0.696, 95%CI 0.403-1.201; P=0.193; I^2=0%) in 3 studies (Fig. 2A). Two studies evaluated endoscopic recurrence at 1 year and no statistically significant difference was found between the 2 groups (21.3% vs. 26.1%, OR 0.799, 95%CI 0.329-1.940; P=0.620; I^2=0%) as shown in Fig. 2B. There was no significant difference in overall clinical recurrence rates between the 2 groups (18.1% vs. 18.5%, OR 0.477, 95%CI 0.477-1.712; P=0.755; I^2=0%) as shown in Fig. 2C.

Risk of bias

Evaluation of publication bias using funnel plots and Egger's regression was impractical because of the low number of studies. Two studies were assessed using the Newcastle-Ottawa scale (Table 3). The score was 7, reflecting a moderate to high quality of studies. The risk of bias for the one RCT was determined to be high, because of its open label format with unblinded clinical and endoscopic evaluations.

Discussion

In a direct head-to-head comparison between the biologics, ADA and IFX did not yield any statistically significant difference in endoscopic or clinical recurrence rate. The study characteristics and risk factors were similar in both groups. The recurrence of CD post-surgery has been under investigation for many decades. Postoperative prophylaxis has been greatly studied, with a variety of therapeutic classes. Current guidelines for initiation of postoperative prophylaxis are variable [2,15]. The latest American Gastroenterology Association guidelines recommend using preoperative risk stratification to consider POR therapy with anti-inflammatory monoclonal antibodies in high-risk patients, including those aged <30, smokers and those with >2 prior surgeries [16]. IBD guidelines from the European Crohn's and Colitis Organization include additional risk factors, such as extensive small bowel resection (>50 cm), perianal disease, histologic evidence of granulomas or myenteric plexitis on resected specimens [15].

Table 2 Characteristics of included studies

Author [ref.]	Subset (ADA/IFX)	Age<3rd year of diagnosis or young age (years)	Smoking (%)	Disease duration (months)	Previous resections (%)	Biologics before surgery (%)	Perianal disease before surgery (%)	Endoscopic recurrence rate at 1 year (%)	Total endoscopic recurrence rate (%)	Clinical recurrence rate (%)	Adverse events	Complications
Kotze [14]	ADA	N/A	4/37 (10.8)	84	12 (32.4)	17 (46)	9/37 (24.3)	9/37 (8.1)	9/37 (24.32)	6/37 (16.2)	N/A	N/A
	IFX	N/A	9/59 (15.3)	82	25 (42.4)	33 (55.9)	22/59 (37.3)	9/59 (5.0)	16/59 (27.11)	10/59 (17)	N/A	N/A
Tursi [13]	ADA	2/10 (20)	2/10 (20)	48	N/A	9/20 (45)	4/10 (40)	1/10 (10)	1/10 (10)	1/10 (10)	N/A	N/A
	IFX	3/10 (30)	3/10 (30)	48	N/A		4/10 (40)	2/10 (20)	2/10 (20)	1/10 (10)	N/A	N/A
Cañete [1]	ADA	N/A	23/97 (23.7)	N/A	37/97 (38.1)	83/97 (85.6)	26/97 (26.8)	66/152 (44)	29/97 (46)	19/97 (20)	1 (1)	N/A
	IFX	N/A	12/55 (21.8)	N/A	29/55 (52.7)	41/55 (74.5)	16/55 (29)		22/55 (51)	12/55 (21)	0 (0)	N/A

ADA, adalimumab; IFX, infliximab

Tursi *et al* observed that active smoking, penetrating disease and previous surgery all significantly increased the possibility of postoperative relapse [13]. Cañete *et al* determined that pan-colonic involvement, rectal involvement and perianal disease were significantly associated with endoscopic POR in a univariate analysis [1]; however, only rectal involvement and a history of perianal disease were shown to be independent risk factors in a multivariate analysis.

The determination and reduction in postoperative endoscopic recurrence rates are critical in managing risk, as these rates can serve as an essential marker to prevent future clinical recurrences. Postoperative recurrence rates have been variable in the literature, as a result of advances in pre- and postoperative therapeutics over the years [15]. Our overall postoperative endoscopic recurrence rate for any biologic use was noted to be 29.4%. Our results are similar to those of large independent studies evaluating anti-TNF therapies. In the Prevent trial, which evaluated IFX, a postoperative endoscopic recurrence rate of 22% was reported, similar to our finding of 27.1% in the IFX group [17]. Similarly, in the Apprecia trial, which evaluated ADA, the postoperative endoscopic recurrence rate was 33%, similar to our results at 32.3% [18]. Regarding the efficacy of anti-TNF agents to treat recurrent disease, a study by Preda *et al*, which compared ADA and IFX in treating POR, showed a complete remission in 68% of patients over long-term follow up, with an endoscopic recurrence of 35% and re-resection rate 11.7% [5].

Both therapeutic options are reasonable and have their individual merits, and decisions should be based on individual patient characteristics and availability. Both therapies have relatively similar side-effect profiles. Including cutaneous musculoskeletal complications or pruritus, dyspnea, urticaria or skin reactions, with some risk of opportunistic infections. Theoretically, ADA can be considered less immunogenic, as it is fully humanized compared to IFX, a chimeric antibody. Therefore, it can potentially be expected to be associated with fewer side-effects and opportunistic infections; however, there are few publications that evaluate the comparison [19].

Patient factors, costs and logistics may also play an important role in therapeutic determination. IFX is an intravenous infusion lasting about 2 h, whereas ADA is a self-administered subcutaneous injection, potentially favoring better compliance and ease of logistics [20]. Cañete *et al* observed that the time to the start of treatment with IFX was significantly longer than with ADA, but this had no effect on treatment efficacy [1]. The most likely explanation for this difference in timing is that IFX has more logistical requirements than ADA, including the need for an infusion unit, which may delay the first administration of the drug [1]. There are no direct postoperative cost analysis comparisons in relation to POR. Previous studies of anti-TNF use in ulcerative colitis have showed that induction and maintenance therapy with IFX or ADA were less expensive than standard care when administered for 1 or 2 years only. In one review, induction and maintenance treatment with ADA was less expensive than IFX infusions. However, these cannot be extrapolated to the postoperative CD population, given the variation in therapy duration and the complex nature of the

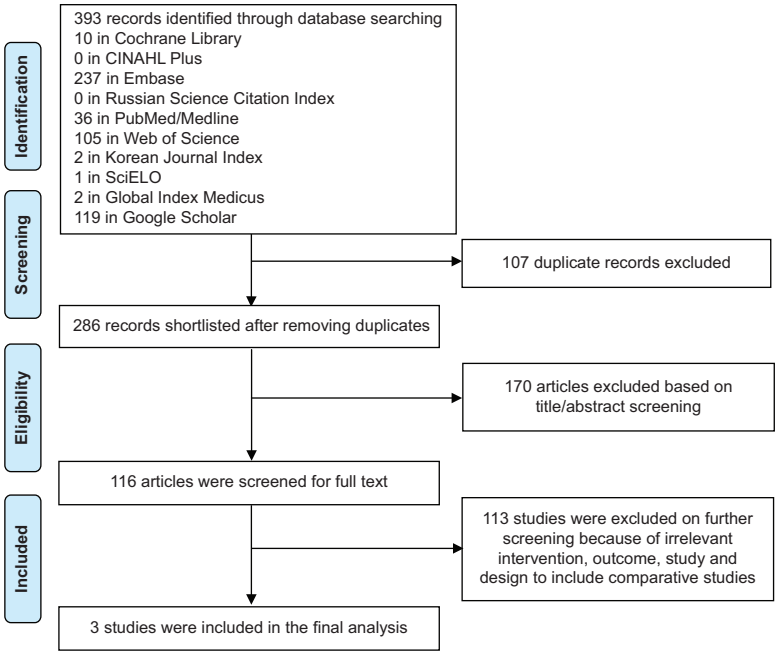

Figure 1 PRISMA flowchart of included studies

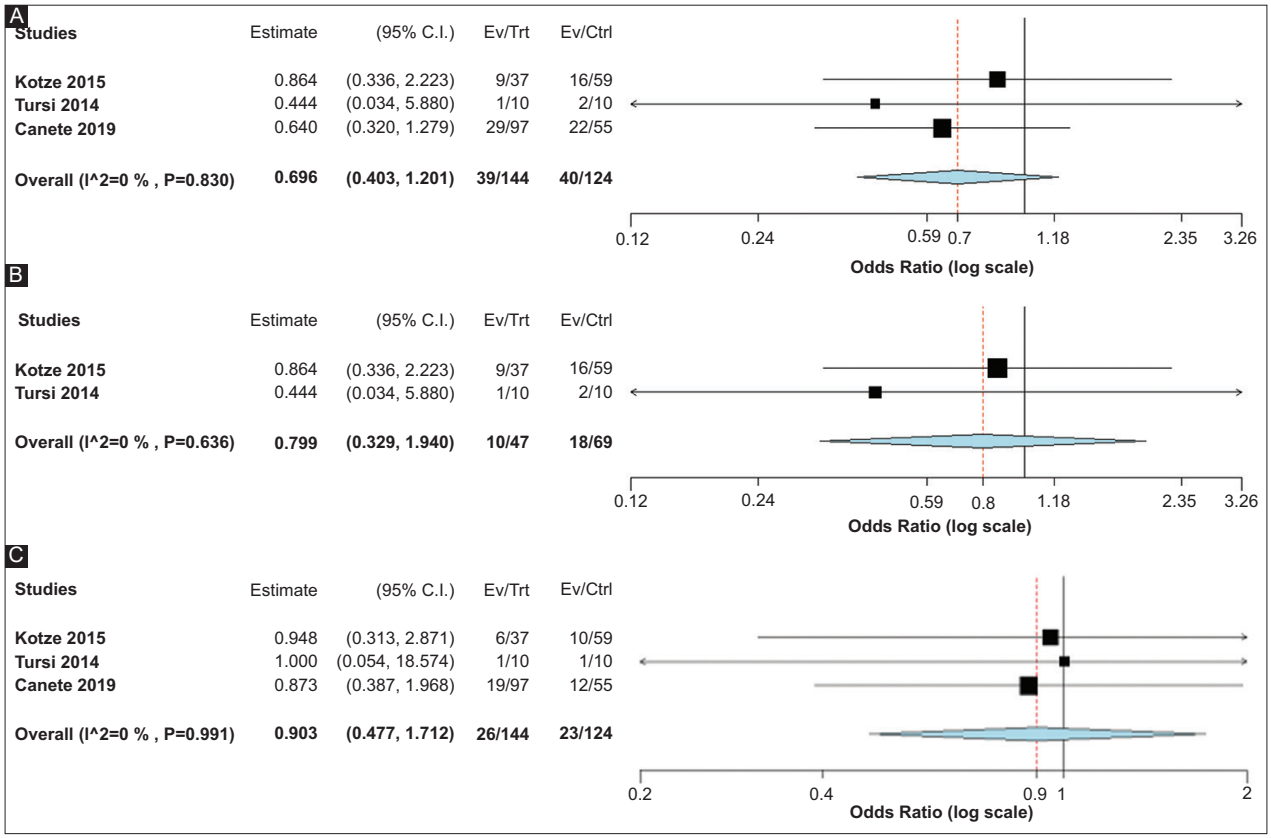

Figure 2 (A) Comparing endoscopic recurrence rate between IFX and ADA. (B) Comparing endoscopic recurrence rate between IFX and ADA at 1 year. (C) Comparing clinical recurrence rate between IFX and ADA
ADA, adalimumab; IFX, infliximab; CI, confidence interval

Table 3 Newcastle-Ottawa scale for illustration of quality of studies

Study	Selection				Comparability	Outcomes			
Author [ref.]	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Confounding factors are controlled	Assessment of outcome	Follow up long enough for outcomes	Adequacy of follow up of cohorts	Total
(9 stars)									
Kotze [14]	*	*	*	-	**	*	-	*	*******
Cañete [1]	*	*	*	-	*	*	*	*	*******

pharmaceutical and insurance coverage systems in the United States [20].

In patients with a high risk of POR, especially after failed anti-TNF therapy, combination therapy of a biologic agent with an immunomodulator could be a reasonable treatment strategy. In a recent study by Huinink *et al*, patients with preoperative anti-TNF treatment failure demonstrated a lower treatment failure rate at 2 years postoperatively under combination therapy of anti-TNF with an immunomodulator compared to anti-TNF monotherapy (30% vs. 49%, P=0.02) [21].

For newer biologics, such as ustekinumab and vedolizumab, there are only limited data evaluating their role in POR [22]. One retrospective study, which evaluated 22 patients with CD receiving vedolizumab compared with 58 patients who received anti-TNF for POR prophylaxis, demonstrated that patients in the vedolizumab group were at greater risk of endoscopic recurrence (75% vs. 34.2%, P=0.005) [23]. In another propensity-matched analysis, endoscopic POR was lower for ustekinumab than for azathioprine (28% vs. 54.5%, P=0.03) with rates similar to other anti-TNF medications, but the data were insufficient to suggest any definitive superiority [24].

Our study had various limitations. We did not stratify for potential risk factors or their impact on our analysis, as the data were too limited for meaningful cumulative analysis. There were only 2 studies evaluating endoscopic recurrence at one year for comparative analysis. Some studies have shown anti-TNF therapy to be effective in patients who are biologic-

Summary Box

What is already known:

- Crohn's disease has endoscopic recurrence in up to 70% of patients, occurring within 1 year of surgery, and histologic recurrence can occur as early as 1 week after surgery
- A variety of therapeutic agents have been evaluated to prevent postoperative recurrence endoscopically and clinically, and to induce and maintain remission
- Anti-tumor necrosis factor (TNF) agents, including adalimumab (ADA) and infliximab (IFX), are superior to other therapeutic agent
- There has been no direct head-to-head comparison between these 2 anti-TNF agents

What the new findings are:

- ADA and IFX have comparable efficacy in preventing postoperative recurrence endoscopically and clinically
- The clinical decision should be based on costs, side-effect profile, tolerability, and patient preferencesy
- Large randomized controlled trials should be performed to determine the generalizability of these findings and the role of anti-TNF agents in combination with thiopurines

naïve, with lower reoperation rates, but not in patients who had failure of biologic therapy prior to surgery. Given the limited data and heterogeneity, we could not stratify for prior therapeutic classes or any history of biologic failure when comparing 2 outcomes [25]. Additionally, we could not include other newer biologics, such as ustekinumab or vedolizumab, since direct comparator data were not available [25]. Data to compare adverse event rates were limited or unavailable. The length of follow up was variable among the studies; therefore, we added a 1-year cutoff for endoscopic recurrence, so as to have a homogenous cutoff point as an outcome.

Our review is the first and only head-to-head direct comparison between IFX and ADA therapy for preventing POR in patients with CD. We believe both therapies have comparable efficacy in preventing POR endoscopically and clinically. The clinical decision should be based on costs, side-effect profile, tolerability and patient preferences. Additional studies, particularly large RCTs, should be performed to determine generalizability, assess the role of anti-TNF in combination with thiopurines to reduce POR and evaluate the newer biologics.

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Supplementary material

Supplementary Table 1 Embase Search Strategy (Embase.com, Elsevier. Performed on 9 September 2022)

No.	Query	Results
#1	'crohn disease'/exp OR 'crohn disease*':ti, ab, kw OR 'cleron disease*':ti, ab, kw OR 'crohn s disease*':ti, ab, kw OR 'crohns disease*':ti, ab, kw OR 'enteritis regionalis*':ti, ab, kw OR 'morbus crohn*':ti, ab, kw OR 'regional enteritis*':ti, ab, kw OR 'regional enterocolitis*':ti, ab, kw OR 'granulomatous enteritis*':ti, ab, kw OR 'granulomatous colitis*':ti, ab, kw OR 'terminal ileitis*':ti, ab, kw OR 'regional ileitis*':ti, ab, kw OR ileocolitis*:ti, ab, kw	118581
#2	'adalimumab'/exp OR 'adalimumab':ti, ab, kw OR 'abp-501':ti, ab, kw OR 'abp501':ti, ab, kw OR 'abrilada':ti, ab, kw OR 'abt-d2e7':ti, ab, kw OR 'abtd2e7':ti, ab, kw OR 'adaly':ti, ab, kw OR 'amgevita':ti, ab, kw OR 'amjevita':ti, ab, kw OR 'amsparity':ti, ab, kw OR 'avt-02':ti, ab, kw OR 'avt02':ti, ab, kw OR 'bat-1406':ti, ab, kw OR 'bat1406':ti, ab, kw OR 'bax-2923':ti, ab, kw OR 'bax-923':ti, ab, kw OR 'ba×2923':ti, ab, kw OR 'ba×923':ti, ab, kw OR 'bcd-057':ti, ab, kw OR 'bcd057':ti, ab, kw OR 'bi-695501':ti, ab, kw OR 'bi695501':ti, ab, kw OR 'bxt-2922':ti, ab, kw OR 'bxt2922':ti, ab, kw OR 'chs-1420':ti, ab, kw OR 'chs1420':ti, ab, kw OR 'cinnora':ti, ab, kw OR 'ct-p17':ti, ab, kw OR 'ctp17':ti, ab, kw OR 'cyltezo':ti, ab, kw OR 'da-3113':ti, ab, kw OR 'da3113':ti, ab, kw OR 'd2e7 antibody':ti, ab, kw OR 'dmb-3113':ti, ab, kw OR 'dmb3113':ti, ab, kw OR 'exemptia':ti, ab, kw OR 'fkb-327':ti, ab, kw OR 'fkb327':ti, ab, kw OR 'fyzoclad':ti, ab, kw OR 'gp-2017':ti, ab, kw OR 'gp2017':ti, ab, kw OR 'hadlima':ti, ab, kw OR 'halimatoz':ti, ab, kw OR 'hefiya':ti, ab, kw OR 'hlx-03':ti, ab, kw OR 'hl×03':ti, ab, kw OR 'hukyndra':ti, ab, kw OR 'hulio':ti, ab, kw OR 'humira':ti, ab, kw OR 'hyrimoz':ti, ab, kw OR 'ibi-303':ti, ab, kw OR 'ibi303':ti, ab, kw OR 'idacio':ti, ab, kw OR 'imraldi':ti, ab, kw OR 'jy-026':ti, ab, kw OR 'jy026':ti, ab, kw OR 'kromeya':ti, ab, kw OR 'libmyris':ti, ab, kw OR 'lu-200134':ti, ab, kw OR 'lu200134':ti, ab, kw OR 'm-923':ti, ab, kw OR 'm923':ti, ab, kw OR 'mabura':ti, ab, kw OR 'monoclonal-antibody-d2e7':ti, ab, kw OR 'msb-11022':ti, ab, kw OR 'msb11022':ti, ab, kw OR 'ons-3010':ti, ab, kw OR 'ons3010':ti, ab, kw OR 'pbp-1502':ti, ab, kw OR 'pbp1502':ti, ab, kw OR 'pf-06410293':ti, ab, kw OR 'pf-6410293':ti, ab, kw OR 'pf06410293':ti, ab, kw OR 'pf6410293':ti, ab, kw OR 'qletli':ti, ab, kw OR 'raheara':ti, ab, kw OR 'sb-5':ti, ab, kw OR 'sb5':ti, ab, kw OR 'solymbic':ti, ab, kw OR 'sulinno':ti, ab, kw OR 'trudexa':ti, ab, kw OR 'yuflyma':ti, ab, kw OR 'yusimry':ti, ab, kw OR 'zrc-3197':ti, ab, kw OR 'zrc3197':ti, ab, kw	42739
#3	'infliximab'/exp OR 'infliximab':ti, ab, kw OR 'abp-710':ti, ab, kw OR 'abp710':ti, ab, kw OR 'avakine':ti, ab, kw OR 'avsola':ti, ab, kw OR 'bcd-055':ti, ab, kw OR 'bcd055':ti, ab, kw OR 'bow-015':ti, ab, kw OR 'bow015':ti, ab, kw OR 'cmab-008':ti, ab, kw OR 'cmab008':ti, ab, kw OR 'ct-p13':ti, ab, kw OR 'ctp13':ti, ab, kw OR 'flixabi':ti, ab, kw OR 'gb-242':ti, ab, kw OR 'gb242':ti, ab, kw OR 'gp-1111':ti, ab, kw OR 'gp1111':ti, ab, kw OR 'inflectra':ti, ab, kw OR 'ixifi':ti, ab, kw OR 'pf-06438179':ti, ab, kw OR 'pf-6438179':ti, ab, kw OR 'pf06438179':ti, ab, kw OR 'pf6438179':ti, ab, kw OR 'remicade':ti, ab, kw OR 'remsima':ti, ab, kw OR 'renflexis':ti, ab, kw OR 'revellex':ti, ab, kw OR 'sti-002':ti, ab, kw OR 'sti002':ti, ab, kw OR 'ta-650':ti, ab, kw OR 'ta650':ti, ab, kw OR 'zessly':ti, ab, kw OR 'mab ca2':ti, ab, kw OR 'monoclonal antibody ca2':ti, ab, kw	60017
#4	#2 AND #3	26988
#5	#1 AND #4	8526
#6	'postoperative period'/de OR 'enhanced recovery after surgery'/de OR 'postoperative care'/exp OR 'postoperative complication'/de OR 'post operati*' OR postoperati* OR 'after operation' OR 'post surg*' OR postsurg* OR 'after surg*' OR 'post resection*' OR postresect* OR 'after resection' OR 'post colectom*' OR postcolectom* OR 'after colectomy' OR 'post enterectom*' OR postenterectom* OR 'after enterectomy' OR 'post ileostomy*' OR postileostomy* OR 'after ileostomy'	1589422
#7	'remission'/exp OR 'recurrence risk'/exp OR 'recurrent disease'/exp OR 'clinical outcome'/exp OR 'treatment response'/exp OR 'drug efficacy'/exp OR recur* OR relaps* OR remission* OR recrudescen* OR 'drug efficac*' OR 'drug effectiv*' OR 'pharmacological effective*' OR 'pharmacological effic*' OR 'treatment response*' OR 'therapeutic response*' OR 'treatment outcome*' OR 'therapeutic outcome*' OR 'clinical outcome*'	3912196
#8	#6 AND #7	488713
#9	#5 AND #8	441
#10	#9 NOT ([animals]/lim NOT [humans]/lim) NOT ('conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR 'tombstone'/it OR 'case report'/de OR 'meta analysis'/de OR 'meta analysis topic'/de OR 'systematic review'/de OR 'systematic review topic'/de)	237

Supplementary Table 2 Study definitions

Author [ref.]	Postoperative endoscopic recurrence	Clinical recurrence
Kotze [14]	Presence of a Rutgeerts' score≥i2 in the neo-terminal ileum at the first postoperative colonoscopy	N/A*
Tursi [13]	Rutgeerts' score >2	Harvey-Bradshaw index >8
Cañete [1]	Rutgeerts' score >i1 Advanced Endoscopic Recurrence: Rutgeerts' score >i2	Digestive symptoms together with disease activity seen at ileocolonoscopy or magnetic resonance enterography

N/A, Definitions not available*

Supplementary Table 3 Therapy initiation time and endoscopic evaluation

Author [ref.]	Time of treatment initiation	Period of postoperative endoscopy (months)
Kotze [14]	4-12 weeks	Variable up to 12 months
Tursi [13]	4-12 weeks	6, 12
Cañete [1]	4-12 weeks	6, 12, 18