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Title: Anti-TNFα agents are the best choice in preventing postoperative Crohn's disease: a meta-analysis

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Keywords: Crohn's disease; postoperative recurrence; preventive treatment; anti-TNFα; infliximab; adalimumab

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Abstract: Background: Despite the high rate of postoperative recurrence (POR) in Crohn's disease (CD), there is no widely accepted consensus on its prevention.
Aim: To compare the efficacy of biological and conventional therapies in preventing POR of CD.
Methods: We searched four electronic databases up to April 2019 for articles that examined the efficacy of different preventive therapies against POR. Our PICO was: (P) adults with CD who underwent intestinal resection, (I) biological agents, (C) conventional therapies or a placebo, and (O) clinical, endoscopic, and histological POR.
Results: Anti-TNFα agents were significantly better in preventing clinical, endoscopic, severe endoscopic and histological POR compared to conventional therapies (OR: 0.508, 95% CI: 0.309-0.834, P = 0.007; OR: 0.312, 95% CI: 0.199-0.380, P < 0.001; OR: 0.195, 95% CI: 0.107-0.356, P < 0.001; and OR: 0.255, 95% CI: 0.106-0.611, P = 0.002, respectively), as well as in the subgroup of nonselected CD patients (OR: 0.324, 95% CI: 0.158-0.664, P = 0.002; OR: 0.225, 95% CI: 0.124-0.409, P < 0.001; and OR: 0.248, 95% CI: 0.070-0.877, P = 0.031, respectively). Infliximab and adalimumab proved to be equally effective in preventing endoscopic POR.
Conclusion: Anti-TNFα agents are more effective in preventing clinical, endoscopic and histological POR than conventional therapies, even in nonselected CD patients.

***Cover Letter**

Dear Roberto de Franchis, Editor-in-Chief,

Thank you very much for evaluating our manuscript entitled “Anti-TNF-alpha agents are the best choice in preventing postoperative Crohn's disease: a meta-analysis.” (Manuscript number: DLD-19-148).

We completed the first sentence of the abstract, as requested. We would like to thank again the editors and the reviewers the time spent on the evaluation of our manuscript and the constructive criticism they expressed.

We hope that you will accept the changes and find this paper suitable for publication in the Journal. Thank you for your consideration of our work!

Sincerely,

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Conflict of interest statement

Title of the article: *Anti-TNFα agents are the best choice in preventing postoperative Crohn's disease: a meta-analysis.*

All authors disclaim any form of conflicts of interest.

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Manuscript number: DLD-19-148

REVIEWERS' COMMENTS TO THE AUTHOR:

Reviewer #1: The article entitled "Anti-TNF<alpha> agents are the best choice in preventing postoperative Crohn's disease: a meta-analysis" by Adirenn Eros et al. is a meta-analysis aimed to compare the efficacy of anti-TNF agents and conventional therapy in preventing POR in patients with CD. The main result is that TNF antagonists resulted to be the best drugs in this regards. Moreover, the authors performed a head-to-head comparison between ADA and IFX by using non-RCT data and they found that the efficacy of these two anti-TNF<alpha> agents is nearly the same. Finally, and interestingly, they concluded that it is unnecessary to select patients after intestinal resection based on risk factors because both high-risk patients and unselected patients benefit from early prophylactic anti-TNF therapy postoperatively.

Overall, the manuscript is well written and the analysis well performed. The strengths of this study are: a high number (709) of CD patients evaluated; an update of the literature with regards to POR compared to the previous systematic reviews with meta-analysis published in 2015 and 2016; most of the included trials were RCTs (8/10); in addition to the comparison analysis between anti-TNF and conventional drugs, a comparative analysis between ADA and IFX was performed. The main limitations are: the inclusion on the same analysis data from RCT and data from retrospective/observational studies; the variability of the follow up period among the studies (6-36 months). I have additional suggestions:

- Methods: It is unclear the nature of the two observational studies in the comparison analysis between ADA and IFX (prospective? retrospective?). This data can only be seen from Table I. Please, add this information to the text.

Thank you for this comment. We added the information required to the ‘Characteristics of the included studies’ section of the manuscript.

- Results. The manuscript would be more interesting if data on Vedolizumab have been considered for the comparative analysis (The Use of Vedolizumab in Preventing Postoperative Recurrence of Crohn's Disease. Yamada A, Komaki Y, Patel N, Komaki F, Pekow J, Dalal S, Cohen RD, Cannon L, Umanskiy K, Smith R, Hurst R, Hyman N, Rubin DT, Sakuraba A. Inflamm Bowel Dis. 2018 Feb 15;24(3):502-509)

Thank you for this valuable comment. In order to capture all the latest literature, we added not only the recommended ‘vedolizumab’ to the search strategy, but also other possible biological drugs used in IBD treatment, namely, certolizumab, golimumab and ustekinumab. This

updated search identified four additional studies: three studies with anti-TNF-alpha were eligible for quantitative analysis and, unfortunately, only one study was available with vedolizumab [Yamada et al.]. We were unable to use the data of the vedolizumab-treated group of the Yamada study in our analysis due to several reasons: (1) the number of patients in this study group was very low; (2) we did not find any other studies that evaluated the efficacy of vedolizumab versus conventional therapies in preventing POR, so that this result would have stood alone in a separate subgroup; and (3) the comparator group was the same for the vedolizumab- and the anti-TNF-alpha-treated groups as well (the thiopurine-treated group) while it is not allowed to use the data of the same study group twice in a meta-analysis (due to overrepresentation). Based on the above-mentioned, we decided to use the data of the anti-TNF-alpha- and thiopurine-treated groups from the study of Yamada in the updated statistical analysis. The results of the original study regarding vedolizumab were interpreted in the discussion section of the manuscript.

Thanks to the extended search, histological POR and safety profile of the applied treatment modalities became processable in meta-analysis.

Reviewer #2: In this meta-analysis by Adrienn Eros and and colleagues, the authors aimed to compare the efficacy of anti-TNF<alpha> agents and conventional therapy in preventing POR of CD. In summary, the pooling of the included studies showed that anti-TNF<alpha> agents are more effective in preventing clinical and endoscopic POR than conventional therapies, both in unselected and high-risk CD patients, without significant heterogeneity, and that there was no significant difference between IFX and ADA.

As also stated by the authors in the discussion, this is a hot topic, which has been repeatedly approached through multiple meta-analyses and a Cochrane review in recent years. Therefore, the novelty of this paper is not very robust. Anyway, search strategy and eligibility criteria, data extraction and study quality evaluation (through the Cochrane Risk of Bias Tool for RCTs, and the Newcastle-Ottawa scale for observational studies) are correct for the purpose of the meta-analysis, and the methodology of this study has sufficient overall quality. However, other strategies of analysis could be applied to improve the strength of the results.

In particular, even if the number of the included studies is quite low, a meta-regression with the variables extracted from each study could be performed.

Thank you for this comment. When comparing the efficacy of anti-TNFα treatment and thiopurines in preventing clinical and endoscopic POR, we complemented the analysis with

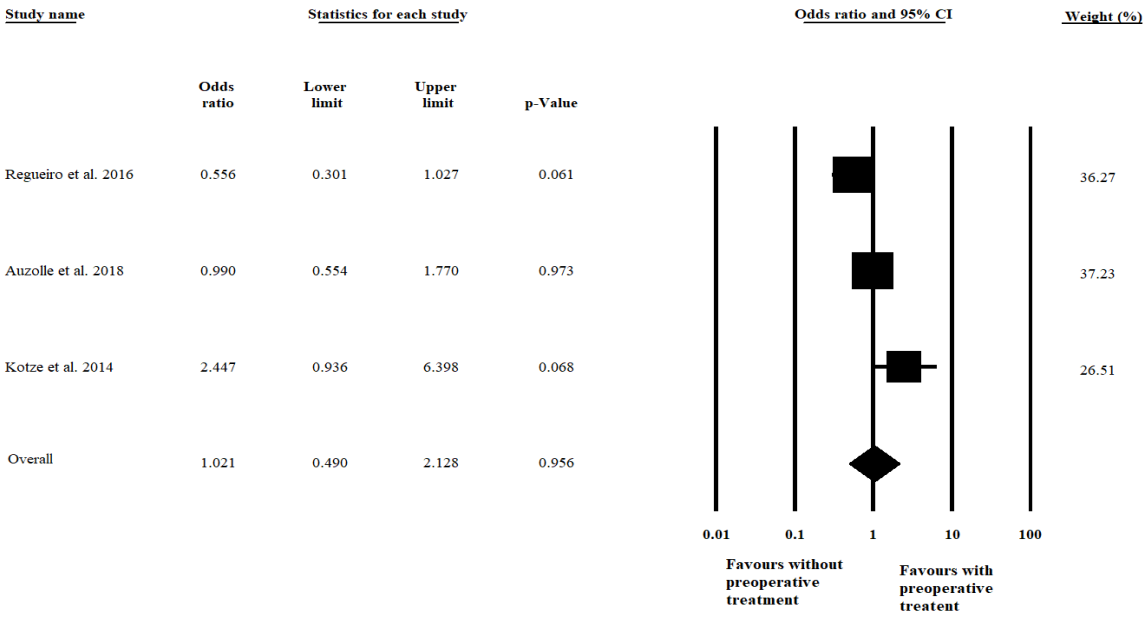
meta-regressions. The results are summarized in the Results section under subheading 'Comparison of preventive anti-TNFα versus conventional therapy for POR'. Graphs of the meta-regressions are presented in Supplementary Appendix (Supplementary figures 4 and 5).

Furthermore, I believe that interesting findings could be obtained by exploring the effects on the outcomes of the study (with subgroup or meta-regression analysis) by adding another relevant patient-level variable: the previous medical history, particularly being naïve or not to anti-TNFs.

Thank you for this comment. We attempted to perform a comparison based on this recommendation but, unfortunately, we were unable to make subgroup analysis according to patient characteristics (e.g., smoking, disease duration, gender, disease behavior). The studies reported only overall descriptive statistics of the included patients and failed to report data by treatment subgroups separately. Similarly, no adjusted analyses were reported.

The POR rate in patients not naïve to anti-TNF-alpha was reported in only three studies (Auzolle, Kotze and Regueiro 2016). We could only examine how the preoperatively given anti-TNF-alpha treatment affected the rate of POR. According to our analysis, the preoperative use of anti-TNF alpha agents did not affect significantly the rate of POR [OR 1.021, 95% CI 0.490-2.128; p = 0.956 (I^2 = 69.8%; p=0.036), with the fixed effect model].

The effect of preventive treatment with biologics after operation could not be examined because we were lacking data regarding subgroups by preoperative treatment.



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Minor points:

- Introduction is too long and needs to be shortened.

Thank you for this comment. We shortened the ‘Introduction’ part of our paper, as it was recommended.

- In the results section, authors state: "Finally, we used the data from ten trials…". Indeed, they included 8 RCTs, and two observational studies, so the word "trials" should be replaced with "studies". This mistake is repeated in other parts of the manuscript.

Thank you for this comment. We carefully read through and corrected our manuscript accordingly. We used the word ‘studies’ instead of ‘trials’ throughout the text.

We would like to thank the reviewers again for their excellent comments, which have significantly improved the quality of our manuscript.

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Anti-TNFα agents are the best choice in preventing postoperative Crohn's disease: a meta-analysis

Erős A *et al.* Preventing recurrence of postoperative Crohn's disease

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List of abbreviations

ADA	adalimumab
AE	adverse event
AZA	azathioprine
CD	Crohn's disease
CI	confidence interval
CRGS	clinical recurrence grading scale
HBI	Harvey–Bradshaw Index
IBD	inflammatory bowel disease
IFX	infliximab
IOIBD	International Organization for the Study of Inflammatory Bowel Diseases
6-MP	6-mercaptopurine
MSN	mesalamine
NOS	Newcastle–Ottawa Scale
OR	odds ratio
PLAC	placebo
POR	postoperative recurrence
RCT	randomized controlled trial
SAE	serious adverse event

TNFα	tumour necrosis factor alpha
UC	ulcerative colitis
VDZ	vedolizumab

Abstract

Background: Despite the high rate of postoperative recurrence (POR) in Crohn's disease (CD), there is no widely accepted consensus on its prevention.

Aim: To compare the efficacy of biological and conventional therapies in preventing POR of CD.

Methods: We searched four electronic databases up to April 2019 for articles that examined the efficacy of different preventive therapies against POR. Our PICO was: (P) adults with CD who underwent intestinal resection, (I) biological agents, (C) conventional therapies or a placebo, and (O) clinical, endoscopic, and histological POR.

Results: Anti-TNFα agents were significantly better in preventing clinical, endoscopic, severe endoscopic and histological POR compared to conventional therapies (OR: 0.508, 95% CI: 0.309–0.834, $P = 0.007$; OR: 0.312, 95% CI: 0.199–0.380, $P < 0.001$; OR: 0.195, 95% CI: 0.107–0.356, $P < 0.001$; and OR: 0.255, 95% CI: 0.106–0.611, $P = 0.002$, respectively), as well as in the subgroup of nonselected CD patients (OR: 0.324, 95% CI: 0.158–0.664, $P = 0.002$; OR: 0.225, 95% CI: 0.124–0.409, $P < 0.001$; and OR: 0.248, 95% CI: 0.070–0.877, $P = 0.031$, respectively). Infliximab and adalimumab proved to be equally effective in preventing endoscopic POR.

Conclusion: Anti-TNFα agents are more effective in preventing clinical, endoscopic and histological POR than conventional therapies, even in nonselected CD patients.

Keywords: Crohn's disease; postoperative recurrence; preventive treatment; anti-TNFα; infliximab; adalimumab

Introduction

Crohn's disease (CD) is one of the main types of inflammatory bowel disease causing transmural inflammation at any part of the gastrointestinal tract. Up to 75% of patients with CD require surgery for disease complications, and a high percentage of CD patients relapse after surgery [1]. Due to postoperative medically refractory disease or complications, around 50–60% of patients require repeat surgical interventions [2]. Early recognition of postoperative recurrence (POR), defined by a continuum of histological, endoscopic and clinical recurrence, is therefore crucial in the management of patients to avoid bowel destruction [3].

Several different activity indices are used to grade clinical POR, such as the Crohn's Disease Activity Index (CDAI) [4], the Clinical Recurrence Grading Scale (CRGS) developed by Hanauer [5], the Harvey–Bradshaw Index (HBI) [6] and the Index of Inflammatory Bowel Disease (IOIBD) [7]. However, these activity indices have not proven adaptable for postoperative conditions, since nearly 70–80% of CD patients develop endoscopic recurrence without any sign of clinical recurrence within the first postoperative year [8]. Therefore, ileocolonoscopy is recommended as the gold standard method for diagnosing endoscopic lesions within the first year after surgery, using the Rutgeerts' scoring system [9]. Histologic recurrence is based on a histologic activity score and the presence of polymorphonuclear cells [10].

To address a major clinical challenge, there is a current need for recommendations on the best choice of preventive treatment for CD patients after bowel resection. In clinical practice, patients with ≥2 established risk factors (e.g., active smoking, previous resections, or penetrating or perianal disease) should be considered as being at high risk for POR [11]. In this high-risk patient population, the initiation of prophylactic medical treatment is recommended to maintain surgically induced remission [9, 12].

Many studies have been conducted over the past years to evaluate the efficacy of different medications in preventing POR. Nitroimidazole antibiotics may reduce POR following ileocolic resection, though frequent side-effects limit their use [13, 14]. Results with 5-aminosalicylates (mesalamine; MSN) are contradictory. Thiopurines such as azathioprine (AZA) and 6-mercaptopurine (6-MP) are obviously superior to placebos (PLAC) in preventing both clinical and endoscopic POR [15]. In contrast, AZA failed to demonstrate its superiority over 5-ASA preparations in a previous Cochrane review [16].

Lately, the use of anti-tumour necrosis factor alpha agents (anti-TNFα; infliximab [IFX] and adalimumab [ADA]) for preventing POR has come into focus. A subanalysis of the POCER study confirmed the superiority of ADA over thiopurines for preventing endoscopic POR in high-risk patients [17]. On the other hand, ADA failed to demonstrate better efficacy than AZA for preventing POR in a nonselected population (APPRECIA study) [18]. The PREVENT authors concluded that IFX prevents endoscopic POR but not clinical POR [19].

Previous head-to-head and network meta-analyses from 2014 and 2015 found that anti-TNFα agents are the most potent in preventing clinical and endoscopic POR [20-23]. Since then, new studies have been released and novel biological agents in the treatment of IBD have been introduced (e.g., vedolizumab (VDZ) and ustekinumab). We therefore aimed to provide an update summarizing the currently available evidence on the efficacy of biological agents in POR prevention. None of the previously published meta-analyses examined which patient population could benefit most from the introduction of preventive anti-TNFα treatment, therefore we also aimed to answer this question.

Material and Methods

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Table 1)[24]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and approved under identification number CRD42017083679.

Literature search

We conducted a computerized search up to 12 April 2019 in the following four electronic databases: PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (https://www.embase.com), the Central Cochrane Register of Controlled Trials (CENTRAL) (http://www.cochranelibrary.com) and Web of Science (www.webofknowledge.com). The filter 'humans' was applied.

Based on the PICO format, we examined the population (P) of adults with CD after intestinal resection. The outcomes (O) examined consisted of clinical, endoscopic, severe endoscopic and histological POR. Biologics (ADA, IFX, VDZ, golimumab, certolizumab and ustekinumab) represented the intervention (I), and the comparators (C) were different conventional, non-biological treatment options (AZA, 6-MP, MSN or PLAC). Preventive therapy was initiated within 2–6 weeks (defined as early initiation) after surgery in all of the studies.

A systematic literature search was performed with a combination of medical subject headings (MeSH) and free text terms: *Crohn AND (adalimumab OR infliximab OR certolizumab OR golimumab OR vedolizumab OR ustekinumab OR "anti-tumor necosis factor" OR "monoclonal antibody" OR biologic) AND (postop* OR surgery OR surgical OR postsurg* OR operation OR resection) AND (recur* OR "flare-up" OR relaps* OR remission) AND (prevent* OR prophyla*).*

Study selection

After the database search, one author (AE) removed the overlapping records and duplicates using reference management software (EndNote X8, Clarivate Analytics, Philadelphia, PA, USA). First, the list of potentially eligible records (by title and abstract) were screened independently by two authors (AE and PS) to capture all relevant records. Two authors (AE and PS) screened the full texts of the remaining articles for eligibility. Consensus involving a third party (PH) resolved discrepancies when necessary.

Studies evaluating human CD patients (aged ≥18 years) who underwent ileocecal, ileocolic or colonic resection due to perforation, stricture and penetrating complications related to intra-abdominal abscess formation, drug therapy failure, disease activity or internal fistula formation were eligible for inclusion. English-language papers were selected, where therapy was initiated with the purpose of POR prevention within 2–7 weeks after surgery. Studies comparing the efficacy of biologics and any conventional, non-biological treatment options were included in our meta-analysis.

We excluded review articles, case reports and scientific studies only published in abstract form, studies evaluating treatment administered with an indication other than prevention of POR and uncontrolled studies.

Data extraction

The following data were extracted from each included study (Tables 1 and Supplementary Table 2): first author, year of publication, study type (prospective/retrospective; randomized/non-randomized), number of participating centres, length of the follow-up, drug regimen and number of patients in each study arm. As for the outcomes, the number of patients with clinical, endoscopic, severe endoscopic and histological POR were collected in

each study arm. The baseline characteristics (Table 1) of the examined population were collected, including gender distribution, age, disease duration and main risk factors (smoking, penetrating disease, perianal location and number of previous resections). Data on the Montreal classification at the time of enrolment was gathered as well.

The endpoints of our meta-analysis were clinical, endoscopic, severe endoscopic and histological POR. Studies used different types of indices to define clinical recurrence, such as CDAI [10, 17-19, 25, 26], HBI [27-29], IOIBD [30] and Hanauer scores [31]. Endoscopic POR and severe endoscopic POR were defined with a Rutgeerts score of ≥i2 and ≥i3, respectively. Histological recurrence was determined by an expert pathologist [29] or by using the modified histology scoring system of D'Haens (an overall score greater than 6 with at least a grade 1 polymorphonuclear score) [10, 28].

Firstly, anti-TNFα agents (ADA or IFX) as interventions were compared to different conventional, non-biological prophylactic options (AZA, 6-MP, MSN or PLAC). Next, comparisons of anti-TNFα agents (ADA or IFX) versus thiopurines alone (AZA or 6-MP) were examined separately. Thereafter, a head-to-head comparison of ADA and IFX was performed.

Subgroup analyses were carried out to investigate the differences deriving from patient selection. In our meta-analysis, patients were considered to have a high risk of POR if they were exposed to >1 of the following risk factors: active smoking, young age at diagnosis, penetrating or perianal disease at diagnosis, >1 resections and a resection within three years. As a comparator, a group of nonselected patients without risk factors for POR was used.

For safety analysis, adverse events (AE) and severe adverse events (SAE) were categorized in accordance with the definitions of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use - Good Clinical Practice (ICH-GCP) consensus guidelines [32].

Risk of bias

The two investigators (AE and PS) first assessed the methodological quality of selected studies independently, and then disagreements were resolved. If consensus could not be reached, the authors asked for a second opinion from a third investigator (PH). The Cochrane Risk of Bias Tool was used [33] for a risk of bias assessment of the included RCTs. Seven items in this tool were rated as having a low risk of bias (marked with a green plus sign), a high risk of bias (marked with a red minus sign) and an unclear risk of bias (marked with a yellow question mark).

A topic-tailored form of the Newcastle–Ottawa Scale (NOS) was used [34] to assess the risk of bias of the included observational studies. We evaluated the included studies with eight items from three domains (selection, comparability and outcome). One star was assigned to each item, except for comparability, for which a maximum of two stars was possible. The highest possible score was nine. Each item was classified as having a low risk of bias (marked as a green plus sign equalling 1 star) or a high or unclear risk of bias (marked as a red minus mark equalling 0 star), corresponding to our specified definitions.

Statistical analysis

All meta-analytic calculations were performed with Comprehensive MetaAnalysis software Version 3 (Biostat, Inc., Englewood, NJ, USA). Since binary outcomes were used, odds ratios (OR) with a 95% confidence interval (CI) were calculated, using the random-effects model developed by DerSimonian and Laird [35]. Forest plots were used to display the results of the statistical analysis. All analyses were two-tailed and $P < 0.05$ was considered as significant.

Heterogeneity was assessed using Cochrane's Q and the I^2 statistics. In the case of the Q statistic, Q exceeds the upper-tail critical value of chi-square with k-1 degree of freedom. I^2

represents the percentage of effect size heterogeneity, which cannot be explained by random chance. According to the Cochrane Handbook, heterogeneity could be interpreted as moderate between 30 and 60%, as substantial between 50 and 90% and as considerable above 75% [33].

Meta-regression was used to detect the effect of length of follow-up on the effect sizes if we had at least 10 publications reporting the same outcomes. Our null-hypothesis was that the coefficients are zero. The results were described with regression coefficients, 95% CI-s, probability-values (*P*) and the explained variances of the models (R^2 analogs).

Publication bias was evaluated by visual inspection of the funnel plot due to the small number of articles included in our meta-analysis.

Results

Study selection

Our comprehensive literature search identified a total of 1,143 records (shown on the PRISMA flow chart; Supplementary Figure 1) in four electronic databases (143 articles in PubMed, 704 in EMBASE, 83 in CENTRAL and 213 in Web of Science). After the removal of duplicates, 722 records remained, of which 694 were excluded by title and abstract. According to our inclusion and exclusion criteria, 23 potentially eligible articles were considered for inclusion based on full texts. Out of these studies, nine were excluded due to the following reasons: two studies did not meet the criteria on the outcome measures [36, 37], three studies were previously published systematic reviews or meta-analyses [38-40], one study did not report the outcomes by treatment [41] and three studies had no control arm [42-44]. Finally, the 14 remaining studies fulfilled all inclusion criteria and were included in the meta-analysis [10, 17-19, 25-31, 45-47].

Characteristics of the studies included

The main characteristics of the included studies are listed in Supplementary Table 2. The studies were published from 2007 to 2018, and the follow-up period in the studies ranged from six to 36 months. Finally, we used the data from 14 studies, including a total of 1,224 CD patients (573 patients received biologics, and 620 patients received non-biological drugs). Ten articles were randomized controlled trials (RCT) [10, 17-19, 25-28, 30, 47], four [17, 18, 25, 47] and six studies [10, 19, 26, 28, 30, 31] compared the efficacy of ADA and IFX to non-biological comparators (AZA, MSN and PLAC), respectively. Two studies compared anti-TNFα agents to conventional, non-biological therapies [29, 46]. Two papers [27, 45] reported on the head-to-head efficacy of ADA and IFX in preventing POR: one of them was a

retrospective study [45], the another one was an RCT [27]. Two articles only included high-risk patients in their analysis [17, 28], and eight ones involved nonselected CD patients [10, 18, 19, 25, 26, 29-31].

Only one study by Yamada compared the efficacy of VDZ and conventional therapies with respect to the prevention of POR [29]. Due to the low number of VDZ patients and to that the same group (AZA) was compared to both VDZ and anti-TNFα patients, we were unable to set up a VDZ subgroup in our meta-analysis.

Comparison of preventive anti-TNFα versus conventional therapy for POR

Twelve studies assessed POR comparing anti-TNFα therapy to different, non-biological prophylactic options [10, 17-19, 25, 26, 28-31, 46, 47] (Figures 1, 2 and 3). There was a significantly lower rate of clinical, endoscopic, severe endoscopic and histological POR in the anti-TNFα group compared to the non-biological treatment group (OR: 0.508, 95% CI: 0.309–0.834, $P = 0.007$; OR: 0.312, 95% CI: 0.199–0.489, $P < 0.001$; OR: 0.195, 95% CI: 0.195–0.356, $P < 0.001$; and OR: 0.255, 95 CI: 0.106–0.611, $P = 0.002$, respectively). Substantial heterogeneity was detected only in the case of histological recurrence ($I^2 = 63.2\%$, $P = 0.066$), while the analysis showed moderate heterogeneity in the case of clinical, endoscopic and severe endoscopic recurrence ($I^2 = 38.4\%$, $P = 0.102$; $I^2 = 38.0\%$, $P = 0.088$; $I^2 = 35.3\%$, $P = 0.159$ and, respectively) (Supplementary Table 3).

The superiority of anti-TNFα treatment over thiopurines could only be demonstrated in the case of endoscopic POR (OR: 0.392, 95% CI: 0.241–0.639; $P < 0.001$) (Supplementary Figures 2, 3 and 4).

Twelve studies were eligible for meta-regression. No statistically significant linear correlation was observed between clinical and endoscopic POR and time during the examined follow-up ($P = 0.154$ and $P = 0.411$, respectively) (Supplementary Figures 5 and 6).

Comparison of infliximab and adalimumab for the prevention of endoscopic POR

An evaluation of the homogeneous data (I^2 = 0.0%; *P* = 0.640) from the two head-to-head comparison studies [27, 45] found no significant difference between ADA and IFX with regard to endoscopic POR rates (OR: 0.799, 95% CI: 0.329–1.940; *P* = 0.620) (Figure 4).

Efficacy of prophylactic anti-TNFα agents in nonselected CD patients

Only two studies assessed the efficacy of anti-TNFα agents with regard to POR in high-risk patients [17, 28], while eight studies did not separate patients into risk groups (i.e., they did not include a selected patient group) [10, 18, 19, 25, 26, 29-31] (Figures 5 a, 5b and 5c). Anti-TNFα agents showed a significantly better efficacy in preventing clinical, endoscopic and severe endoscopic POR in a nonselected CD population (OR: 0.324, 95% CI: 0.158–0.664, *P* = 0.002; OR: 0.225, 95% CI: 0.124–0.409, *P* < 0.001; and OR: 0.248, 95% CI: 0.070–0.877, *P* = 0.031, respectively). The overall heterogeneity was the highest in the analysis of severe endoscopic POR (I^2 = 55.3%; *P* = 0.062) (Supplementary Table 3).

Safety analysis

Six of the fourteen studies reported the rate of adverse events (AEs) of postoperative preventive treatments [10, 17-19, 25, 28], while three studies reported the rate of SAEs [17-19]. No significant difference was observed in AE or SAE rates between the anti-TNFα and the conventional treatment groups (OR: 0.86, 95% CI: 0.457-1.617, P = 0.639; and OR: 1.018, 95% CI: 0.641-1.617, P = 0.94, respectively) (Supplementary Figure 7a and 7b).

Risk of bias assessment

Risk of bias assessments of the included studies are shown in Supplementary Figure 8. In RTCs, random sequence generation was described in sufficient detail in only 40% and allocation concealment in only 30% of the articles. Four studies were open-label studies; they therefore carried a high risk of bias due to lack of blinding among participants and personnel. In four studies, the assessment of outcomes was unblinded or not described accurately. All of the studies were judged as being low risk with regard to the item of incomplete outcome, excepting the study of Scapa, which was only published in abstract form. All of the studies were judged as being free from other potential sources of bias, excepting the study of Scapa (unclear risk of bias) and the study of Fukushima (high risk of bias). As for selective reporting, we failed to identify half of the studies in trial protocol databases; they were therefore considered to have an unclear risk of bias in this regard.

All of the included observational studies were considered low-risk studies with regard to each item, except for assessment of outcome. From this point of view, they were both assigned zero stars because none of them detailed blinding for the outcome assessment (whether endoscopic operators performing control endoscopies were blinded or not). In the study of Auzolle, the comparability of the cohorts of patients could not be judged based on the article content. According to our assessment, the included observational studies achieved six to eight points out of a maximum of nine.

Discussion

Most of the patients with CD require surgery during their lifetime. Within one year, 80% of operated patients develop endoscopic POR. However, there is no widely accepted consensus on the prevention of POR, though the issue has been approached through multiple meta-analyses and a Cochrane review in recent years.

In our meta-analysis, we used the most up-to-date data from 14 clinical studies, of which most were RCTs. Most of the included studies compared the efficacy of anti-TNFα agents to non-biological comparators in preventing clinical, endoscopic, severe endoscopic and histological POR. The minority compared the efficacy of ADA and IFX. We made an effort to synthesize all the possible comparisons in our meta-analysis.

Firstly, we evaluated the efficacy of anti-TNFα agents compared to non-biological comparators. Based on our results, anti-TNFα agents were significantly more effective in preventing clinical, endoscopic, severe endoscopic and histological POR. Our findings confirm results from previous meta-analyses [20-22]. As part of our comparison, we analysed the efficacy of anti-TNFα agents compared to the thiopurine-treated group. Anti-TNFα agents proved to be better in all kinds of analysed POR prevention, but their superiority over thiopurines could only be detected in the case of endoscopic POR.

Secondly, we performed a direct, head-to-head comparison between ADA and IFX in preventing endoscopic POR. We found that the efficacy of these two anti-TNFα agents is nearly the same, thus confirming previously performed indirect comparisons [21, 48].

Thirdly, uniquely in the literature so far, we aimed to identify groups of patients who will benefit most from a preventive anti-TNFα treatment after resection. We therefore compared the anti-TNFα agents to controls in the high-risk and nonselected CD patient subgroups. The analysis indicated that nonselected patients enjoy the benefits of preventive

anti-TNFα treatment with respect to clinical, endoscopic and severe endoscopic POR as well, independently from risk stratification.

Our meta-analysis has several strengths worth highlighting. A high number (1,124) of operated CD patients were enrolled in the analyses, and most of the included studies were RCTs. This is the first meta-analysis involving subgroup analyses on patient selection upon risk stratification. A head-to-head comparison between IFX and ADA was also possible, which confirmed previous indirect comparisons. Today, mucosal healing is considered as one of the hardest endpoints in predicting long-term clinical success in IBD [49]. Closely related to this, we examined the efficacy of anti-TNFα treatment compared to conventional therapies with respect to the prevention of histological POR.

However, we are aware that our findings suffer from several limitations. First, we could not investigate the effect of co-treatments used in the different treatment arms. Second, the follow-up period in the included studies ranged between six and 36 months, although most reported the results at one year. Finally, we could not evaluate the effect of new biologics (e.g., VDZ and ustekinumab) on POR prevention, since there have been just very few results published on this field.

In summary, the results from our meta-analysis confirm that early initiated postoperative anti-TNFα treatment is currently the most effective therapeutic choice in preventing the continuum of histological, endoscopic, and clinical POR without increasing the frequency of AEs. Our findings suggest that it is unnecessary to select patients after intestinal resection based on risk factors since even nonselected populations can benefit from early initiated prophylactic anti-TNFα therapy postoperatively. Both IFX and ADA are equally effective in preventing endoscopic POR. Further large RCTs are needed to confirm and strengthen our results.

Author contributions Statement: PS, AE and NF designed the research; PS, AE and NF conducted the research and statistical analyses as well as analysing and interpreting the data; AE and PS wrote the article, AS, MB, GV, LC, JB, AH, ZR, AM, TH, BE and BB made critical revisions related to important intellectual content in the manuscript; and PS, BE and PH gave final approval to the version of the article to be published.

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Legend of tables and figures

Supplementary data

Supplementary Figure 2 **Comparison of preventive anti-TNFα therapy versus azathioprine for clinical postoperative recurrence**

Supplementary Figure 3 **Comparison of preventive anti-TNFα therapy versus azathioprine for endoscopic postoperative recurrence**

Supplementary Figure 4 **Comparison of preventive anti-TNFα therapy versus azathioprine for severe endoscopic postoperative recurrence**

Supplementary Figure 5 **Meta-regression performed for comparing the efficacy of anti-TNFα treatment and thiopurines in preventing clinical POR**

Each study is depicted by a hollow circle with a size proportional to the number of observed events per outcome. The fitted line is derived from the meta-regression model.

Supplementary Figure 6 **Meta-regression performed for comparing the efficacy of anti-TNFα treatment and thiopurines in preventing endoscopic POR**

Supplementary Figure 7 **Comparison of anti-TNFα agents versus comparators for (a) adverse events and (b) severe adverse events**

Supplementary Figure 8 **Methodological quality of eligible studies using the Cochrane risk of bias tool for randomized controlled trials or the Newcastle–Ottawa Scale criteria for observational studies**

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Anti-TNFα agents are the best choice in preventing postoperative Crohn's disease: a meta-analysis

Erős A *et al.* Preventing recurrence of postoperative Crohn's disease

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List of abbreviations

ADA	adalimumab
AE	adverse event
AZA	azathioprine
CD	Crohn's disease
CI	confidence interval
CRGS	clinical recurrence grading scale
HBI	Harvey–Bradshaw Index
IBD	inflammatory bowel disease
IFX	infliximab
IOIBD	International Organization for the Study of Inflammatory Bowel Diseases
6-MP	6-mercaptopurine
MSN	mesalamine
NOS	Newcastle–Ottawa Scale
OR	odds ratio
PLAC	placebo
POR	postoperative recurrence
RCT	randomized controlled trial
SAE	serious adverse event

TNFα	tumour necrosis factor alpha
UC	ulcerative colitis
VDZ	vedolizumab

Abstract

Background: Despite the high rate of postoperative recurrence (POR) in Crohn's disease (CD), there is no widely accepted consensus on its prevention.

Aim: To compare the efficacy of biological and conventional therapies in preventing POR of CD.

Methods: We searched four electronic databases up to April 2019 for articles that examined the efficacy of different preventive therapies against POR. Our PICO was: (P) adults with CD who underwent intestinal resection, (I) biological agents, (C) conventional therapies or a placebo, and (O) clinical, endoscopic, and histological POR.

Results: Anti-TNFα agents were significantly better in preventing clinical, endoscopic, severe endoscopic and histological POR compared to conventional therapies (OR: 0.508, 95% CI: 0.309–0.834, $P = 0.007$; OR: 0.312, 95% CI: 0.199–0.380, $P < 0.001$; OR: 0.195, 95% CI: 0.107–0.356, $P < 0.001$; and OR: 0.255, 95% CI: 0.106–0.611, $P = 0.002$, respectively), as well as in the subgroup of nonselected CD patients (OR: 0.324, 95% CI: 0.158–0.664, $P = 0.002$; OR: 0.225, 95% CI: 0.124–0.409, $P < 0.001$; and OR: 0.248, 95% CI: 0.070–0.877, $P = 0.031$, respectively). Infliximab and adalimumab proved to be equally effective in preventing endoscopic POR.

Conclusion: Anti-TNFα agents are more effective in preventing clinical, endoscopic and histological POR than conventional therapies, even in nonselected CD patients.

Keywords: Crohn's disease; postoperative recurrence; preventive treatment; anti-TNFα; infliximab; adalimumab

Introduction

Crohn's disease (CD) is one of the main types of inflammatory bowel disease causing transmural inflammation at any part of the gastrointestinal tract. Up to 75% of patients with CD require surgery for disease complications, and a high percentage of CD patients relapse after surgery [1]. Due to postoperative medically refractory disease or complications, around 50–60% of patients require repeat surgical interventions [2]. Early recognition of postoperative recurrence (POR), defined by a continuum of histological, endoscopic and clinical recurrence, is therefore crucial in the management of patients to avoid bowel destruction [3].

Several different activity indices are used to grade clinical POR, such as the Crohn's Disease Activity Index (CDAI) [4], the Clinical Recurrence Grading Scale (CRGS) developed by Hanauer [5], the Harvey–Bradshaw Index (HBI) [6] and the Index of Inflammatory Bowel Disease (IOIBD) [7]. However, these activity indices have not proven adaptable for postoperative conditions, since nearly 70–80% of CD patients develop endoscopic recurrence without any sign of clinical recurrence within the first postoperative year [8]. Therefore, ileocolonoscopy is recommended as the gold standard method for diagnosing endoscopic lesions within the first year after surgery, using the Rutgeerts' scoring system [9]. Histologic recurrence is based on a histologic activity score and the presence of polymorphonuclear cells [10].

To address a major clinical challenge, there is a current need for recommendations on the best choice of preventive treatment for CD patients after bowel resection. In clinical practice, patients with ≥2 established risk factors (e.g., active smoking, previous resections, or penetrating or perianal disease) should be considered as being at high risk for POR [11]. In this high-risk patient population, the initiation of prophylactic medical treatment is recommended to maintain surgically induced remission [9, 12].

Many studies have been conducted over the past years to evaluate the efficacy of different medications in preventing POR. Nitroimidazole antibiotics may reduce POR following ileocolic resection, though frequent side-effects limit their use [13, 14]. Results with 5-aminosalicylates (mesalamine; MSN) are contradictory. Thiopurines such as azathioprine (AZA) and 6-mercaptopurine (6-MP) are obviously superior to placebos (PLAC) in preventing both clinical and endoscopic POR [15]. In contrast, AZA failed to demonstrate its superiority over 5-ASA preparations in a previous Cochrane review [16].

Lately, the use of anti-tumour necrosis factor alpha agents (anti-TNFα; infliximab [IFX] and adalimumab [ADA]) for preventing POR has come into focus. A subanalysis of the POCER study confirmed the superiority of ADA over thiopurines for preventing endoscopic POR in high-risk patients [17]. On the other hand, ADA failed to demonstrate better efficacy than AZA for preventing POR in a nonselected population (APPRECIA study) [18]. The PREVENT authors concluded that IFX prevents endoscopic POR but not clinical POR [19].

Previous head-to-head and network meta-analyses from 2014 and 2015 found that anti-TNFα agents are the most potent in preventing clinical and endoscopic POR [20-23]. Since then, new studies have been released and novel biological agents in the treatment of IBD have been introduced (e.g., vedolizumab (VDZ) and ustekinumab). We therefore aimed to provide an update summarizing the currently available evidence on the efficacy of biological agents in POR prevention. None of the previously published meta-analyses examined which patient population could benefit most from the introduction of preventive anti-TNFα treatment, therefore we also aimed to answer this question.

Material and Methods

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Table 1)[24]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and approved under identification number CRD42017083679.

Literature search

We conducted a computerized search up to 12 April 2019 in the following four electronic databases: PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (https://www.embase.com), the Central Cochrane Register of Controlled Trials (CENTRAL) (http://www.cochranelibrary.com) and Web of Science (www.webofknowledge.com). The filter 'humans' was applied.

Based on the PICO format, we examined the population (P) of adults with CD after intestinal resection. The outcomes (O) examined consisted of clinical, endoscopic, severe endoscopic and histological POR. Biologics (ADA, IFX, VDZ, golimumab, certolizumab and ustekinumab) represented the intervention (I), and the comparators (C) were different conventional, non-biological treatment options (AZA, 6-MP, MSN or PLAC). Preventive therapy was initiated within 2–6 weeks (defined as early initiation) after surgery in all of the studies.

A systematic literature search was performed with a combination of medical subject headings (MeSH) and free text terms: *Crohn AND (adalimumab OR infliximab OR certolizumab OR golimumab OR vedolizumab OR ustekinumab OR "anti-tumor necosis factor" OR "monoclonal antibody" OR biologic) AND (postop* OR surgery OR surgical OR postsurg* OR operation OR resection) AND (recur* OR "flare-up" OR relaps* OR remission) AND (prevent* OR prophyla*).*

Study selection

After the database search, one author (AE) removed the overlapping records and duplicates using reference management software (EndNote X8, Clarivate Analytics, Philadelphia, PA, USA). First, the list of potentially eligible records (by title and abstract) were screened independently by two authors (AE and PS) to capture all relevant records. Two authors (AE and PS) screened the full texts of the remaining articles for eligibility. Consensus involving a third party (PH) resolved discrepancies when necessary.

Studies evaluating human CD patients (aged ≥18 years) who underwent ileocecal, ileocolic or colonic resection due to perforation, stricture and penetrating complications related to intra-abdominal abscess formation, drug therapy failure, disease activity or internal fistula formation were eligible for inclusion. English-language papers were selected, where therapy was initiated with the purpose of POR prevention within 2–7 weeks after surgery. Studies comparing the efficacy of biologics and any conventional, non-biological treatment options were included in our meta-analysis.

We excluded review articles, case reports and scientific studies only published in abstract form, studies evaluating treatment administered with an indication other than prevention of POR and uncontrolled studies.

Data extraction

The following data were extracted from each included study (Tables 1 and Supplementary Table 2): first author, year of publication, study type (prospective/retrospective; randomized/non-randomized), number of participating centres, length of the follow-up, drug regimen and number of patients in each study arm. As for the outcomes, the number of patients with clinical, endoscopic, severe endoscopic and histological POR were collected in

each study arm. The baseline characteristics (Table 1) of the examined population were collected, including gender distribution, age, disease duration and main risk factors (smoking, penetrating disease, perianal location and number of previous resections). Data on the Montreal classification at the time of enrolment was gathered as well.

The endpoints of our meta-analysis were clinical, endoscopic, severe endoscopic and histological POR. Studies used different types of indices to define clinical recurrence, such as CDAI [10, 17-19, 25, 26], HBI [27-29], IOIBD [30] and Hanauer scores [31]. Endoscopic POR and severe endoscopic POR were defined with a Rutgeerts score of ≥i2 and ≥i3, respectively. Histological recurrence was determined by an expert pathologist [29] or by using the modified histology scoring system of D'Haens (an overall score greater than 6 with at least a grade 1 polymorphonuclear score) [10, 28].

Firstly, anti-TNFα agents (ADA or IFX) as interventions were compared to different conventional, non-biological prophylactic options (AZA, 6-MP, MSN or PLAC). Next, comparisons of anti-TNFα agents (ADA or IFX) versus thiopurines alone (AZA or 6-MP) were examined separately. Thereafter, a head-to-head comparison of ADA and IFX was performed.

Subgroup analyses were carried out to investigate the differences deriving from patient selection. In our meta-analysis, patients were considered to have a high risk of POR if they were exposed to >1 of the following risk factors: active smoking, young age at diagnosis, penetrating or perianal disease at diagnosis, >1 resections and a resection within three years. As a comparator, a group of nonselected patients without risk factors for POR was used.

For safety analysis, adverse events (AE) and severe adverse events (SAE) were categorized in accordance with the definitions of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use - Good Clinical Practice (ICH-GCP) consensus guidelines [32].

Risk of bias

The two investigators (AE and PS) first assessed the methodological quality of selected studies independently, and then disagreements were resolved. If consensus could not be reached, the authors asked for a second opinion from a third investigator (PH). The Cochrane Risk of Bias Tool was used [33] for a risk of bias assessment of the included RCTs. Seven items in this tool were rated as having a low risk of bias (marked with a green plus sign), a high risk of bias (marked with a red minus sign) and an unclear risk of bias (marked with a yellow question mark).

A topic-tailored form of the Newcastle–Ottawa Scale (NOS) was used [34] to assess the risk of bias of the included observational studies. We evaluated the included studies with eight items from three domains (selection, comparability and outcome). One star was assigned to each item, except for comparability, for which a maximum of two stars was possible. The highest possible score was nine. Each item was classified as having a low risk of bias (marked as a green plus sign equalling 1 star) or a high or unclear risk of bias (marked as a red minus mark equalling 0 star), corresponding to our specified definitions.

Statistical analysis

All meta-analytic calculations were performed with Comprehensive MetaAnalysis software Version 3 (Biostat, Inc., Englewood, NJ, USA). Since binary outcomes were used, odds ratios (OR) with a 95% confidence interval (CI) were calculated, using the random-effects model developed by DerSimonian and Laird [35]. Forest plots were used to display the results of the statistical analysis. All analyses were two-tailed and $P < 0.05$ was considered as significant.

Heterogeneity was assessed using Cochrane's Q and the I^2 statistics. In the case of the Q statistic, Q exceeds the upper-tail critical value of chi-square with k-1 degree of freedom. I^2

represents the percentage of effect size heterogeneity, which cannot be explained by random chance. According to the Cochrane Handbook, heterogeneity could be interpreted as moderate between 30 and 60%, as substantial between 50 and 90% and as considerable above 75% [33].

Meta-regression was used to detect the effect of length of follow-up on the effect sizes if we had at least 10 publications reporting the same outcomes. Our null-hypothesis was that the coefficients are zero. The results were described with regression coefficients, 95% CI-s, probability-values (*P*) and the explained variances of the models (R^2 analogs).

Publication bias was evaluated by visual inspection of the funnel plot due to the small number of articles included in our meta-analysis.

Results

Study selection

Our comprehensive literature search identified a total of 1,143 records (shown on the PRISMA flow chart; Supplementary Figure 1) in four electronic databases (143 articles in PubMed, 704 in EMBASE, 83 in CENTRAL and 213 in Web of Science). After the removal of duplicates, 722 records remained, of which 694 were excluded by title and abstract. According to our inclusion and exclusion criteria, 23 potentially eligible articles were considered for inclusion based on full texts. Out of these studies, nine were excluded due to the following reasons: two studies did not meet the criteria on the outcome measures [36, 37], three studies were previously published systematic reviews or meta-analyses [38-40], one study did not report the outcomes by treatment [41] and three studies had no control arm [42-44]. Finally, the 14 remaining studies fulfilled all inclusion criteria and were included in the meta-analysis [10, 17-19, 25-31, 45-47].

Characteristics of the studies included

The main characteristics of the included studies are listed in Supplementary Table 2. The studies were published from 2007 to 2018, and the follow-up period in the studies ranged from six to 36 months. Finally, we used the data from 14 studies, including a total of 1,224 CD patients (573 patients received biologics, and 620 patients received non-biological drugs). Ten articles were randomized controlled trials (RCT) [10, 17-19, 25-28, 30, 47], four [17, 18, 25, 47] and six studies [10, 19, 26, 28, 30, 31] compared the efficacy of ADA and IFX to non-biological comparators (AZA, MSN and PLAC), respectively. Two studies compared anti-TNFα agents to conventional, non-biological therapies [29, 46]. Two papers [27, 45] reported on the head-to-head efficacy of ADA and IFX in preventing POR: one of them was a

retrospective study [45], the another one was an RCT [27]. Two articles only included high-risk patients in their analysis [17, 28], and eight ones involved nonselected CD patients [10, 18, 19, 25, 26, 29-31].

Only one study by Yamada compared the efficacy of VDZ and conventional therapies with respect to the prevention of POR [29]. Due to the low number of VDZ patients and to that the same group (AZA) was compared to both VDZ and anti-TNFα patients, we were unable to set up a VDZ subgroup in our meta-analysis.

Comparison of preventive anti-TNFα versus conventional therapy for POR

Twelve studies assessed POR comparing anti-TNFα therapy to different, non-biological prophylactic options [10, 17-19, 25, 26, 28-31, 46, 47] (Figures 1, 2 and 3). There was a significantly lower rate of clinical, endoscopic, severe endoscopic and histological POR in the anti-TNFα group compared to the non-biological treatment group (OR: 0.508, 95% CI: 0.309–0.834, $P = 0.007$; OR: 0.312, 95% CI: 0.199–0.489, $P < 0.001$; OR: 0.195, 95% CI: 0.195–0.356, $P < 0.001$; and OR: 0.255, 95 CI: 0.106–0.611, $P = 0.002$, respectively). Substantial heterogeneity was detected only in the case of histological recurrence ($I^2 = 63.2\%$, $P = 0.066$), while the analysis showed moderate heterogeneity in the case of clinical, endoscopic and severe endoscopic recurrence ($I^2 = 38.4\%$, $P = 0.102$; $I^2 = 38.0\%$, $P = 0.088$; $I^2 = 35.3\%$, $P = 0.159$ and, respectively) (Supplementary Table 3).

The superiority of anti-TNFα treatment over thiopurines could only be demonstrated in the case of endoscopic POR (OR: 0.392, 95% CI: 0.241–0.639; $P < 0.001$) (Supplementary Figures 2, 3 and 4).

Twelve studies were eligible for meta-regression. No statistically significant linear correlation was observed between clinical and endoscopic POR and time during the examined follow-up ($P = 0.154$ and $P = 0.411$, respectively) (Supplementary Figures 5 and 6).

Comparison of infliximab and adalimumab for the prevention of endoscopic POR

An evaluation of the homogeneous data (I^2 = 0.0%; *P* = 0.640) from the two head-to-head comparison studies [27, 45] found no significant difference between ADA and IFX with regard to endoscopic POR rates (OR: 0.799, 95% CI: 0.329–1.940; *P* = 0.620) (Figure 4).

Efficacy of prophylactic anti-TNFα agents in nonselected CD patients

Only two studies assessed the efficacy of anti-TNFα agents with regard to POR in high-risk patients [17, 28], while eight studies did not separate patients into risk groups (i.e., they did not include a selected patient group) [10, 18, 19, 25, 26, 29-31] (Figures 5 a, 5b and 5c). Anti-TNFα agents showed a significantly better efficacy in preventing clinical, endoscopic and severe endoscopic POR in a nonselected CD population (OR: 0.324, 95% CI: 0.158–0.664, *P* = 0.002; OR: 0.225, 95% CI: 0.124–0.409, *P* < 0.001; and OR: 0.248, 95% CI: 0.070–0.877, *P* = 0.031, respectively). The overall heterogeneity was the highest in the analysis of severe endoscopic POR (I^2 = 55.3%; *P* = 0.062) (Supplementary Table 3).

Safety analysis

Six of the fourteen studies reported the rate of adverse events (AEs) of postoperative preventive treatments [10, 17-19, 25, 28], while three studies reported the rate of SAEs [17-19]. No significant difference was observed in AE or SAE rates between the anti-TNFα and the conventional treatment groups (OR: 0.86, 95% CI: 0.457-1.617, P = 0.639; and OR: 1.018, 95% CI: 0.641-1.617, P = 0.94, respectively) (Supplementary Figure 7a and 7b).

Risk of bias assessment

Risk of bias assessments of the included studies are shown in Supplementary Figure 8. In RTCs, random sequence generation was described in sufficient detail in only 40% and allocation concealment in only 30% of the articles. Four studies were open-label studies; they therefore carried a high risk of bias due to lack of blinding among participants and personnel. In four studies, the assessment of outcomes was unblinded or not described accurately. All of the studies were judged as being low risk with regard to the item of incomplete outcome, excepting the study of Scapa, which was only published in abstract form. All of the studies were judged as being free from other potential sources of bias, excepting the study of Scapa (unclear risk of bias) and the study of Fukushima (high risk of bias). As for selective reporting, we failed to identify half of the studies in trial protocol databases; they were therefore considered to have an unclear risk of bias in this regard.

All of the included observational studies were considered low-risk studies with regard to each item, except for assessment of outcome. From this point of view, they were both assigned zero stars because none of them detailed blinding for the outcome assessment (whether endoscopic operators performing control endoscopies were blinded or not). In the study of Auzolle, the comparability of the cohorts of patients could not be judged based on the article content. According to our assessment, the included observational studies achieved six to eight points out of a maximum of nine.

Discussion

Most of the patients with CD require surgery during their lifetime. Within one year, 80% of operated patients develop endoscopic POR. However, there is no widely accepted consensus on the prevention of POR, though the issue has been approached through multiple meta-analyses and a Cochrane review in recent years.

In our meta-analysis, we used the most up-to-date data from 14 clinical studies, of which most were RCTs. Most of the included studies compared the efficacy of anti-TNFα agents to non-biological comparators in preventing clinical, endoscopic, severe endoscopic and histological POR. The minority compared the efficacy of ADA and IFX. We made an effort to synthesize all the possible comparisons in our meta-analysis.

Firstly, we evaluated the efficacy of anti-TNFα agents compared to non-biological comparators. Based on our results, anti-TNFα agents were significantly more effective in preventing clinical, endoscopic, severe endoscopic and histological POR. Our findings confirm results from previous meta-analyses [20-22]. As part of our comparison, we analysed the efficacy of anti-TNFα agents compared to the thiopurine-treated group. Anti-TNFα agents proved to be better in all kinds of analysed POR prevention, but their superiority over thiopurines could only be detected in the case of endoscopic POR.

Secondly, we performed a direct, head-to-head comparison between ADA and IFX in preventing endoscopic POR. We found that the efficacy of these two anti-TNFα agents is nearly the same, thus confirming previously performed indirect comparisons [21, 48].

Thirdly, uniquely in the literature so far, we aimed to identify groups of patients who will benefit most from a preventive anti-TNFα treatment after resection. We therefore compared the anti-TNFα agents to controls in the high-risk and nonselected CD patient subgroups. The analysis indicated that nonselected patients enjoy the benefits of preventive

anti-TNFα treatment with respect to clinical, endoscopic and severe endoscopic POR as well, independently from risk stratification.

Our meta-analysis has several strengths worth highlighting. A high number (1,124) of operated CD patients were enrolled in the analyses, and most of the included studies were RCTs. This is the first meta-analysis involving subgroup analyses on patient selection upon risk stratification. A head-to-head comparison between IFX and ADA was also possible, which confirmed previous indirect comparisons. Today, mucosal healing is considered as one of the hardest endpoints in predicting long-term clinical success in IBD [49]. Closely related to this, we examined the efficacy of anti-TNFα treatment compared to conventional therapies with respect to the prevention of histological POR.

However, we are aware that our findings suffer from several limitations. First, we could not investigate the effect of co-treatments used in the different treatment arms. Second, the follow-up period in the included studies ranged between six and 36 months, although most reported the results at one year. Finally, we could not evaluate the effect of new biologics (e.g., VDZ and ustekinumab) on POR prevention, since there have been just very few results published on this field.

In summary, the results from our meta-analysis confirm that early initiated postoperative anti-TNFα treatment is currently the most effective therapeutic choice in preventing the continuum of histological, endoscopic, and clinical POR without increasing the frequency of AEs. Our findings suggest that it is unnecessary to select patients after intestinal resection based on risk factors since even nonselected populations can benefit from early initiated prophylactic anti-TNFα therapy postoperatively. Both IFX and ADA are equally effective in preventing endoscopic POR. Further large RCTs are needed to confirm and strengthen our results.

Author contributions Statement: PS, AE and NF designed the research; PS, AE and NF conducted the research and statistical analyses as well as analysing and interpreting the data; AE and PS wrote the article, AS, MB, GV, LC, JB, AH, ZR, AM, TH, BE and BB made critical revisions related to important intellectual content in the manuscript; and PS, BE and PH gave final approval to the version of the article to be published.

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Legend of tables and figures

Supplementary data

Supplementary Figure 2 Comparison of preventive anti-TNFα therapy versus azathioprine for clinical postoperative recurrence

Supplementary Figure 3 Comparison of preventive anti-TNFα therapy versus azathioprine for endoscopic postoperative recurrence

Supplementary Figure 4 Comparison of preventive anti-TNFα therapy versus azathioprine for severe endoscopic postoperative recurrence

Supplementary Figure 5 Meta-regression performed for comparing the efficacy of anti-TNFα treatment and thiopurines in preventing clinical POR

Each study is depicted by a hollow circle with a size proportional to the number of observed events per outcome. The fitted line is derived from the meta-regression model.

Supplementary Figure 6 Meta-regression performed for comparing the efficacy of anti-TNFα treatment and thiopurines in preventing endoscopic POR

Supplementary Figure 7 Comparison of anti-TNFα agents versus comparators for (a) adverse events and (b) severe adverse events

Supplementary Figure 8 Methodological quality of eligible studies using the Cochrane risk of bias tool for randomized controlled trials or the Newcastle–Ottawa Scale criteria for observational studies

Figure_1

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Study name	Anti-TNF-alpha-treatment	Comparator	Odds ratio	Lower limit	Upper limit	p-Value	Anti-TNF-alpha treated	Comparator-treated	Weight (%)
Savarino et al. 2013	ADA	AZA	0.028	0.001	0.271	0.002	1 / 16	12 / 17	22.19
Lopez-Sanroman et al. 2017	ADA	AZA	0.329	0.116	0.929	0.036	7 / 45	14 / 39	39.50
De Cruz et al. 2015	ADA	AZA or 6-MP	0.774	0.254	2.361	0.653	5 / 28	16 / 73	38.30
ADA Total			0.264	0.062	1.116	0.070	13 / 89	42 / 129	
Yanuda et al. 2018	ANTI-TNF_alpha	AZA or 6-MP	0.912	0.376	2.215	0.840	18 / 49	14 / 36	100.00
ANTI-TNF_alpha Total			0.912	0.376	2.215	0.840	18 / 49	14 / 36	
Regueiro et al. 2009	IFX	PLAC	0.074	0.004	1.528	0.092	0 / 10	5 / 13	4.58
Fukushima et al. 2018	IFX	MSN	0.076	0.008	0.696	0.023	1 / 19	8 / 19	8.42
Sorrentino et al. 2007	IFX	MSN	0.139	0.007	2.907	0.204	0 / 7	5 / 16	4.57
Yoshida et al. 2011	IFX	MSN	0.462	0.071	2.994	0.418	2 / 15	4 / 16	11.53
Regueiro et al. 2016	IFX	PLAC	0.594	0.317	1.111	0.103	19 / 147	30 / 150	65.96
Ammitzi et al. 2013	IFX	AZA	0.900	0.049	16.594	0.944	1 / 11	1 / 10	4.95
IFX Total			0.421	0.218	0.814	0.010	23 / 209	53 / 224	
Overall			0.508	0.309	0.834	0.007	54 / 347	109 / 389	

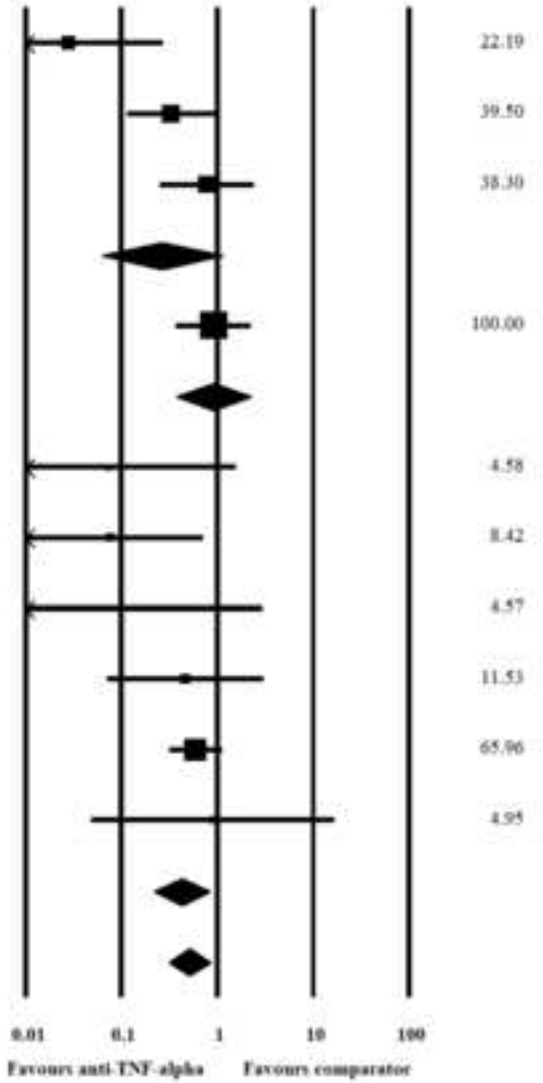

Figure_2

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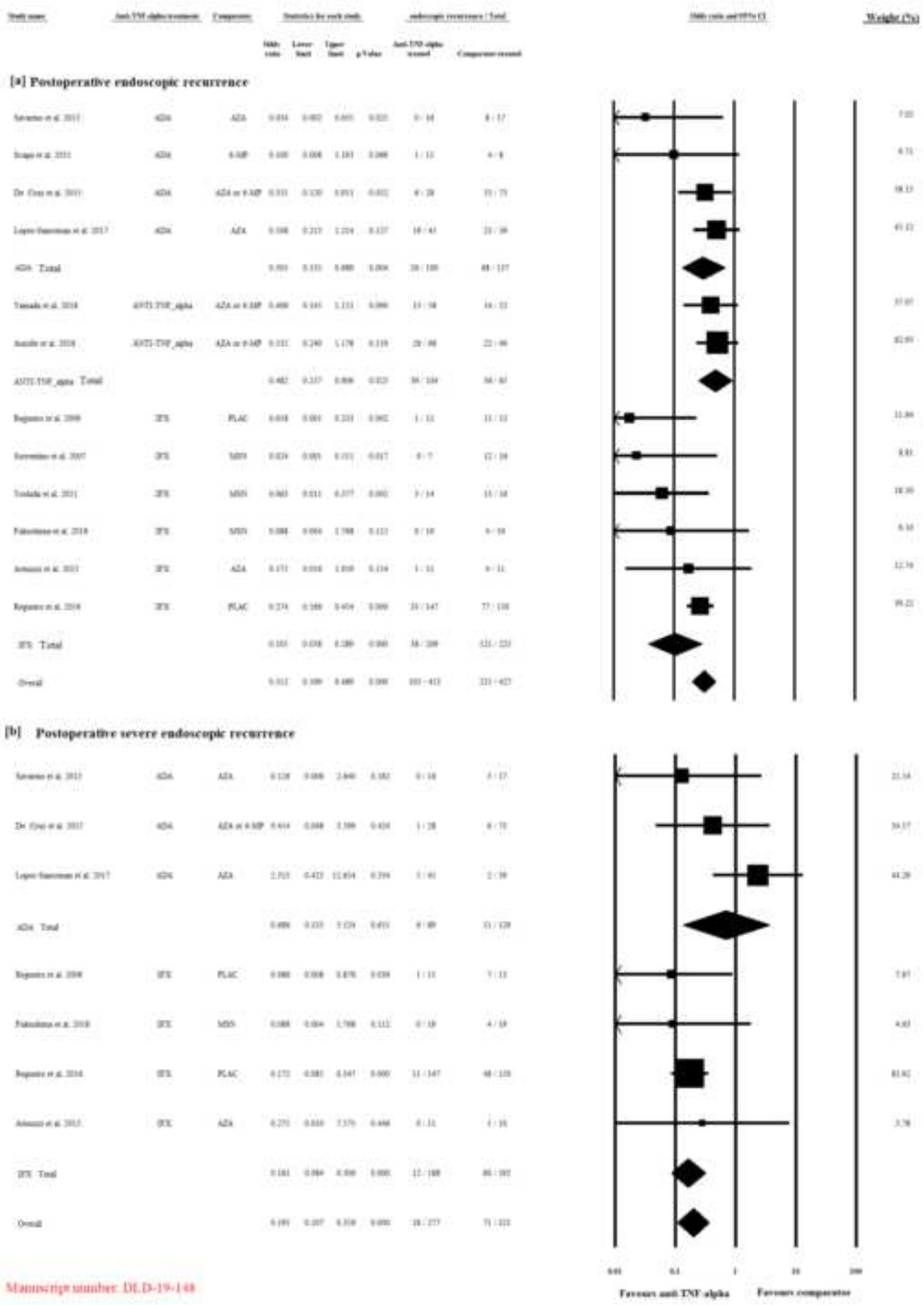

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Figure_3

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Study name	Anti-TNF-alpha-treatment	Comparator	Odds ratio	Lower limit	Upper limit	p-Value	severe endoscopic recurrence / Total: Anti-TNF-alpha treated	severe endoscopic recurrence / Total: Comparator-treated	Weight (%)
Yamada et al. 2018	ANTI-TNF_alpha	AZA or 6-MP	0.547	0.184	1.620	0.276	15 / 28	19 / 28	100.00
ANTI-TNF_alpha Total			0.547	0.184	1.620	0.276	15 / 28	19 / 28	
Amuzzi et al. 2013	IFX	AZA	0.056	0.006	0.491	0.009	2 / 11	8 / 10	45.91
Regueiro et al. 2009	IFX	PLAC	0.068	0.009	0.508	0.009	3 / 11	11 / 13	54.09
IFX Total			0.062	0.014	0.272	0.000	5 / 22	19 / 23	
Overall			0.255	0.106	0.611	0.002	20 / 50	38 / 51	

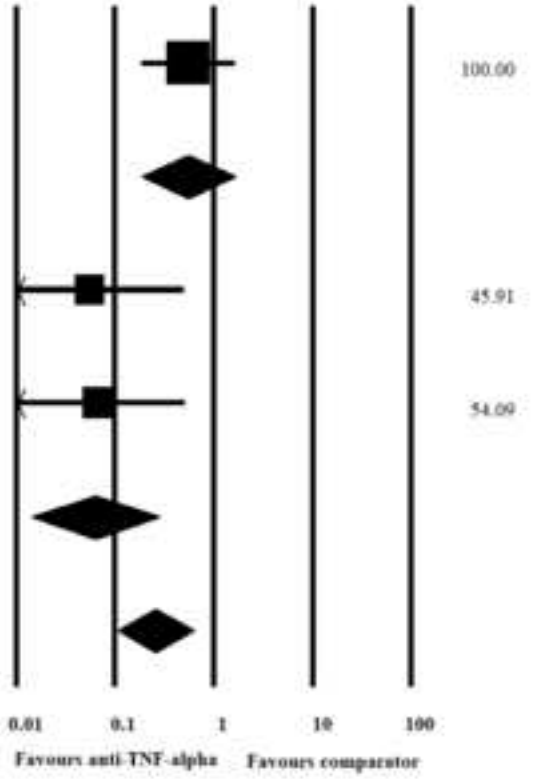

Figure_4
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Study name	Anti-TNF-alpha-treatment	Comparator	Odds ratio	Lower limit	Upper limit	p-Value	ADA treated	IFX treated	Weight (%)
Tursi et al. 2014	ADA	IFX	0.444	0.034	5.880	0.538	1 / 10	2 / 10	11.81
Kotze et al. 2014	ADA	IFX	0.864	0.336	2.223	0.762	9 / 37	16 / 59	88.19
Overall			0.799	0.329	1.940	0.620	10 / 47	18 / 69	

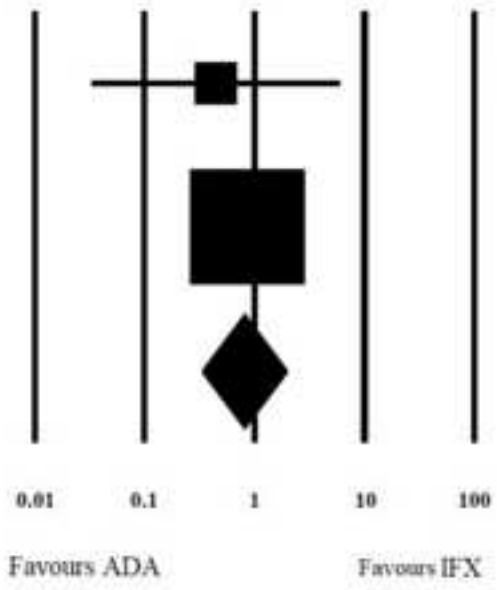

Figure_5

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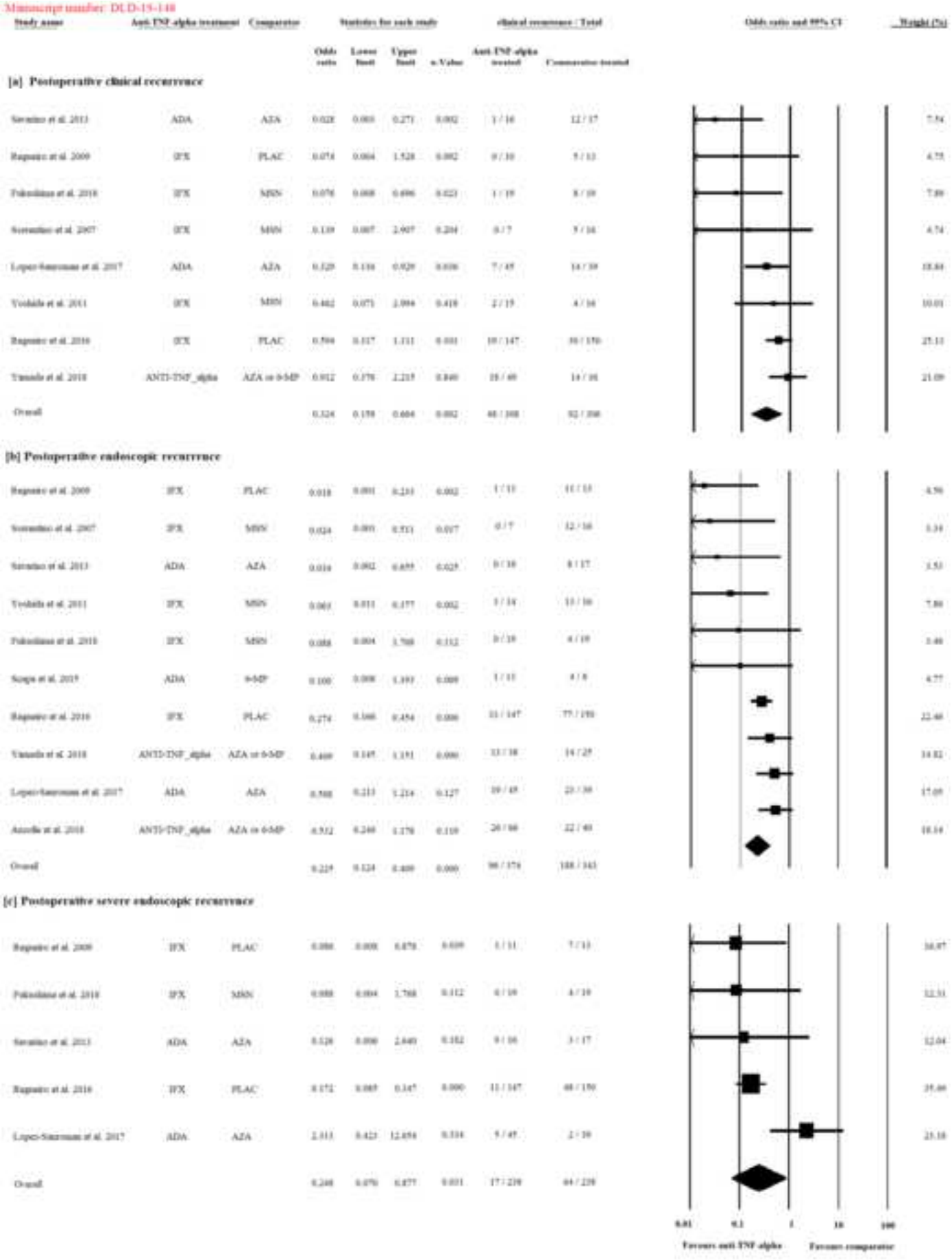

Table 1 Baseline characteristics of patients in the studies analyzed

Author (year)	Study type (number of centers)	Drug (n)	Male (%)	Age at surgery (years)	Disease duration	Smoking n (%)	Perianal disease n (%)	≥1 previous resections n (%)	Disease location at surgery n (%)				Disease behavior at surgery n (%)		
									L1	L2	L3	L4	B1	B2	B3
Armuzzi et al. (2013)	RCT (1)	IFX (11)	7 (64)	34 (24-37)[c]	24 (15-81)[c**]	5 (46)	5 (46)	4 (36)	NA	NA	NA	NA	NA	NA	7 (64)
		AZA (11)	8 (73)	32 (21-45)[c]	24 (12-54)[c**]	5 (46)	6 (55)	4 (36)	NA	NA	NA	NA	NA	NA	5 (46)
Auzolle et al. (2018)	prospective cohort (1)	anti-TNFα (66)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		AZA/6-MP (40)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
De Cruz et al. (2015)	RCT (18)	ADA (28)	11 (39)	39 (30-49)[c]	11 (6-18)[c**]	10 (36)	NA	12 (43)	17 (61)	2 (7)	9 (32)	0 (0)	3 (11)	8 (29)	17 (61)
		AZA/6-MP (73)	40 (55)	33 (24-45)[c]	8 (3-18)[c**]	28 (38)	NA	21 (29)	34 (47)	4 (5)	35 (48)	0 (0)	5 (7)	16 (22)	52 (71)
Fukushima et al (2018)	RCT (13)	IFX (19)	17 (90)	36.6 (19–55)[*]	5.5 (1–11)[*]	5 (26)	NA	2 (11)	4 (21)	3 (16)	12 (63)	0 (0)	1 (5)	13 (68)	5 (26)
		MSN (19)	13 (68)	37.6 (23–74)[*]	6.2 (1–11)[*]	2 (11)	NA	4 (21)	7 (37)	1 (5)	11 (58)	0 (0)	0 (0)	11 (58)	8 (42)
Kotze et al. (2014)	retrospective (7)	ADA (37)	21 (57)	33.6 ± 12.1[a]	84 (2-300)[f**]	4 (11)	9 (24)	12 (32)	13 (35)	4 (11)	20 (54)	0 (0)	4 (11)	18 (49)	15 (41)
		IFX (59)	38 (64)	31.1 ± 10.9[a]	82 (2-240)[f**]	9 (15)	22 (37)	25 (42)	21 (36)	2 (3)	36 (61)	0 (0)	1 (2)	33 (56)	25 (42)
Lopez-Sanroman et al. (2017)	RCT (24)	ADA (45)	19 (42)	35 (30-40)[c]	8.1[b*]	11 (24)	4 (9)	3 (7)	26 (58)	0 (0)	19 (42)	2 (4)	0 (0)	0 (0)	20 (44)
		AZA (39)	23 (59)	37 (31-47)[c]	7.3[b*]	9 (23)	8 (21)	3 (8)	23 (59)	0 (0)	16 (41)	3 (8)	0 (0)	0 (0)	11 (28)
Regueiro at al. (2009)	RCT (1)	IFX (11)	5 (46)	43 (28; 49)[e]	13 (1; 19)[e*]	5 (46)	NA	11 (100)	2 (18)	0 (0)	9 (82)	0 (0)	0 (0)	4 (25)	12 (75)
		PLAC (13)	3 (23)	32 (26; 45)[e]	9 (2; 12)[e*]	1 (8)	NA	13 (100)	3 (23)	0 (0)	10 (77)	0 (0)	0 (0)	4 (25)	12 (75)
Regueiro at al. (2016)	RCT (104)	IFX (147)	77 (52)	35 (26-45)[c]	8.4 ± 8.7[a*]	38 (26)	17 (12)	68 (46)	144 (99)	0 (0)	89 (61)	6 (4)	NA	NA	NA
		PLAC (150)	81 (54)	34 (25-44)[c]	6.4 ± 7.5[a*]	37 (25)	13 (9)	79 (53)	146 (97)	0 (0)	76 (51)	6 (4)	NA	NA	NA
Savarino at al. (2013)	RCT (1)	ADA (16)	8 (50)	45 (22-66)[d]	8.4 (1-17)[d*]	9 (56)	NA	4 (25)	9 (56)	0 (0)	7 (44)	0 (0)	0 (0)	4 (25)	12 (75)
		AZA (17)	9 (53)	49 (24-69)[d]	7.9 (1-17)[d*]	4 (24)	NA	2 (12)	8 (47)	0 (0)	9 (53)	0 (0)	0 (0)	5 (29)	12 (71)
		MSN (18)	8 (44)	46 (25-65)[d]	6.9 (1-18)[d*]	6 (33)	NA	5 (29)	8 (44)	0 (0)	10 (56)	0 (0)	0 (0)	4 (22)	14 (78)
Scapa et al. (2015)	RCT (1)	ADA (11)	NA	30.5 ± 2.3[a*]	NA	1 (9)	NA	NA	NA	NA	NA	NA	NA	NA	NA
		6-MP (8)	NA	34.4 ± 2.5[a*]	NA	3 (38)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sorrentino at al. (2007)	prospective pilot study (1)	IFX+MTX (7)	4 (57)	36 (23-64)[b]	7 (3-14)[b*]	2 (29)	NA	2 (29)	5 (71)	0 (0)	2 (29)	0 (0)	NA	NA	NA
		MSN (16)	11 (69)	40.5 (23-70)[b]	5.5 (1-23)[b*]	4 (25)	NA	1 (6)	11 (69)	3 (19)	2 (13)	0 (0)	NA	NA	NA
Tursi et al. (2014)	RCT (1)	ADA (10)	5 (50)	34.5 (22-39)[b]	48 (6-144)[b*]	2 (20)	4 (40)	3 (30)	NA	NA	NA	NA	0 (0)	0 (0)	8 (80)
		IFX (10)	4 (40)	30.5 (20-33)[b]	48 (6-130)[b*]	3 (30)	4 (40)	4 (40)	NA	NA	NA	NA	0 (0)	0 (0)	3 (30)
Yamada et al. (2018)	retrospective (1)	VDZ (22)	8 (36)	25.5 (23.0-30.7)[c*]	9 (2.5-12.0)[c*]	3 (14)	12 (55)	13 (59)	4 (18)	5 (23)	13 (59)	2 (9)	6 (27)	10 (46)	6 (27)
		anti-TNFα (58)	30 (52)	36.0 (28.5-48.5)[c*]	12 (4.0-18.0)[c*]	7 (12)	16 (28)	37 (64)	16 (28)	8 (14)	34 (59)	4 (7)	9 (16)	24 (41)	25 (43)
		AZA/6-MP (38)	18 (47)	40.5 (25.0-49.5)[c*]	9 (1.0-15.0)[c*]	4 (11)	6 (16)	17 (45)	14 (37)	5 (13)	19 (50)	4 (11)	4 (11)	11 (29)	23 (61)
		MZD (16)	7 (44)	44.0 (34.7-53.0)[c*]	8 (5.5-18.2)[c*]	1 (6)	8 (50)	8 (50)	6 (38)	4 (25)	6 (38)	0 (0)	3 (19)	6 (38)	7 (44)
		PLAC (69)	34 (49)	41.0(30.0-54.0)[c*]	8 (2.0-19.0)[c*]	15 (22)	11 (16)	46 (67)	18 (28)	18 (28)	29 (45)	1 (1)	17 (25)	23 (33)	29 (42)
Yoshida et al. (2011)	RCT (1)	IFX + MSN (15)	11 (73)	36.9 ± 11.6[a]	11.6 ± 8.8[a*]	3 (20)	NA	11 (73)	4 (27)	0 (0)	11 (73)	0 (0)	NA	NA	NA
		MSN (16)	12 (75)	32.9 ± 10.2[a]	9.2 ±7.1[a*]	3 (19)	NA	10 (63)	4 (25)	0 (0)	12 (75)	0 (0)	NA	NA	NA

RCT: randomized controlled trial; IFX: infliximab; AZA: azathioprine; NA: non-available; 6-MP: 6-mercaptopurin; anti-TNFα: anti-tumor necrosis factor alpha; ADA: adalimumab; MTX: methotrexate; MSN: mesalamine; PLAC: placebo; [a] mean +/-SD; [b] median (range); [c] median (IQR); [d] mean (range); [e] median (25%; 75%); [f] median (min – max.); * years; ** months; VDZ: vedolizumab; MZD: metronidazole

Table S_1

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PRISMA Checklist for Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**5**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**6-7**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**8**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**8**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**9**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**8**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**8-9**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**9**

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**9-10**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**10**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**11**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**11-12**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**11-12**

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**15-16**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**10, 12**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**12-13**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**9-10**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**15-16**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**13-15**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**13-15**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**15-16**

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**13-15**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**16-17**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**17**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**17-18**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**2**

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Table S_2

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Supplementary Table 2 Outcomes of enrolled studies on clinical, endoscopic, severe endoscopic and histological postoperative recurrence

References (year)	Follow up (months)	Drug regimen (n)	Clinical recurrence (%)	Endoscopic recurrence (i2-4) (%)	Severe endoscopic recurrence (i3-4) (%)	Histological recurrence (%)
Armuzzi et al (2013)	12	IFX: 5 mg/kg at 0, 2. 6. wks, then q8w (11)	1 (9)	1 (9)	0 (0)	2 (18)
		AZA: 2.5 mg/kg/day (11)	1 (10)	4 (40)	1 (10)	8 (73)
Auzolle et al. (2018)	6-12	anti-TNFα: NA (66)	NA	26 (39)	NA	NA
		AZA/6MP: NA (40)	NA	22 (55)	NA	NA
De Cruz et al. (2015)	6	ADA: 160/80 mg at 0, 2. wks, then 40 mg eow (28)	5 (18)	6 (21)	1 (4)	NA
		AZA: 2 mg/kg/day or 6-MP: 1.5 mg/kg/day (73)	16 (22)	33 (45)	6 (8)	NA
Fukushima et al. (2018)	24	IFX: 5 mg/kg at 0, 2. 6. wks, then q8w (19)	1 (5)	0 (0)	0 (0)	NA
		MSN: NA (19)	8 (50)	4 (21)	4 (21)	
Kotze et al. (2014)	12	IFX: NA (59)	NA	16 (27)	NA	NA
		ADA: NA (37)	NA	9 (24)	NA	NA
Lopez-Sanroman et al (2017)	12	ADA: 160/80 mg at 0, 2. wks, then 40 mg eow +MZD (45)	7 (16)	19 (42)	5 (14)	NA
		AZA: 2.5 mg/kg/day + MZD (39)	14 (36)	23 (59)	2 (8)	
Regueiro at al (2009)	12	IFX: 5 mg/kg at 0, 2. 6. wks, then q8w (11)	0 (0)	1 (9)	1 (9)	3 (27)
		PLAC: (13)	5 (39)	11 (85)	7 (54)	11 (85)
Regueiro at al. (2016)	18	IFX: 5 mg/kg q8w (147)	19 (13)	33 (22)	11 (19)	NA
		PLAC: (150)	30 (20)	77 (51)	48 (81)	NA
Savarino at al. (2013)	24	ADA: 160/80 mg at 0, 2. wks, then 40 mg eow (16)	1 (6)	0 (0)	0 (0)	NA
		AZA: 2 mg / kg / day (17)	12 (71)	8 (47)	3 (18)	NA
		MSN: 3 g / day (18)	9 (50)	7 (39)	3 (17)	NA
Scapa et al. (2015)	6	ADA: 160/80 mg at 0, 2. wks, then 40 mg eow (11)	NA	1 (9)	NA	NA
		6-MP: 1.5 mg/kg/day (8)	NA	4 (50)	NA	NA
Sorrentino at al (2007)	24	IFX: 5 mg/kg at 0, 2. 6. wks, then q8w + MTX: 10 mg/wk (7)	0 (0)	0 (0)	0 (0)	NA
		MSN: 800 mg tid (16)	5 (31)	12 (75)	NA	
Tursi et al.(2014)	12	IFX: 5 mg/kg at 0, 2. 6. wks, then q8w (10)	1 (10)	2 (20)	1 (10)	NA
		ADA: 160/80 mg at 0, 2. wks, then 40 mg eow (10)	1 (10)	1 (10)	0 (0)	
Yamada et al. (2018)	6-12	VDZ: NA (22)	10 (46)	15 (68)	NA	15 (68)
		Anti TNFα: NA (58)	18 (31)	13 (22)	NA	15 (26)
		AZA/6-MP: NA (38)	14 (37)	14 (37)	NA	19 (50)
		MZD: NA (16)	10 (63)	5 (31)	NA	2 (13)
		PLAC: NA (69)	29 (42)	26 (38)	NA	16 (23)
Yoshida et al. (2011)	36	IFX+MSN: 5 mg/kg q8w (15)	2 (13)	3 (21)	NA	NA
		MSN (16)	4 (25)	13 (81)	NA	NA

IFX: infliximab; AZA: azathioprine; 6-MP: 6-mercaptopurin; NA: non-available; anti-TNFα: anti-tumor necrosis factor alpha; ADA: adalimumab; MSN: mesalamine; MTX: methotrexat; MZD: metronidazole; PLAC: placebo; wks: weeks; eow: every other week; sc: subcutaneously; tid: three times a day; VDZ: vedolizumab

Table S_3

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Supplementary Table 3 The results of test for heterogeneity. Chi-square statistic (Q-value) with degree of freedom (df), associated *p*-value and I^2 values are shown.

	Clinical recurrence				Endoscopic recurrence				Severe endoscopic recurrence				Histological recurrence			
	Q value	**df**	**P**	**I^2 (%)**	**Q value**	**df**	**P**	**I^2 (%)**	**Q value**	**df**	**P**	**I^2 (%)**	**Q value**	**df**	**P**	**I^2 (%)**
Biologics vs. Non-biological comparators																
ADA subgroup	6.70	2	0.04	70.2	4.09	3	0.25	26.6	3.27	2	0.19	38.9	-	-	-	-
ANTI-TNFα subgroup	$1.65x10^{-17}$	0	1	0	0.16	1	0.69	0	-	-	-	-	$4.70x10^{-15}$	0	1	0
IFX subgroup	5.37	5	0.37	6.9	8.64	5	0.12	42.1	0.57	3	0.90	0	0.02	1	0.89	0
Overall	14.61	9	0.10	38.4	17.75	11	0.09	38.0	9.27	6	0.16	35.3	5.43	2	0.07	63.2
Biologics vs. Non-biological comparators																
High-risk subgroup	$8.90x10^{-3}$	1	0.92	0	0.23	1	0.63	0	0.04	1	0.84	0	-	-	-	-
Nonselected subgroup	13.70	7	0.06	48.9	17.51	9	0.04	48.6	8.95	4	0.06	55.3	-	-	-	-
Overall	14.61	9	0.10	38.4	17.75	11	0.09	38.0	9.27	6	0.16	35.3	-	-	-	-
Biologics vs. Thiopurines																
ADA subgroup	6.70	2	0.04	70.2	4.09	3	0.25	26.6	3.27	2	0.19	38.9	-	-	-	-
ANTI-TNFα subgroup	$1.65x10^{-17}$	0	1	0	0.16	1	0.69	0	-	-	-	-	-	-	-	-
IFX subgroup	$9.73x10^{-19}$	0	1	0	$5.50x10^{-15}$	0	1	0	0	0	1	0	-	-	-	-
Overall	9.26	4	0.05	56.8	5.25	6	0.51	0	3.65	3	0.30	17.8	-	-	-	-

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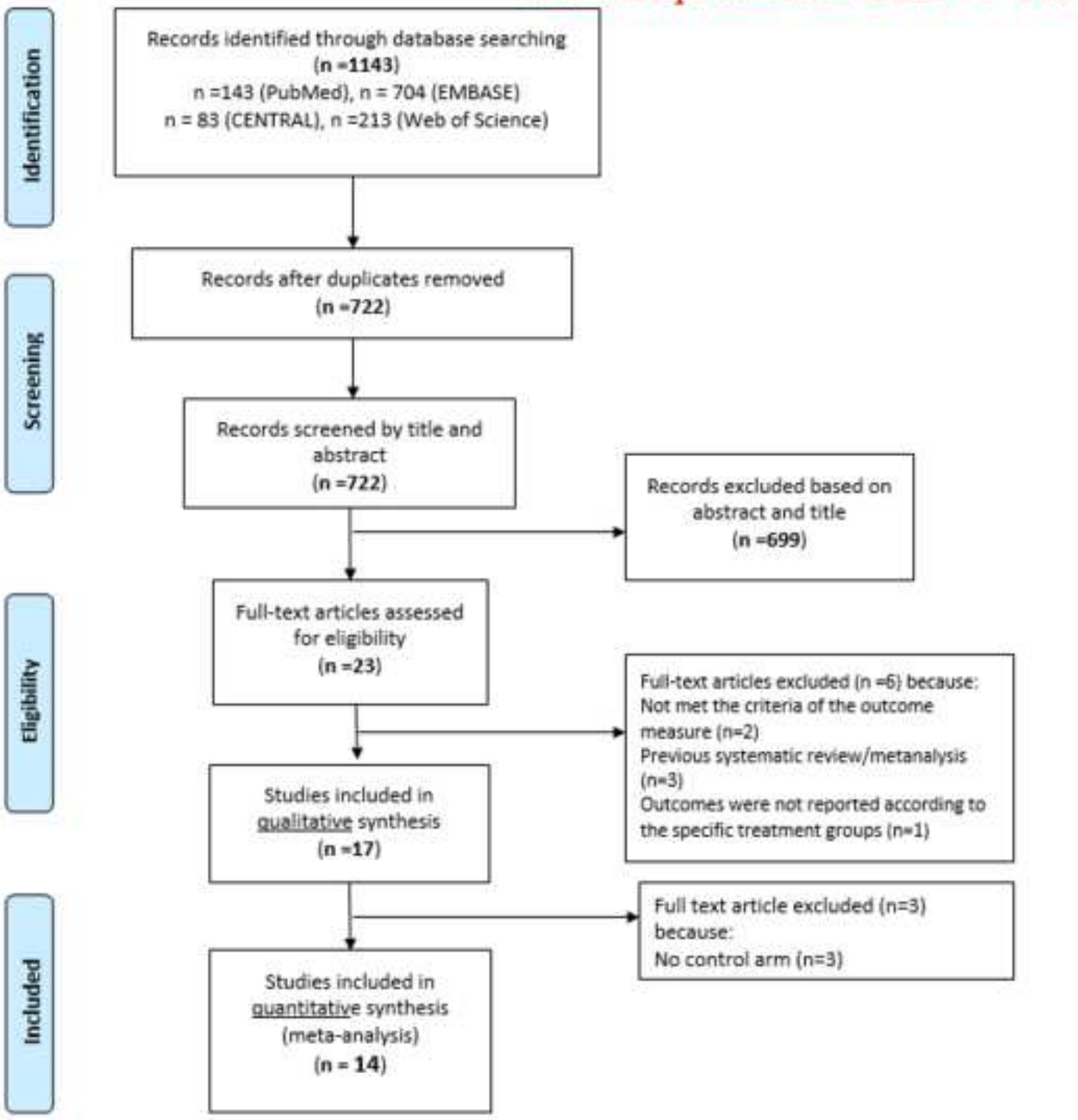

Figure 1: Flowchart of study selection.

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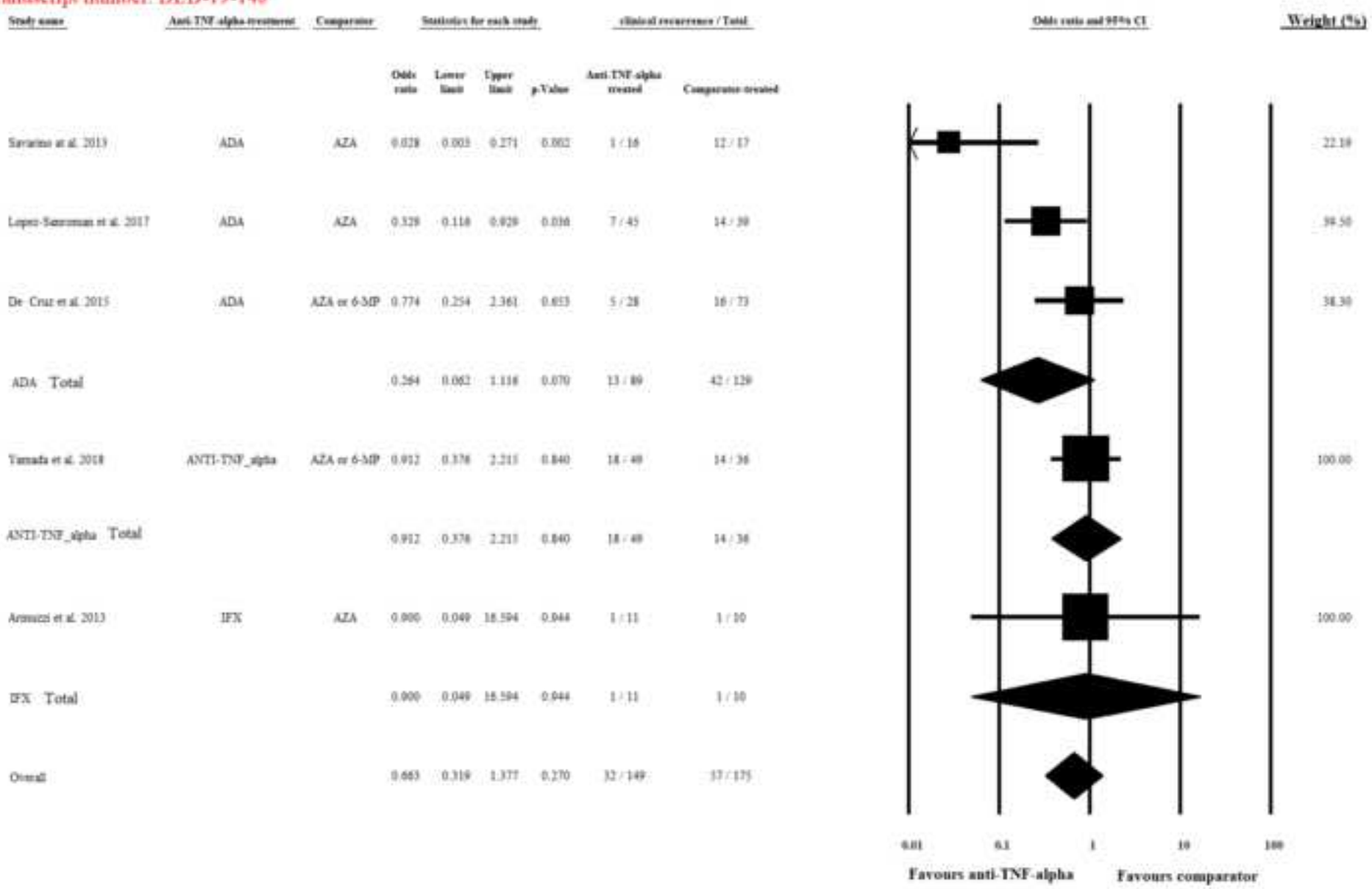

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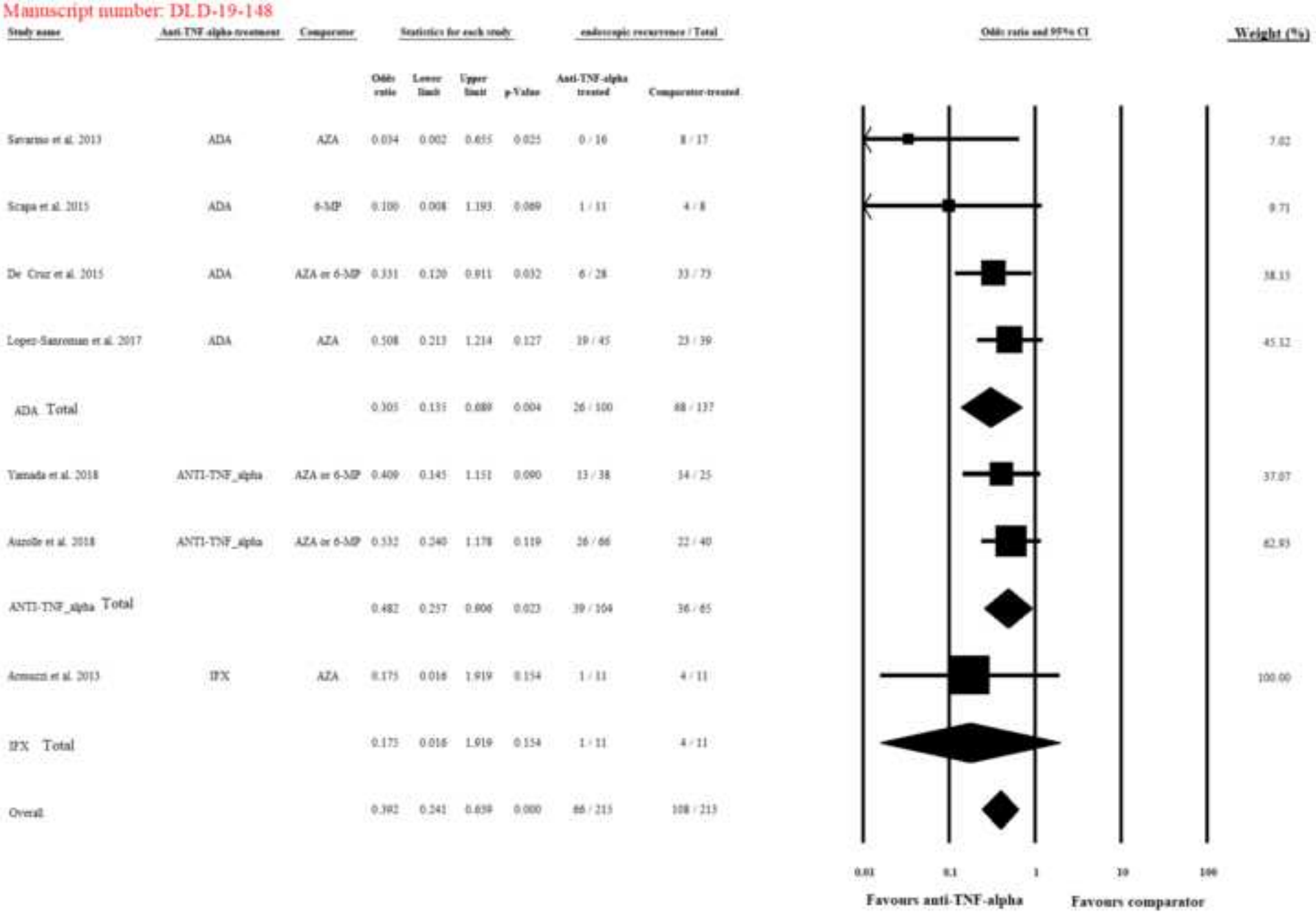

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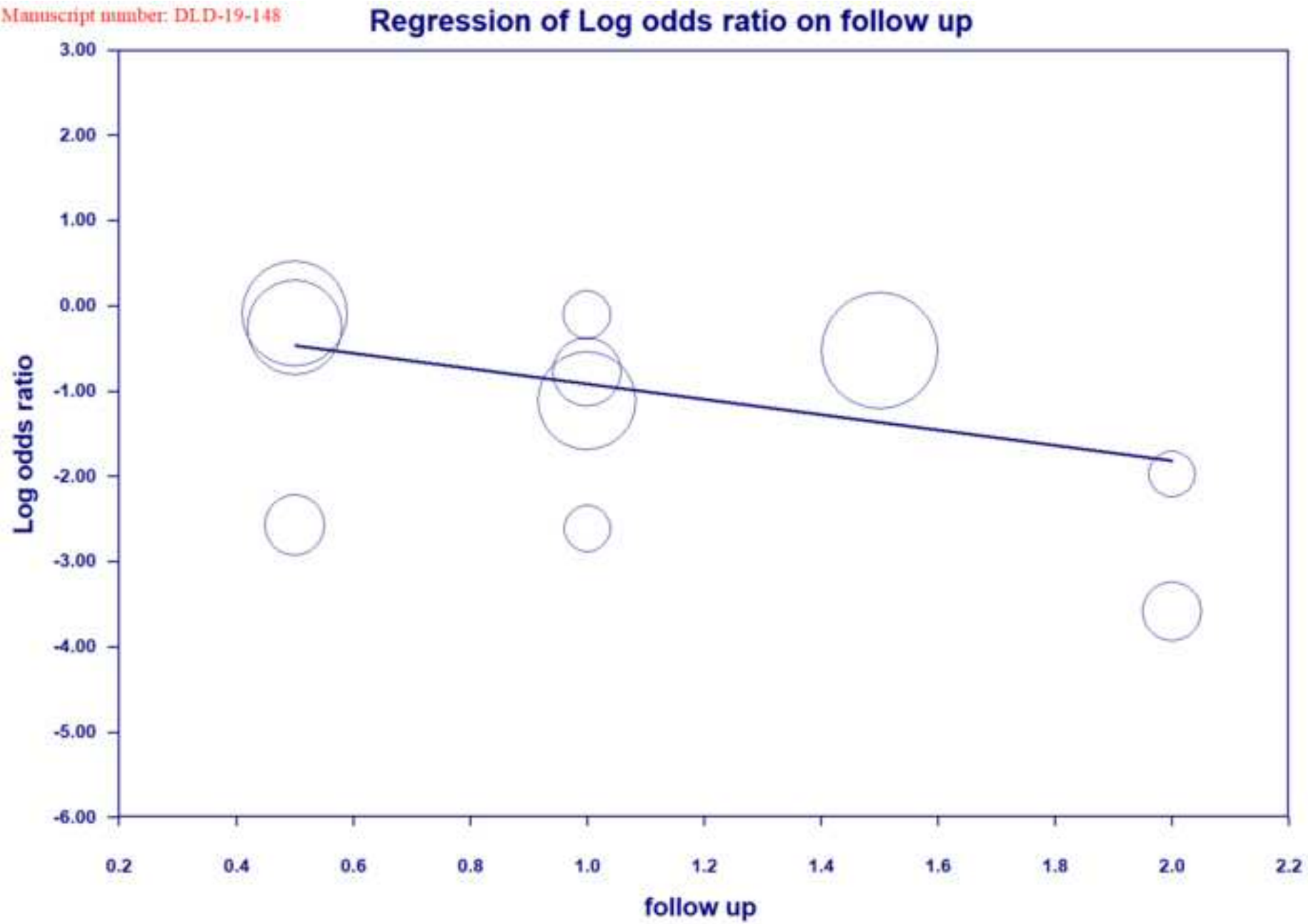

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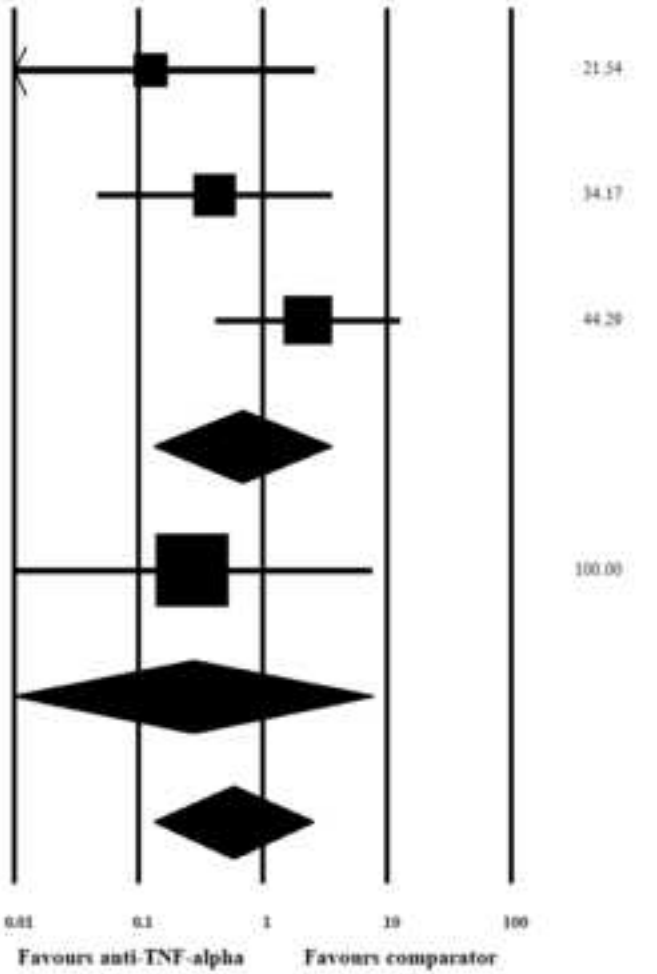
Study name	Anti-TNF-alpha treatment	Comparator	Odds ratio	Lower limit	Upper limit	p-Value	Anti-TNF-alpha treated	Comparator-treated	Weight (%)
Savarino et al. 2013	ADA	AZA	0.120	0.006	2.640	0.182	0 / 16	3 / 17	21.54
De Cruz et al. 2015	ADA	AZA or 6-MP	0.414	0.048	3.599	0.424	1 / 28	6 / 73	34.17
Lopez-Sanromán et al. 2017	ADA	AZA	2.313	0.423	12.654	0.334	5 / 45	2 / 39	44.29
ADA Total			0.688	0.133	3.524	0.651	6 / 89	11 / 129	
Armuzzi et al. 2013	IFX	AZA	0.275	0.010	7.571	0.446	0 / 11	1 / 10	100.00
IFX Total			0.275	0.010	7.571	0.446	0 / 11	1 / 10	
Overall			0.573	0.132	2.488	0.458	6 / 100	12 / 139	



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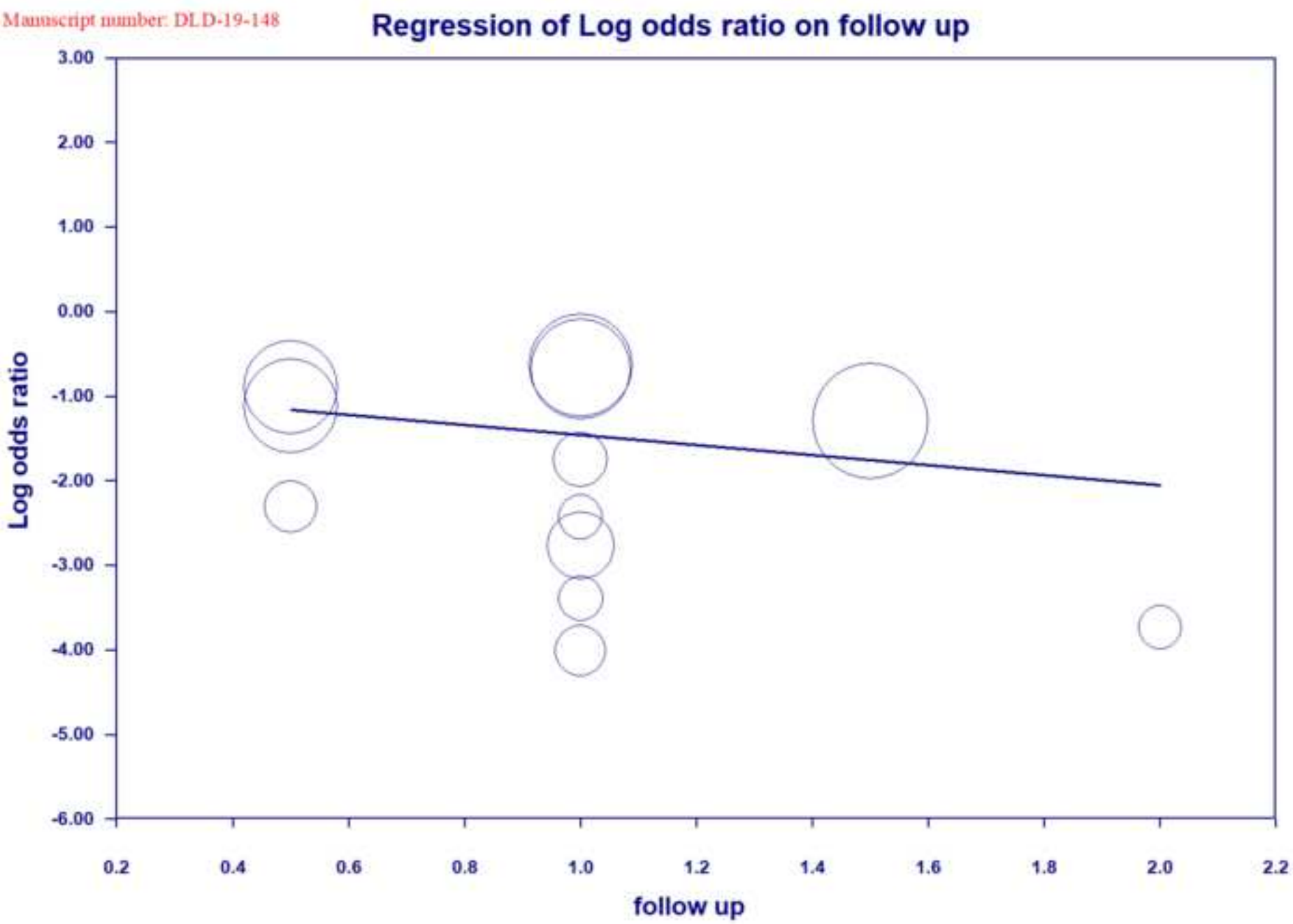

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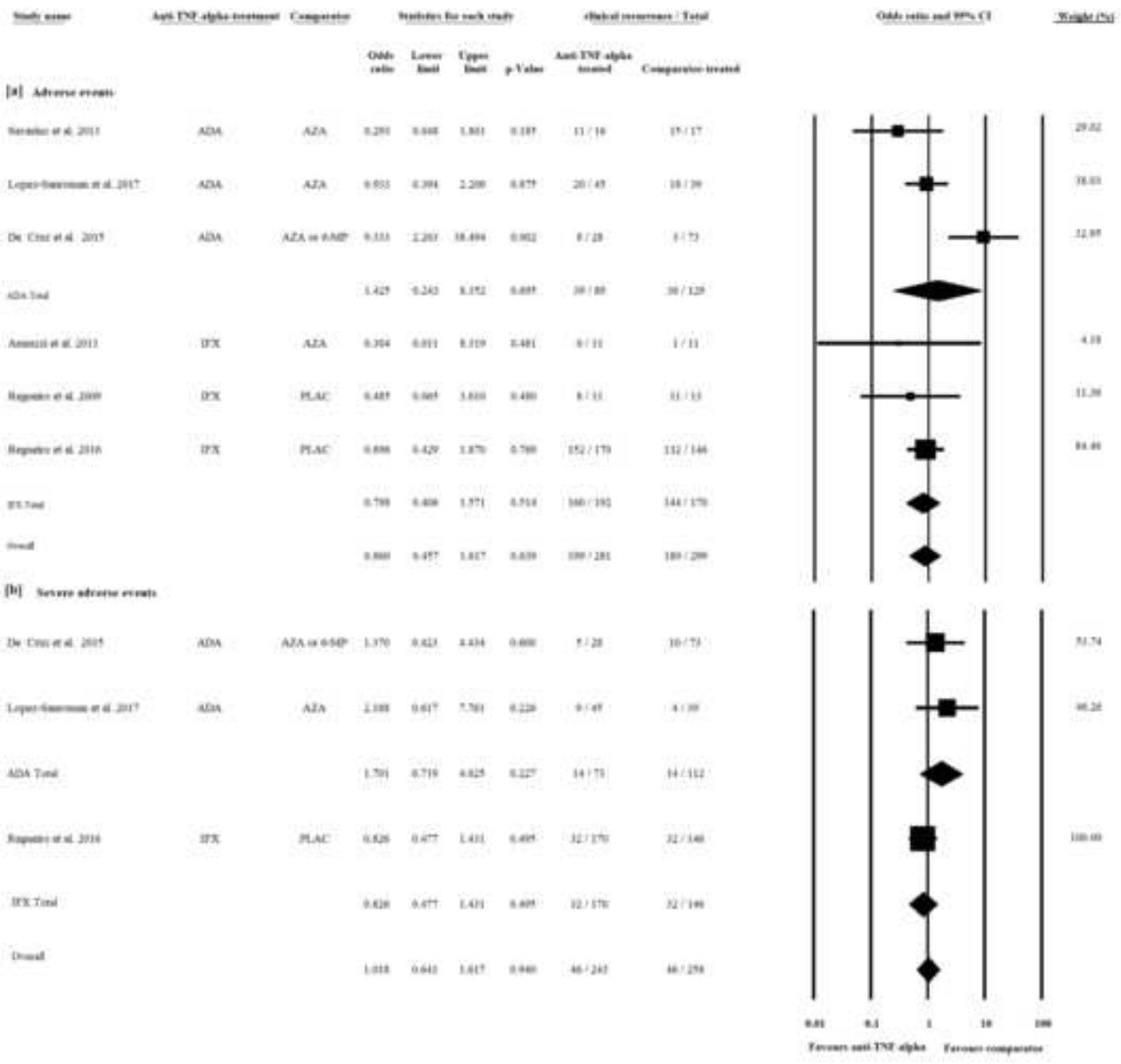

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