Review Article

Tumor Necrosis Factor-alpha Antibodies in Fistulizing Crohn's Disease: An Updated Systematic Review and Meta-analysis

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Received: March 2017.
Accepted: June 2017.

Abstract

Medical treatment for fistulizing Crohn's disease (FCD) is changing rapidly over the time by the introduction of novel therapeutic medicines, while no global consensus is available. This study aims to accomplish a systematic review and meta-analysis on the efficacy of tumor necrosis factor-alpha antibodies (anti-TNF-α antibodies) versus placebo in FCD. A systematic review of published literature was carried out till December 2016, and a meta-analysis of identified studies was done. Data have been explored from PubMed, Scopus, Cochrane Library Database, and Web of Science. Predefined exclusion criteria for included studies in meta-analysis are based on search methodology and are as follows: Randomized clinical trial about Crohn's disease (CD) patients without fistula, pediatrics CD, randomized clinical trials about pregnant women with FCD, nonhuman studies, randomized clinical trials with surgical therapies interventions, conference abstracts, case reports, and language other than English studies. All randomized placebo-controlled trials were included. To assess risk of bias, Jadad score was applied to evaluate trials' methodological quality. Relative risk (RR) and 95% confidence intervals were computed using Mantel-Haenszel and/or Rothman-Boice (for fixed effects) or Der Simonian-Laird (for random effects) techniques. Nine studies attained defined inclusion criteria. The meta-analysis results showed that anti-TNF-α antibodies are remarkably more effective in comparison to placebo for fistula closure maintenance (RR = 2.36; 95% confidence interval: 1.58–3.55; $P < 0.0001$) in patients with FCD, whereas anti-TNF-α antibodies were not superior to placebo neither in fistula improvement nor in fistula closure. We concluded that adalimumab and certolizumab pegol are both effective in fistula closure maintenance in adult patients with FCD.

Keywords: *Fistulizing Crohn's disease, meta-analysis, tumor necrosis factor-α antibodies*

Introduction

Crohn's disease (CD) is an idiopathic, lifelong, ongoing, inflammatory gastrointestinal system disorder which can impact all parts of the gastrointestinal tract (from mouth to anal canal). Commonly, the CD has a deteriorating course which can make patients' symptoms varied over time.[1-3] During recent years, CD incidence has raised up globally, and now, it is around 12.7/100,000 and 20.2./100,000 person-years in Europe and North America, respectively. Although CD can involve pediatrics and adults, it mainly affects adolescents and young adults. The most probable time for its commencement is usually from 15 to 30 years old.[4] In practice, the CD can be categorized variously according to its severity, location, and behavior.[5,6]

One of the most complicated categories of CD to treat is fistulizing CD (FCD), which impresses almost 20%–30% of patients with CD.[7-10] As defined, fistula is an unusual

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Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_17_46

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How to cite this article: Zaboli P, Abdollahi M, Mozaffari S, Nikfar S. Tumor necrosis factor-alpha antibodies in fistulizing Crohn's disease: An updated systematic review and meta-analysis. J Res Pharm Pract 2017;6:135-44.

connection between two epithelial surfaces. FCD is difficult to treat and no clear assent is available for its best treatment. Two main available treatment strategies are medically and surgically approaches which should be chosen by the clinicians. Despite these, most patients have undesirable results, which can lead to proctectomy in 10%–18% of cases.[11-15]

During recent years, introduction of disease-specific biologic medicines has predominantly altered CD and specially FCD medical treatment. Tumor necrosis factor-alpha antibodies (anti-TNF-α medicines) are specific monoclonal antibodies targeted against TNF-α which is a basic pro-inflammatory cytokine in CD and FCD development. There are three extensively used anti-TNF-α medicines in FCD treatment such as infliximab, adalimumab, and certolizumab pegol. Etanercept and CDP 571 are genetically engineered humanized antibodies to TNF, which produced by humanization process. This protein engineering procedure is applied to reduce the murine protein amount. Therefore, these medicines cause less immunogenicity than chimeric monoclonal antibodies. Different studies have shown the efficacy of these remedies in induction and maintenance of remission in FCD patients in comparison with placebo.[16-20]

In spite of a great work done to explore the clinical efficacy of anti-TNF-α medicines, their most favorable case of dispensing is not fully transparent yet. This is mainly owing to lack of enough studies investigating comparative efficacy of these medicines.[21-25]

Since FCD medical treatment is changing rapidly over the time by the introduction of novel therapeutic medicines and on the other hand lack of global consensus, this study aims to accomplish a systematic review and meta-analysis and summarize the literature on anti-TNF-α antibodies' efficacy versus placebo in FCD to provide reliable recommendations.

Methods

Study design

This meta-analysis was done in accordance with the recent guidelines for meta-analysis reporting (PRISMA guidelines).[26] The PICOT of studies which were included in meta-analysis was based on a predefined search methodology and is as follows – population: FCD, intervention: anti-TNF-α medicines, comparator: placebo, outcome: fistula improvement and fistula closure, and time: 4–56 weeks.

Data sources

Data were searched from PubMed, Scopus, Cochrane Library Database, and Web of Science (ISI) published before December 2016. Applied Mesh terms were "infliximab," "remicade," "Crohn's disease," "adalimumab," "certolizumab pegol," "etanercept," "CDP571." To include all the relevant studies, primary search was not limited to FCD. The "related articles" function from PubMed was used to broaden the search. Abstracts, studies, and citations scanned were reviewed too. In addition, aforementioned studies' references were also searched to identify additional studies for inclusion.

Inclusion criteria

All randomized, placebo-controlled clinical trials (RCTs) evaluating efficacy of anti-TNF-α medicines in CD patients were included in this meta-analysis. Publications' references were inspected to identify any potential inclusion, and further selection was in accordance with their full text. To be included in this analysis, studies had to report on medical therapy and response to therapy in FCD patients. Studies were excluded from quantitative analysis if: (a) study population was CD patients without fistula; (b) study population was pediatrics with CD; (c) study population was pregnant women with CD; (d) study population was nonhuman; (e) study evaluates surgical therapy efficacy in FCD; (f) study outcomes of the measure were not similar to ours; (g) it is conference abstracts, case reports, letters, reviews, or comments; and (h) study language was other than English.

Study selection

Data extraction was conducted by three reviewers (P.Z. and S.N. and S.M.) who read search results independently. First, search results have been screened by title and irrelevant or duplicate records were excluded. Second, remained records' abstracts have been read to eliminate reviews, case studies, uncontrolled trials, and controlled trials without placebo. At last, enrolled studies' full text has been reviewed. At this time, reviewers held a face-to-face session to announce included studies from their own point of view. In case of disagreement, they debate to reach a single decision about a certain study. Then, reviewers extracted data from included studies as follows: first author, year of publication, study design, sample size, patients' characteristics (number, with or without fistula), treatment groups, treatment duration, outcomes, response to therapy, and results.

Assessment of trial quality

To assess the risk of bias, Jadad score, which indicates the studies' quality upon their description of randomization, blinding, and withdrawals, was applied to assess trials' methodological quality. The quality scale ranges from 0 to 5 points with a score of 2 or less for a

low-quality report and a score of at least 3 or more for a high-quality report.[27]

Outcomes of interest and definitions

Following outcomes and definitions were used in this analysis:

1. Fistula improvement was defined as closure of 50% of fistulas for at least two consecutive visits[28-31]
2. Fistula closure was defined as closure of 100% of fistulas for at least two consecutive visits.[28-33]

Statistical analysis

When we want to describe exposure and control and report their defined outcomes to change it to quantified manifestation, design of 2 × 2 table is needed. Therefore, anti-TNF-α medicines were considered as exposure and placebo was considered as control. Fistula closure and fistula improvement were considered as outcomes. All included studies were weighted in meta-analysis software based on their sample size and the results were pooled. Data were analyzed using StatDirect Ltd StatsDirect software version 3.07.187. Relative risk (RR) and 95% confidence intervals (95% CIs) were calculated using Mantel-Haenszel and/or Rothman-Boice (for fixed effects) or Der Simonian-Laird (for random effects) methods. The Cochran's *Q*-test was used to test heterogeneity and $P < 0.05$ was considered statistically significant. In case of heterogeneity or few included studies, random effects model was used. Funnel plot was used as publication bias indicator. Egger and Begg-Mazumdar tests were used to evaluate publication bias indicators in funnel plot.

Results

The electronic searches lead to 12,146 records: 266 from PubMed, 896 from Scopus, and 2908 from Cochrane library database, and 8076 from Web of Science (ISI). First, search results have been screened by title and irrelevant or duplicate records were excluded; thereby, searches decreased to 9828 records. Second, remained records' abstracts have been read to eliminate reviews, case studies, uncontrolled trials, and controlled trials without placebo. At last, 192 records enrolled to studies' full-text review. At this time, reviewers held a face-to-face session to announce included studies from their own point of view. In case of disagreement, they debate to reach a joint decision about a certain study. Primarily, the reviewers selected 13 articles in sum. Finally, nine articles were considered eligible to be included in meta-analysis. The PRISMA flow diagram depicts selection process [Figure 1].

Included studies' quality was appraised by Jadad score. All included studies[18,21,28-30,32-35] had high-quality scores (Jadad scores ≥4) as tabulated in Table 1.

Then, reviewers extracted data from included studies as follows: first author, year of publication, study design, sample size, patients' characteristics number of patients with fistula, treatment groups (type of anti-TNF-α medicine or placebo), treatment duration, outcomes, and results which are summarized in Table 2.

Results are presented in terms of fistula improvement and fistula closure. To summarize results, only significant tables are reported. Two subgroups of studies were structured for data analyzing: (a) fistula improvement and (b) fistula closure and for each subgroup as

Table 1: Jadad quality score of randomized controlled trials included in the meta-analysis

Study	Randomization	Blinding	Withdrawals and dropouts	Total
Hanauer *et al.*[18]	2	2	1	5
Sandborn *et al.*[34]	2	1	1	4
Present *et al.*[35]	2	2	1	5
Sandborn *et al.*[32]	2	2	1	5
Schreiber *et al.*[28]	2	1	1	4
Sandborn *et al.*[29]	2	1	1	4
Sandborn *et al.*[30]	2	2	1	5
Colombel *et al.*[33]	2	1	1	4
Sandborn *et al.*[21]	2	1	1	4

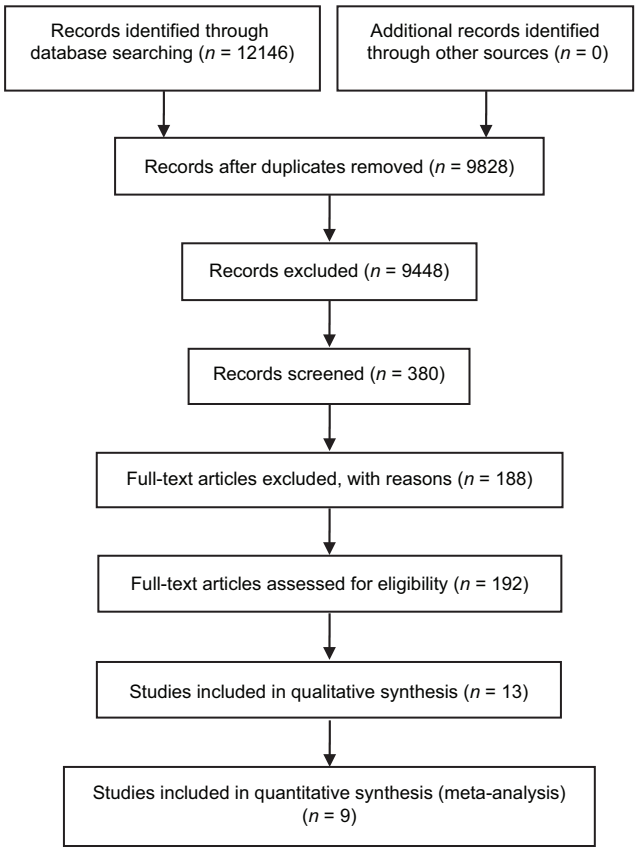

Figure 1: Flow diagram of the study selection process

short-term induction and short- and long-term induction and maintenance.

Fistula improvement (closure of 50% of fistulas for at least two consecutive visits)

Efficacy of short-term induction of anti-tumor necrosis factor-alpha medicines on fistula improvement in comparison to placebo in fistulizing Crohn's disease patients

The summary of RR for efficacy on fistula improvement in FCD patients calculated from four studies comparing short-term induction of anti-TNF-α medicines to placebo which three of them evaluated three different doses and one of them evaluated two different doses[18,32,34,35] was 1.6 with 95% CI = 0.95–2.7 [P = 0.08, Figure 2]. The Cochrane Q-test for heterogeneity indicated that the studies are not heterogeneous [P = 0.21, Figure 3] and could be combined; however, because of publication bias, the random effects model for individual and summary of RR was applied. For evaluation of publication bias, Egger regression of normalized effect versus precision for all included studies for fistula improvement in FCD patients among short induction of anti-TNF-α medicines versus placebo therapy was −1.9 (95% CI = −3.56 to −0.25, P = 0.03) and Begg-Mazumdar Kendall's test on the standardized effect versus variance indicated tau was −0.62, P = 0.03 [Figure 4].

Efficacy of short- and long-term induction of anti-tumor necrosis factor-alpha medicines in comparison to placebo in fistulizing Crohn's disease patients on fistula improvement

The summary of RR for efficacy on fistula improvement

Table 2: Characteristics of included studies

Study	Patients	Study design/ trial name	Patient number (with fistula)	Anti-TNF-α medicines	Treatment protocol	Evaluation time (weeks)	Outcomes
Hanauer *et al*.[18]	Moderate to severe CD naive to anti-TNF therapy	R, DB, PC/ Classic-I	32	Adalimumab	Adalimumab 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg or placebo at weeks 0, 2	4	Adalimumab was superior to placebo for induction of remission
Sandborn *et al*.[34]	Moderate to severe CD naive to infliximab therapy	R, DB, PC	45	Adalimumab	Adalimumab 160 mg/80 mg or placebo at weeks 0, 2	4	Adalimumab induces remissions more than placebo
Colombel *et al*.[33]	Moderate to severe CD	R, DB, PC/ CHARM	260	Adalimumab	Adalimumab 80 mg/40 mg or placebo at weeks 0, 2; at week 4: Placebo or adalimumab 40 mg eow, or weekly (to week 56)	26, 56	Adalimumab eow and weekly were more effective than placebo in maintaining remission
Present *et al*.[35]	CD with draining fistulas	R, DB, PC	94	Infliximab	Infliximab 5, 10 mg/kg, or placebo at weeks 0, 2, 6	18	Infliximab was effective for fistula treatment
Sandborn *et al*.[32]	Moderate to severe CD	R, DB, PC	5	Etanercept	Etanercept 25 mg or placebo twice weekly	8	Etanercept was safe, but not effective
Schreiber *et al*.[28]	CD with draining fistulas	R, DB, PC/ PRECiSE 2	108	Certolizumab pegol	Certolizumab pegol 400 mg or placebo q4 weeks	26	Certolizumab pegol improved the likelihood of sustained perianal fistula closure
Sandborn *et al*.[21]	Moderate to severe CD	R, DB, PC/ PRECiSE 1	107	Certolizumab pegol	Certolizumab pegol 400 mg or placebo at weeks 0, 2, 4 and then q4 weeks	26	Certolizumab pegol improved the response rates but not remission rates
Sandborn *et al*.[29]	Moderate to severe CD	R, DB, PC	37	CDP571	CDP571 10 or 20 mg/kg (single dose), then 10 mg/kg or placebo q8 weeks or q12 weeks	24	CDP571 was safe and effective
Sandborn *et al*.[30]	Moderate to severe CD	R, DB, PC	86	CDP571	CDP571 10 mg/kg or placebo q8 weeks (to week 24)	28	CDP571 was modestly effective for short but not long-term treatment

CD=Crohn's disease, DB=Double-blind, eow=Every other week, PC=Placebo controlled, R=Randomized, TNF=Tumor necrosis factor

in FCD patients in two studies comparing short- and long-term induction of anti-TNF-α medicines to placebo[29,30] was 1.83 with 95% CI = 0.83–4.02 [P = 0.13, Figure 5]. The Cochrane Q-test for heterogeneity indicated that the studies are not heterogeneous [P = 0.3, Figure 6] and could be combined; however, because of few included trials, the random effects model for individual and summary of RR was applied. For evaluation of publication bias, regression of normalized effect versus precision for all included studies for fistula improvement in FCD patients among short and long induction of anti-TNF-α medicines versus placebo therapy could not be calculated because of few strata.

Efficacy of anti-tumor necrosis factor-alpha medicines on fistula improvement maintenance in comparison to placebo in fistulizing Crohn's disease patients

The RR for efficacy on fistula improvement maintenance in FCD patients in one study comparing induction of anti-TNF-α medicines to placebo[28] was 1.24 with 95% CI = 0.72–2.11 (P = 0.44).

Fistula closure (closure of 100% of fistulas for at least two consecutive visits)

Efficacy of short-term induction of anti-tumor necrosis factor-alpha medicines on fistula closure in comparison to placebo in fistulizing Crohn's disease patients

The summary of RR for efficacy of fistula closure in FCD patients calculated from four studies comparing short-term induction of anti-TNF-α medicines to placebo which one of them evaluated two different doses and one of them evaluated three different doses[18,32,34,35] was 1.83 with 95% CI = 0.77–4.36 [P = 0.17, Figure 7]. The Cochrane Q-test for heterogeneity indicated that the studies are not heterogeneous [P = 0.15, Figure 8] and could be combined; however, because of publication bias, the random effects model for individual and summary of RR was applied. For evaluation of publication bias, Egger regression of normalized effect versus precision for all included studies for fistula closure in FCD patients among short induction of anti-TNF-α medicines versus placebo therapy was −2.16 (95% CI = −3.56–−0.76, P = 0.01) and Begg-Mazumdar Kendall's test on the standardized effect versus variance indicated tau was −0.62, P = 0.03 [Figure 9].

Efficacy of short- and long-term induction of anti-tumor necrosis factor-alpha medicines on fistula closure in comparison to placebo in fistulizing Crohn's disease patients

The summary of RR for efficacy of fistula closure in FCD patients in two studies comparing short- and long-term induction of anti-TNF-α medicines to placebo[21,30] was 1.061 with 95% CI = 0.65–1.72 [P = 0.81, Figure 10]. The Cochrane Q-test for heterogeneity indicated that

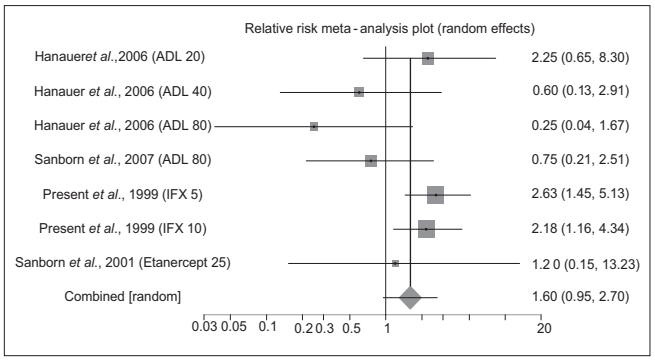

Figure 2: Individual and pooled relative of "fistula improvement" in the studies induction of anti-tumor necrosis factor-alpha medicines placebo therapy in fistulizing Crohn's disease patients

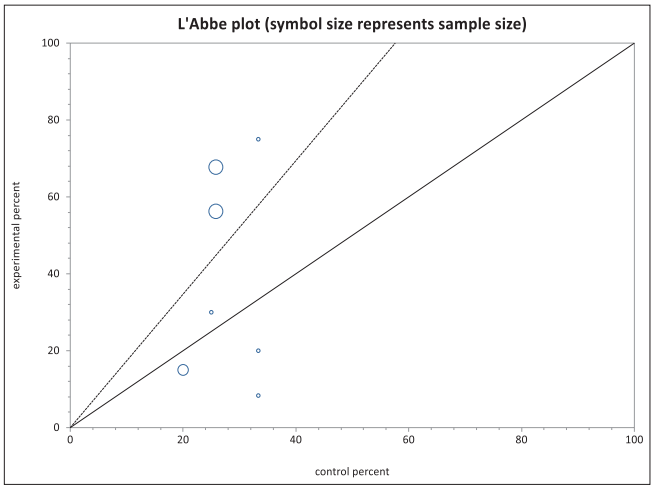

Figure 3: Heterogeneity indicators for the outcome of "fistula improvement" in the studies considering short-term induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

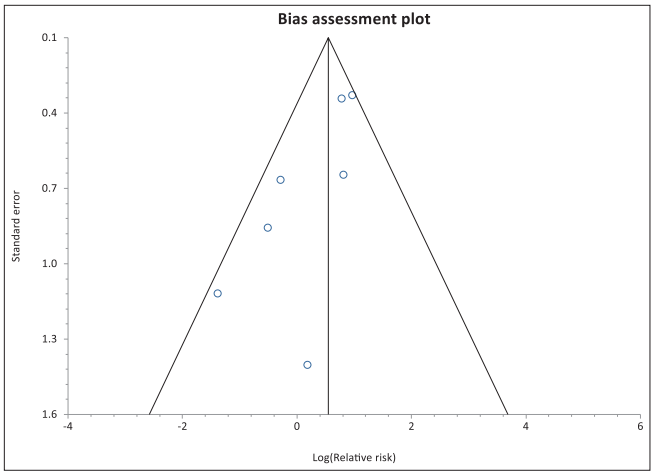

Figure 4: Publication bias indicators for the outcome of "fistula improvement" in the studies considering short-term induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

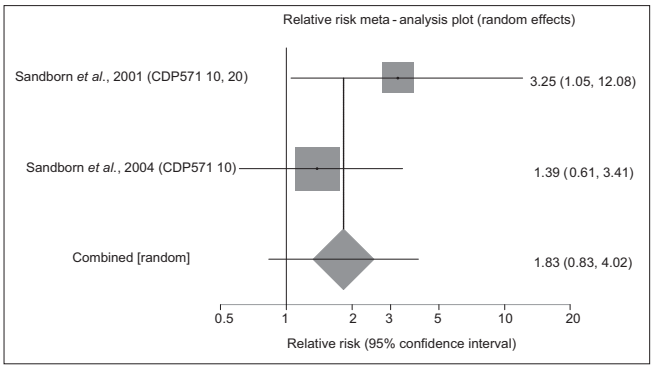

Figure 5: Individual and pooled relative risk for the outcome of "fistula improvement" in the studies considering short- and long-term induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

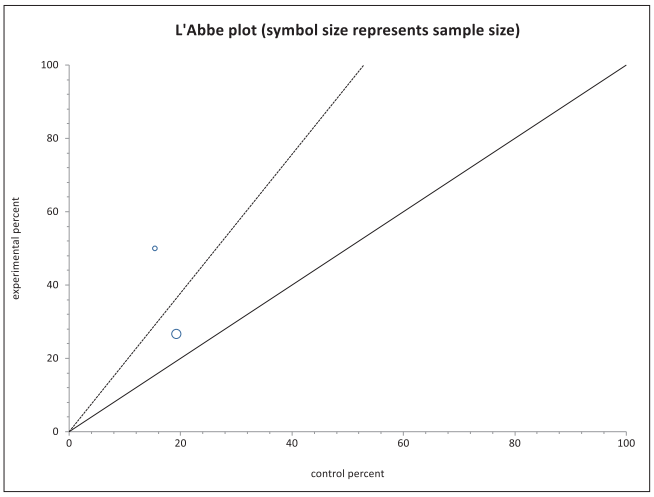

Figure 6: Heterogeneity indicators for the outcome of "fistula improvement" in the studies considering short- and long-term induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

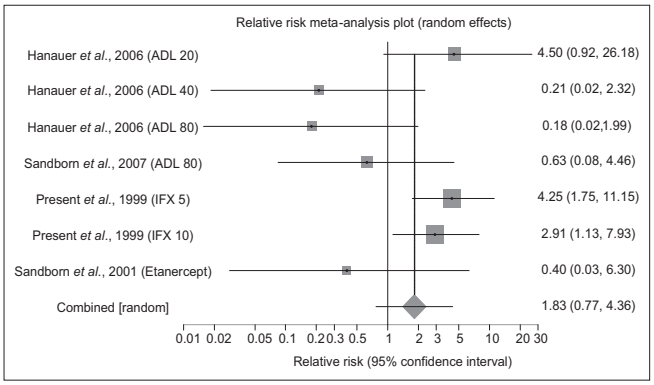

Figure 7: Individual and pooled relative risk for the outcome of "fistula closure" in the studies considering short-term induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

the studies are not heterogeneous [P = 0.6, Figure 11] and could be combined; however, because of few included trials, the random effects model for individual and summary of RR was applied. For evaluation of publication bias, regression of normalized effect versus precision for all included studies for fistula closure in FCD patients among short and long induction of anti-TNF-α medicines versus placebo therapy could not be calculated because of few strata.

Efficacy of anti-tumor necrosis factor-alpha medicines on fistula closure maintenance in comparison to placebo in fistulizing Crohn's disease patients

The RR for efficacy on fistula closure maintenance in FCD patients calculated from two studies comparing fistula closure maintenance of anti-TNF-α medicines to placebo which one of them evaluated four different doses[28,33] was 2.36 with 95% CI = 1.58–3.55 [P < 0.0001, Figure 12]. The Cochrane Q-test for heterogeneity indicated that the studies are not heterogeneous [P = 0.99, Figure 13] and could be combined; thus, the fixed effects model for individual and summary of RR was applied. For evaluation of publication bias, Egger regression of normalized effect versus precision for all included studies for fistula closure maintenance in FCD patients among induction of anti-TNF-α medicines versus placebo therapy was −3.81 (95% CI = −19.12–11.51, P = 0.49) and Begg-Mazumdar Kendall's test on the standardized effect versus variance indicated tau was 0.11, P > 0.99 [Figure 14].

Conclusion

During recent years, the introduction of anti-TNF-α medicines has changed FCD medical treatment typically. Various studies have shown these remedies efficacy in FCD patient's remission induction and maintenance toward placebo. However, their most favorable case of dispensing is still a debate. We aimed to systematically review these medicines efficacy in FCD.

Our included studies are classified upon anti-TNF-α medicine type as follows: one study for infliximab versus placebo, three for adalimumab versus placebo, two for certolizumab pegol versus placebo, two for CDP571, and one for etanercept versus placebo. The total sample size of these included RCTs is 3804 patients, which consist of both with or without fistula patients. From this, 774 patients are enrolled to meta-analysis with different kinds of fistulas from baseline.

However, this meta-analysis goal was to include all available RCTs regarding FCD; we had to exclude some important trials due to their different treatment protocols, crossover treatment, and designs.[17,36-40] This reduction causes us to have limited studies for each medicine. For infliximab, one trial was available which reported its outcomes in terms of fistula improvement and fistula closure in short-term induction.[35] For adalimumab, three trials were identified reporting their outcomes in different

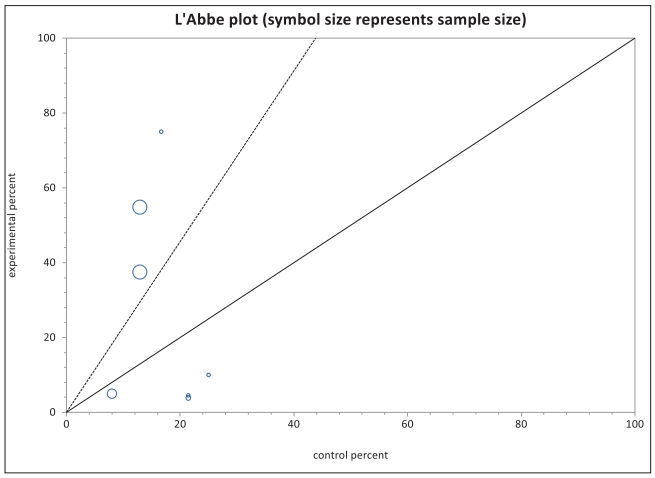

Figure 8: Heterogeneity indicators for the outcome of "fistula closure" in the studies considering short-term induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

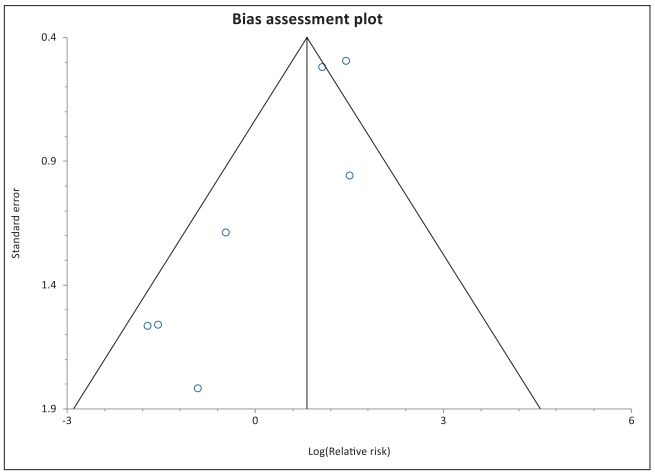

Figure 9: Publication bias indicators for the outcome of "fistula closure" in the studies considering short-term induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

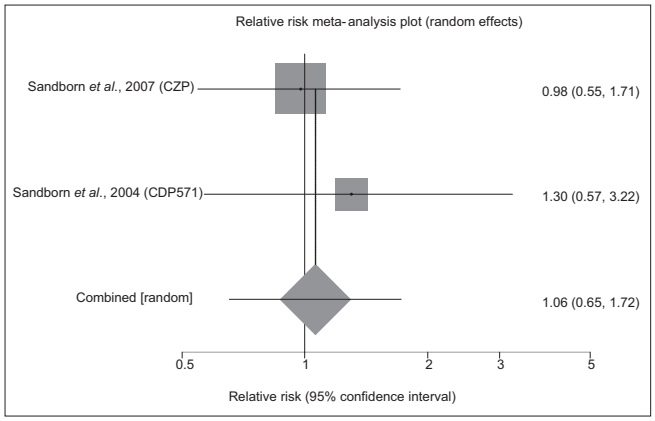

Figure 10: Individual and pooled relative risk for the outcome of "fistula closure" in the studies considering short- and long-term induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

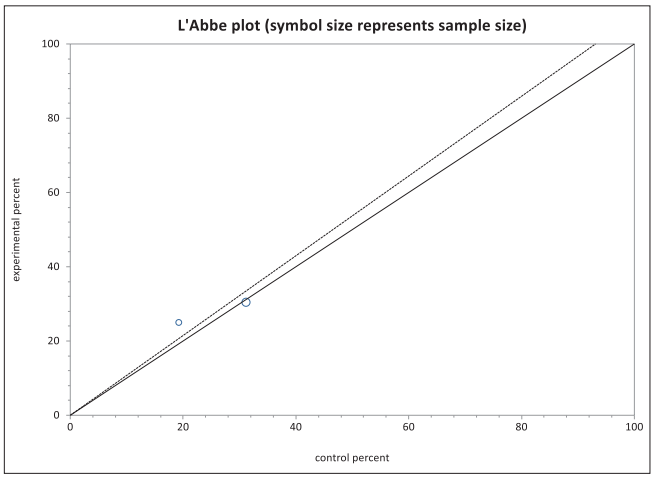

Figure 11: Heterogeneity indicators for the outcome of "fistula closure" in the studies considering short- and long-term induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

terms. Hanauer *et al*. and Sandborn *et al*. reported fistula improvement and fistula closure in short-term induction, but Colombel *et al*. reported fistula closure maintenance, vice versa those two trials.[18,33-34] For certolizumab pegol, two trials were enrolled. Schreiber *et al*. reported their outcomes in terms of fistula improvement and fistula closure maintenance.[28] On the other hand, Sandborn *et al*. reported short- and long-term induction for fistula closure.[21] Furthermore, two trials were included for CDP571. Both study's results were upon short- and long-term induction for fistula improvement and fistula closure.[29,30] Regarding etanercept, one trial included which results are in terms of short-term induction in fistula improvement.[32] According to our available data stratification, we obligate to run subgroup analysis based on trials' outcome of measure type. Obviously, it is more favorable to combine each medicine efficacy data with its own from different trials.

Our meta-analysis results demonstrate that adalimumab and certolizumab pegol are more effective than placebo regarding fistula closure in maintenance trials ($P < 0.0001$). In this subgroup analysis, CHARM and PRECiSE 2 studies are included.[28,33]

On the other hand, we found no significant decrease in fistula improvement in short-term induction and short- and long-term induction and maintenance trials.[18,32,34,35] At the same time, no remarkable difference found in fistula closure in short-term induction and short- and long-term induction trials.[29,30]

Our finding updates the previously published meta-analysis. A meta-analysis of Kawalec *et al*. has concluded that adalimumab, infliximab, and certolizumab pegol are all effective in both induction and maintenance

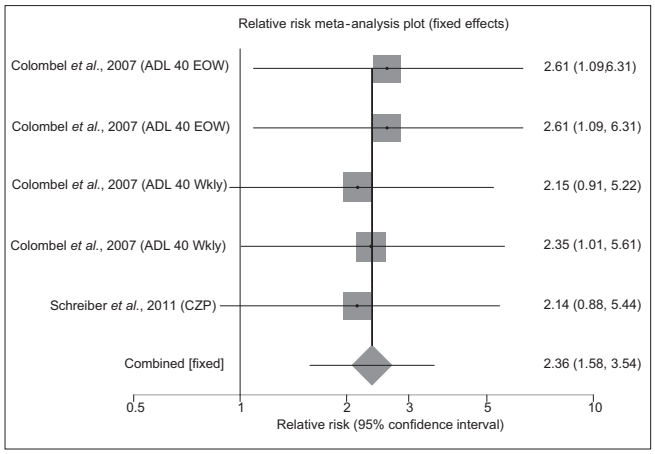

Figure 12: Individual and pooled relative risk for the outcome of "maintenance of fistula closure" in the studies considering induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

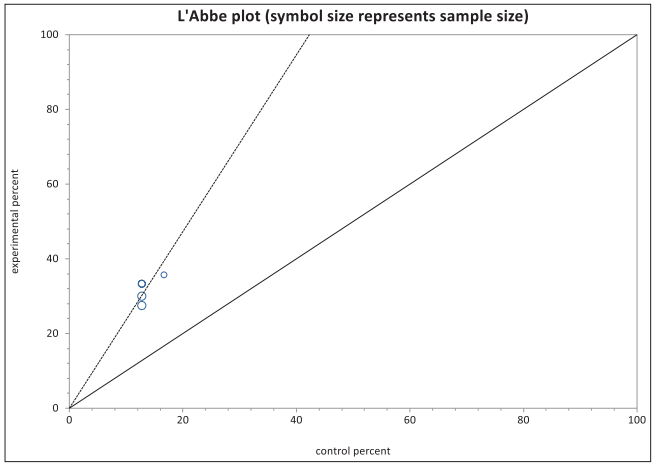

Figure 13: Heterogeneity indicators for the outcome of "maintenance of fistula closure" in the studies considering induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

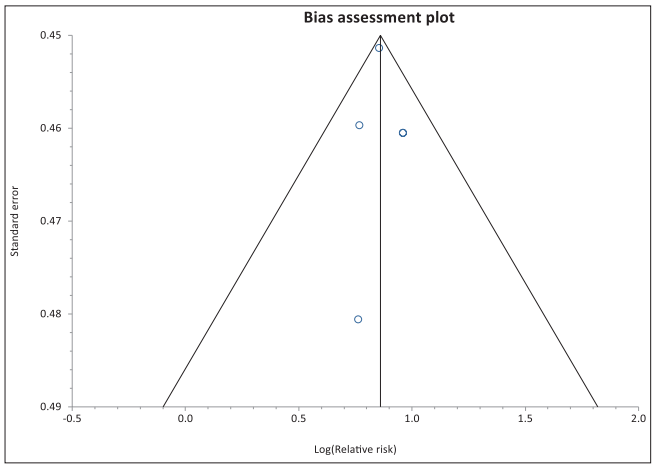

Figure 14: Publication bias indicators for the outcome of "maintenance of fistula closure" in the studies considering induction of anti-tumor necrosis factor-alpha medicines comparing to placebo therapy in fistulizing Crohn's disease patients

which is controversial with ours. This different result can be due to some methodological mistakes. First of all in this study, etanercept and CDP571 studies[29,30,32] have not been included as anti-TNF-α medicines to consider these medicines' effectiveness too. Second, Sandborn *et al.*'s study[38] has been included in this meta-analysis despite its different study design. As the patients in the infliximab maintenance group may experience a cross-over treatment to 10 mg/kg of infliximab at week 22 in case of no response. At last, in Hanauer *et al.*'s study[34] and Colombel *et al.*'s study,[33] different dose regimens have been administered to patients. Obviously, these different regimens should be categorized in analysis to reduce any possible biases. Hence, it seems that by combining some irrelevant data, this study result may have some biases.[31] Another study by Peyrin-Biroulet *et al.* had either same methodological mistakes.[41] Again, they did not classify various doses of adalimumab in Hanauer *et al.*'s study,[18] and short-term results of study have not been reported. Therefore, by this study results, it cannot be justified that anti-TNF-α medicines whether useful in induction of remission or not.

Another important point is that Present *et al.* reported other outcomes in different terms, such as perianal activity index, time to onset or response, and duration of response.[35] Although these data seem to be proper for reassessing FCD patients, they cannot be applied in quantitative analysis. Hence, it can be suggested that there should be common outcome measures for at least infliximab trials evaluating these patients to increase infliximab weight in FCD studies.

It should be considered that in FCD treatment, because of patients various needs, treatment goals may vary too. In patients who are in active phase, induction of remission is important; however, on the other hand for patients who are already in remission phase, maintaining them in this phase is optimal. Hence, it raises up the need for more long RCTs design to assess these medicines' long-term efficacy in cases whose favor is remission maintenance. To reduce such biases, it is essential to design longer head-to-head trials which especially included CD patients with fistula. Most recent researches are focusing on medical and surgical combination therapy, which somehow proved to be more effective than each of them alone in FCD treatment. Other studies claim that anti-TNF-α medicine may lead to malignancies in patients who had gone surgery. Hence, it is still opaque whether combination therapy is more beneficial or not.[31,41-44]

To the best of our knowledge, this is the most comprehensive systematic review with meta-analysis on the effect of anti-TNF-α medicines in FCD treatment

which includes all of these medicines. To avoid any possible bias, we do not pool different-designed RCTs efficacy with each other. The present meta-analysis limitation is that excluding languages other than English may cause language bias which is not negligible.

Due to limited published trials, results should be applied with caution. As a result, we should mention that only trials which make direct comparison possible among various anti-TNF-α medicines will provide attributable data. It should be notably considered that there are sufficient reviews available for FCD treatment, which have controversial results, due to lack of common designs in RCTs exploring anti-TNF-α medicines efficacy although with placebo. Hence, authors recommend that identical design, time for reassessment, dose regimen, and outcome measures should be applied to reach a valid comparison among these medicines. By this, upcoming therapeutically guidelines may provide evidence based recommendations to practitioners to improve the decision-making process and this will magnify the value of each anti-TNF-α medicine, leading to better outcomes.

Authors' Contribution

Zaboli P, Abdollahi M, Mozaffari S, and Nikfar S made contributions to conception and study design, data acquisition, data acquisition, data analysis, data interpretation, drafting the article, revising the article, critical revision, and final edit.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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