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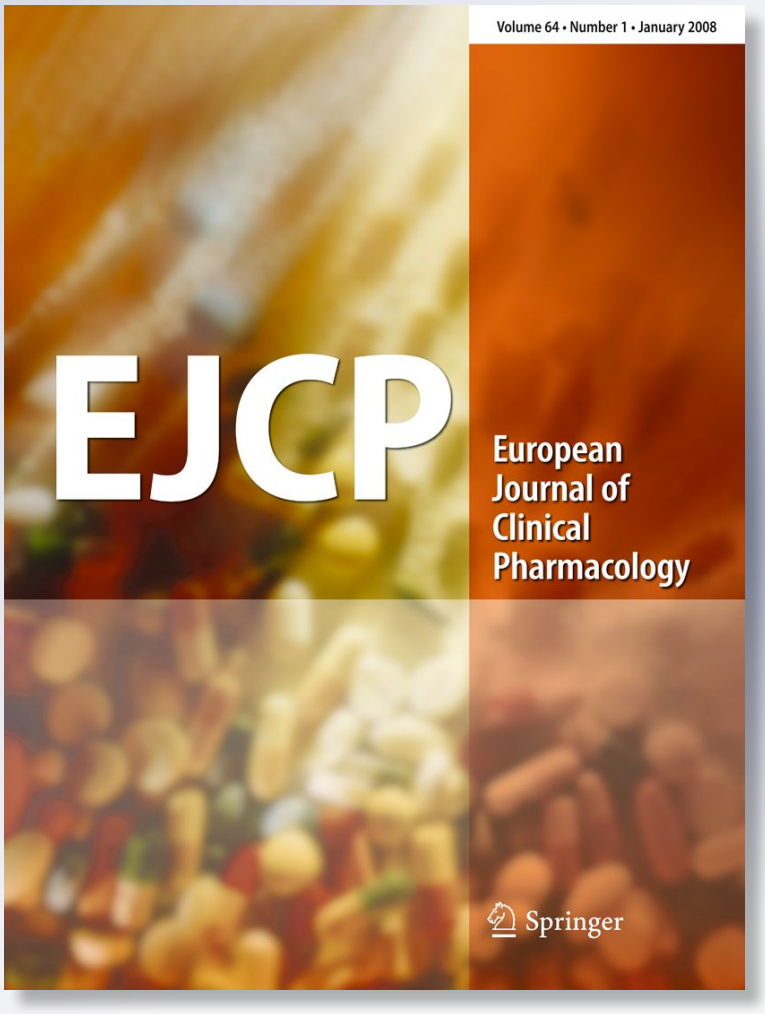

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REVIEW ARTICLE

A meta-analysis of the therapeutic effects of tumor necrosis factor-α blockers on ulcerative colitis

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Abstract
Purpose To evaluate the therapeutic effects of TNF-α blockers on ulcerative colitis (UC) and their safety.
Methods Randomized controlled trials (RCTs) of TNF-α blockers for treatment of UC were retrieved from databases. Heterogeneity test was performed on all data to select effects models. Finally, sensitivity analysis was carried out, and a funnel plot was drawn to evaluate publication bias.
Results A total of nine RCTs conformed to the inclusion criteria. Of 1,226 patients with UC, 806 were given a TNF-α blocker, and 420 were given placebo or other drugs as control. Infliximab was used in eight papers and adalimumab in one paper. Placebo was used in seven papers and hormones in two papers. Short-term response, short-term relief, long-term response, and long-term relief were better in the TNF-α blocker group than in the control group ($P<0.05$). TNF-α blockers decreased the colectomy rate ($P<0.05$). There were no significant differences in mucosal healing and quality of life between the two groups ($P>0.05$). The rates of adverse reactions were similar in the two groups ($P>0.05$), but the rate of severe adverse reactions was significantly lower in the TNF-α blocker group than in the control group ($P<0.05$). The funnel plot of each parameter was symmetrical with the lower part broader than the upper.
Conclusions TNF-α blockers have better therapeutic effects on moderate or severe UC, which shows little response to conventional therapy. TNF-α blockers can induce short-term response, maintain long-term clinical response and clinical relief, and decrease the colectomy rate and the severe adverse reaction rate, but they fail to improve quality of life and mucosal healing.

Keywords Ulcerative colitis · Tumor necrosis factor-α blocker · Meta-analysis · Therapeutic effects

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Introduction

In recent years, the incidence of UC has markedly increased in Eastern Europe, South America, and Asia [1]. UC pathogenesis remains unclear, and more and more patients with UC have poor or no response to conventional therapy. Although 5-aminosalicylic acid, glucocorticoids, and immunosuppressive agents can induce UC relief, there are still some problems such as no response to treatment, hormone dependency, severe adverse drug reactions, and higher colectomy rate in some patients [2, 3]. With the development of molecular biology and immunology, the UC pathogenesis has been further studied. It has been reported that there is high tumor necrosis factor (TNF-α) expression in blood, colonic tissue, and stool of patients with UC [4]. Some meta-analyses have indicated that TNF-α blockers can improve the clinical relief and clinical response and reduce colectomy in patients with UC, but the selected papers were older, there were few observations, and only infliximab was included in these meta-analyses [5–7]. Recently, TNF-α blockers such as adalimumab and etanercept have been developed, and there are different reports about their therapeutic effects, adverse

reactions, and safety. In order to objectively evaluate the therapeutic effects and safety of TNF-α blockers in the treatment of moderate and severe UC, randomized controlled trials (RCTs) published in recent years were meta-analyzed.

Methods

Inclusion and exclusion criteria

Inclusion criteria were (1) RCTs, (2) patients with moderate or severe UC, (3) study design that included a TNF-α blocker group and a placebo, glucocorticoid, or other drug control group, and (4) assessment of therapeutic effects including one or more parameters such as short-term response, short-term relief, long-term response, long-term relief, mucosal healing, colectomy rate, quality of life, adverse reactions, and severe adverse reactions. Exclusion criteria were (1) incomplete data, (2) repeated papers, (3) combined use of TNF-α blockers in control group, (4) no diagnostic criteria for UC, and (5) baseline data that were not similar to those in other papers.

Literature retrieval and collection data

Databases included Cochrane Library (Issue 3, 2010), PubMed (January 1992 to March 2010), OVID Evidence-Based Medicine Database (January 1994 to March 2010), EMBASE, full-text database of Chinese journals (January 1994 to March 2010), VIP database (January 1994 to March 2010), and Wanfang database (January 1994 to March 2010). Search terms included English search terms such as tumor necrosis factor, anti-TNF, TNF, infliximab, adalimumab, CDP571, certolizumab pegol, thalidomide, CNI-1493, etanercept, onercept, ulcerative colitis, randomized, random, randomly, and controlled trial and Chinese search terms such as 抗肿瘤坏死因子 (anti-tumor necrosis factor), 英夫利昔 (infliximab), 阿达木单抗 (adalimumab), 塞妥珠单抗 (certolizumab pegol), 依那西普 (etanercept), 溃疡性结肠炎 (ulcerative colitis), and 随机对照 (randomized controlled trial). Original papers or review articles about children or pregnant woman were excluded. This year's papers were also retrieved from *Chinese Journal of Digestion*, *Chinese Journal of Internal Medicine*, *Chinese Journal of Gastroenterology*, *Gastroenterology* and *Gut* by manual searches. We also retrieved papers from the U.S. Digestive Disease Week and European colitis conferences, and from the references of the selected papers. Two authors independently selected papers according to the same standards. The controversial papers were discussed by all authors.

Quality evaluation

The quality of the papers was evaluated according to quality evaluation criteria described in version 4.2.2 of the the *Cochrane Handbook for Systematic Reviews of Interventions*. The papers were assigned grades of A, B, and C based on randomized method, hidden method, double-blind method, missing follow-up, and withdrawal from observation. Grade A completely conforms to the four quality standards and has the lowest possibility of bias. Grade B partially conforms to one or more quality standards and shows moderate possibility of bias. Grade C does not conform to any of the four quality standards and has a high possibility of bias.

Data analysis

Data analysis was performed with Revman 5.0 software. Heterogeneity test was performed on dichotomous data

Table 1 Clinical characteristics of the nine randomized controlled trials (treatment group/control group)

Authors	Published year	Cases (*n*)	Male:female (*n*)	Mean age (years)	Mean duration of disease (years)	Control group	TNF-α blocker group	Grade of paper
Sands	2001	8/3	6:2/2:1	-/40.3	-/4	Placebo	Infliximab	B
Probert	2003	23/20	-	41/40	-	Placebo	Infliximab	A
Armuzzi	2004	10/10	-	36.2/36.3	-	Methylprednisolone	Infliximab	B
Ochsenkuhn	2004	6/7	3:3/3:4	31/42	5/5.9	Prednisolone	Infliximab	B
Rutgeerts	2005	484/244	294:190/143:101	41.3/40.3	-	Placebo	Infliximab	A
Jarnerot	2005	24/21	16:8/8:13	37.5/36.2	-	Placebo	Infliximab	A
Feagan	2007	484/244	294:190/143:101	41.3/40.3	6.9/6.5	Placebo	Infliximab	A
Sandborn	2009	484/244	294:190/143:101	41.3/40.3	6.9/6.4	Placebo	Infliximab	A
Reinisch	2010	260/130	-	-	-	Placebo	Adalimumab	A

- indicates no description in the paper

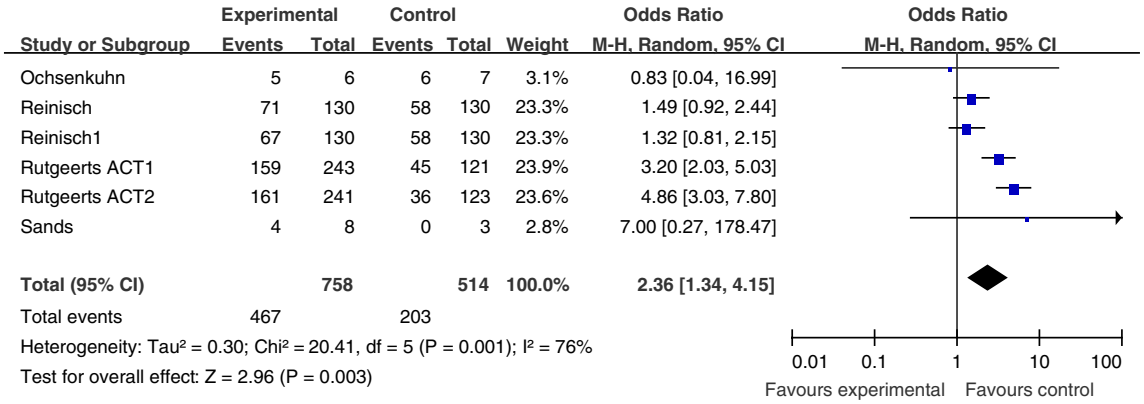

Fig. 1 The forest plot of short-term response to TNF-α blockers for the treatment of ulcerative colitis

including short-term response, short-term relief, long-term response, long-term relief, mucosal healing rate, colectomy rate, adverse reactions, and severe adverse reactions with odds ratio (OR) value and on continuous data (quality of life) with weighted mean differences (WMD). All OR and WMD were indicated with 95% confidence intervals (CI). If the α value of the homogeneity test was 0.1 and the *P* value was more than 0.1, OR was homogeneous, otherwise OR was not homogeneous. If OR was homogeneous, a fixed effects model was used for combinatorial effects. If OR was not homogeneous, a random effects model was used. If there was significant clinical heterogeneity between papers, combination was not carried out and only qualitative analysis was performed.

Publication bias

The funnel plots were drawn with OR values of short-term response, short-term relief, long-term response, long-term relief, mucosal healing rate, colectomy rate, adverse reactions, and severe adverse reactions and WMD of quality of life as the *x*-axis and with SE (log OR and MD) as the *y*-axis. Publication bias was evaluated by observing whether the funnel plot was symmetrical.

Results

Literature retrieval

First, 128 papers were retrieved. Through reading titles and abstracts, 119 papers which did not conform to entry criteria were excluded. Finally, nine RCT papers were selected [8–16]. Of the nine papers, six papers received grade A and three papers grade B. The subjects were the same population in three papers, but observed parameters were different; the number of these patients were only counted towards the total once. In the end, our study included 1,226 patients; 806 were given TNF-α blockers, and 420 placebo or other drugs as control. Patients were given infliximab in eight papers [5–12] and adalimumab in one paper [13]. Placebo was used in seven papers [5, 6, 9–13] and hormones in two papers [7, 8] (Table 1).

Analysis of each parameter

Clinical response and clinical relief

Short-term response was reported in four RCT papers. Heterogeneity test indicated χ^2=20.41 and *P*=0.001,

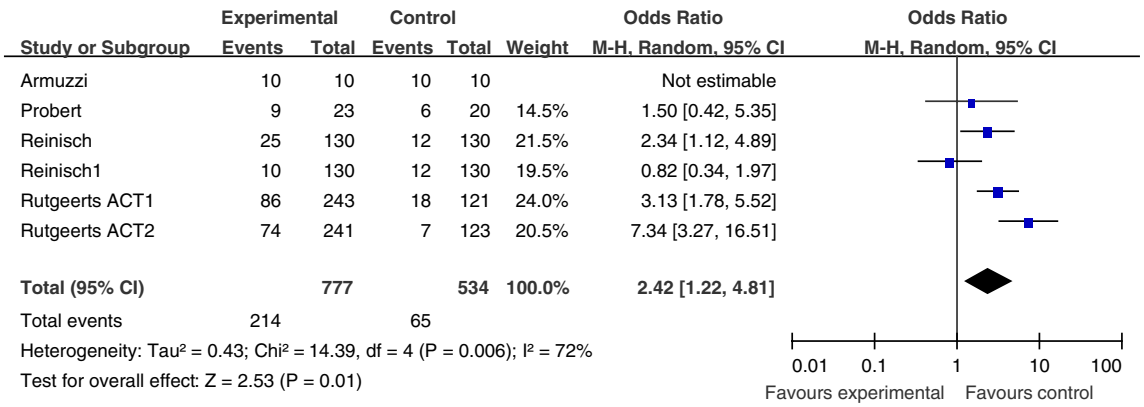

Fig. 2 The forest plot of short-term relief owing to TNF-α blockers for the treatment of ulcerative colitis

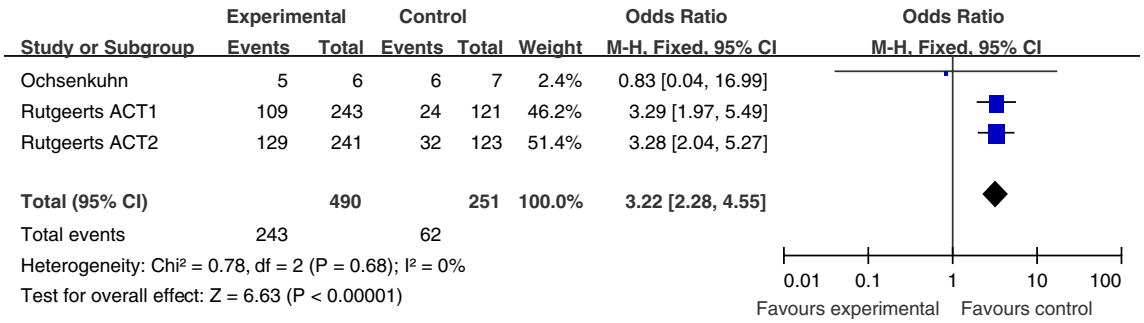

Fig. 3 The forest plot of long-term response to TNF-α blockers for the treatment of ulcerative colitis

demonstrating heterogeneity. Therefore, the random effects model was adopted, and the OR value was 2.36 (95% CI: 1.34–4.15, P=0.003) (Fig. 1). Short-term relief was reported in four RCT papers. Heterogeneity test indicated χ^2=14.39 and P=0.006, demonstrating heterogeneity. Therefore, a random effects model was adopted, and the OR value was 2.42 (95% CI: 1.22–4.81, P=0.01) (Fig. 2). Long-term response was reported in two RCT papers. Heterogeneity test indicated χ^2=0.78 and P=0.68, demonstrating homogeneity. Therefore, a fixed effects model was adopted, and the OR value was 3.22 (95% CI: 2.28–4.55, P<0.0001) (Fig. 3). Long-term relief was reported in four RCT papers. Heterogeneity test indicated χ^2=4.17 and P=0.38, demonstrating homogeneity. Therefore, a fixed effects model was adopted, and the OR value was 2.82 (95% CI: 1.91–4.16, P<0.0001) (Fig. 4). The TNF-α blocker group was better than the control group for short-term response, short-term relief, long-term response, and long-term relief.

Colectomy

Colectomy was reported in three RCT papers. Heterogeneity test indicated χ^2=1.67 and P=0.43, demonstrating homogeneity. Therefore, a fixed effects model was adopted, and the OR value was 0.31 (95% CI: 0.20–0.48, P<0.0001) (Fig. 5).

Mucosal healing

Mucosal healing was reported in five RCT papers. Heterogeneity test indicated χ^2=25.58 and P=0.0003, demonstrating heterogeneity. Therefore, a random effects model was adopted, and the OR value was 1.59 (95% CI: 0.91–2.78, P=0.10) (Fig. 6).

Quality of life

Quality of life was assessed in two RCT papers, and it was evaluated by using the Inflammatory Bowel Disease Questionnaire (IBDQ) in one paper (WMD: 24.00, 95% CI: −0.95 to 48.95, P=0.06). TNF-α blockers failed to improve the quality of life of patients with UC.

Side effects

Adverse reactions were reported in four papers. The adverse reactions included abdominal pain, nausea, arthralgia, and upper respiratory tract infection. The rates of adverse reactions were 77.4% in the TNF-α blocker group and 76.5% in the control group. Heterogeneity test indicated χ^2=19.93 and P=0.0005, demonstrating heterogeneity. Therefore, a random effects model was adopted, and the OR value was 1.07 (95% CI: 0.55–2.09, P=0.84)

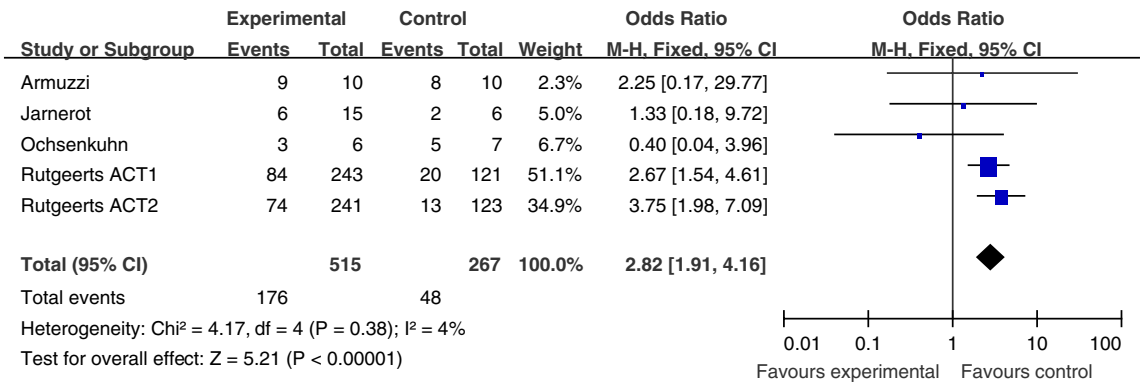

Fig. 4 The forest plot of long-term relief owing to TNF-α blockers for the treatment of ulcerative colitis

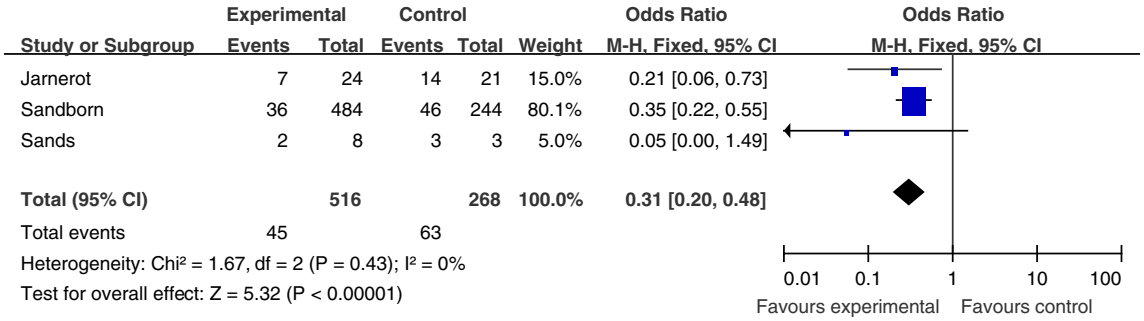

Fig. 5 The forest plot of colectomy rate following the use of TNF-α blockers for the treatment of ulcerative colitis

(Fig. 7). Severe adverse reactions were reported in five papers. The severe adverse reactions included pneumonia, septicemia, tuberculosis, drug-induced lupus, and tumor. The rates of severe adverse reactions were 13.3% in the TNF-α blocker group and 17.0% in the control group. Heterogeneity test indicated χ^2=5.35 and P=0.38, demonstrating homogeneity. Therefore, a fixed effects model was adopted, and the OR value was 0.65 (95% CI: 0.48–0.89, P=0.007) (Fig. 8). Malignant tumor was reported in two papers. Four patients had malignant tumor in the TNF-α blocker group and three in the control group. Heterogeneity test indicated χ^2=2.39 and P=0.50, demonstrating homogeneity. Therefore, a fixed effects model was adopted, and the OR value was 0.57 (95% CI: 0.17–1.90, P=0.36).

Publication bias

In the TNF-α blocker and control groups, all funnel plots of short-term response, short-term relief, long-term response, long-term relief, colectomy rate, mucosal healing, adverse reactions, and severe adverse reactions were symmetrical with the lower part broader than the upper, suggesting no publication bias. A publication bias failed to be observed in IBDQ, because IBDQ was used only in one paper.

Discussion

Recent studies have indicated that abnormal immune regulation is strongly associated with UC pathogenesis [17]. Cytokines, including pro-inflammatory cytokines and anti-inflammatory cytokines, play an important role in regulating intestinal immunity. TNF-α, an important pro-inflammatory cytokine, is mainly produced by activated monocytes and macrophages. It affects intestinal mucosa in both a paracrine and autocrine manner. Much experimental evidence shows that TNF-α is strongly associated with the pathogenesis and progression of inflammatory bowel disease (IBD) [18, 19]. TNF-α may allow neutrophils, lymphocytes, and mononuclear macrophages to adhere to vascular endothelial cells, and then these cells migrate and extravasate into local tissue to cause inflammatory reactions, leading to intestinal mucosal tissue damage and necrosis [20, 21]. Interrupting the excessive inflammatory reaction with TNF-α blockers has become an important targeted treatment for UC.

There are some differences in the therapeutic mechanism of various TNF-α blockers. Infliximab, a kind of human-mouse chimeric recombinant TNF-α IgGI monoclonal antibody, can combine with both soluble TNF-α and

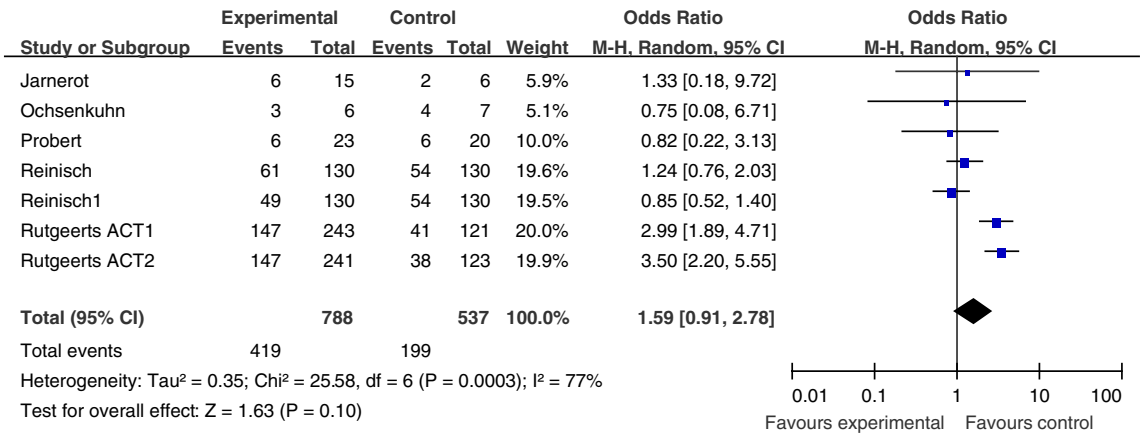

Fig. 6 The forest plot of mucosal healing rate following the use of TNF-α blockers for the treatment of ulcerative colitis

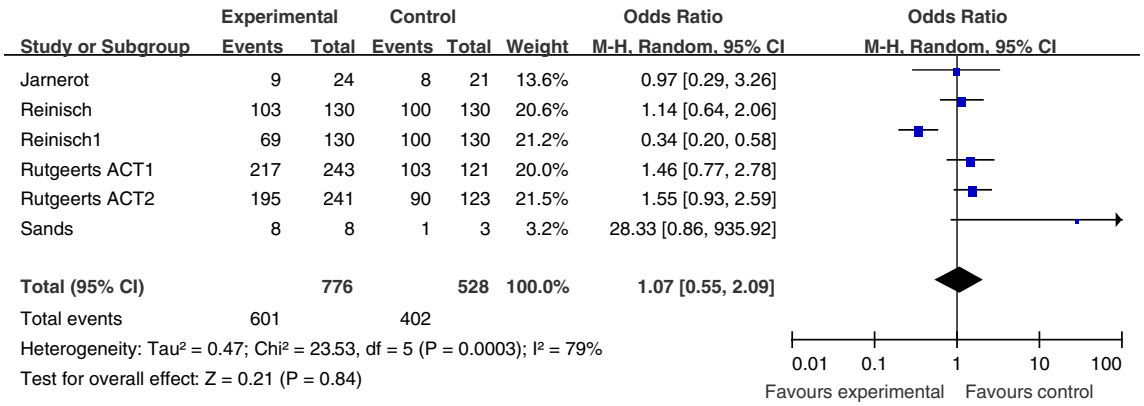

Fig. 7 The forest plot of adverse reactions with regard to the use of TNF-α blockers for the treatment of ulcerative colitis

membrane-bound TNF-α. Infliximab can induce inflammatory cell lysis through activating complement and antibody-mediated cytotoxicity to eliminate T-cells and can promote T-cell apoptosis through activating apoptosis-related protein Bax/Bcl-2 to inhibit inflammatory reaction. Adalimumab, a kind of humanized recombinant TNF-α IgGI monoclonal antibody, can eliminate TNF effects through blocking the combination of TNF-α with the soluble TNF-α receptors including p55 and p75 and can induce cell apoptosis. Adalimumab may be more safe and effective than infliximab because it has weaker immunogenicity than infliximab.

In 1998, the U.S. Food and Drug Administration approved infliximab for treatment of moderate or severe Crohn's disease (CD) that does not respond to conservative treatment or that is in combination with active fistulae formation. The therapeutic effects of TNF-α blocker on CD [22–24] provide a basis for the use of TNF-α blockers in the treatment of UC. A recent global multicenter random double-blind clinical control study in a large sample population provides new evidence. In this study, 728 patients with moderate or severe UC who had no response to hormone and immunosuppressive agents obtained better long-term therapeutic effects by intravenous injection of infliximab. However, there has been considerable debate on the therapeutic effects of infliximab. Regueiro et al. [25] reported that after 12 patients who had no response to hormone were given infliximab, 75% still required colectomy. Probert et al. [26] found that when 42 patients with UC were given infliximab for 2 or 6 weeks, there were no significant differences in the rate of clinical relief, IBDQ scores, and EuroQol compared with placebo group. TNF-α blockers all play their roles through elimination of TNF-α, so in this study, RCTs about all TNF-α blockers for treatment of moderate and severe UC in recent years were meta-analyzed.

RCTs about TNF-α blockers for the treatment of moderate and severe UC were not numerous. We retrieved nine RCT papers. Of the nine, six papers received grade A and three papers grade B. We found that short-term response (OR: 2.36, 95% CI: 1.34–4.15), short-term relief (OR: 2.42, 95% CI: 1.22–4.81), long-term response (OR: 3.22, 95% CI: 2.28–4.55) and long-term relief (OR: 2.82,

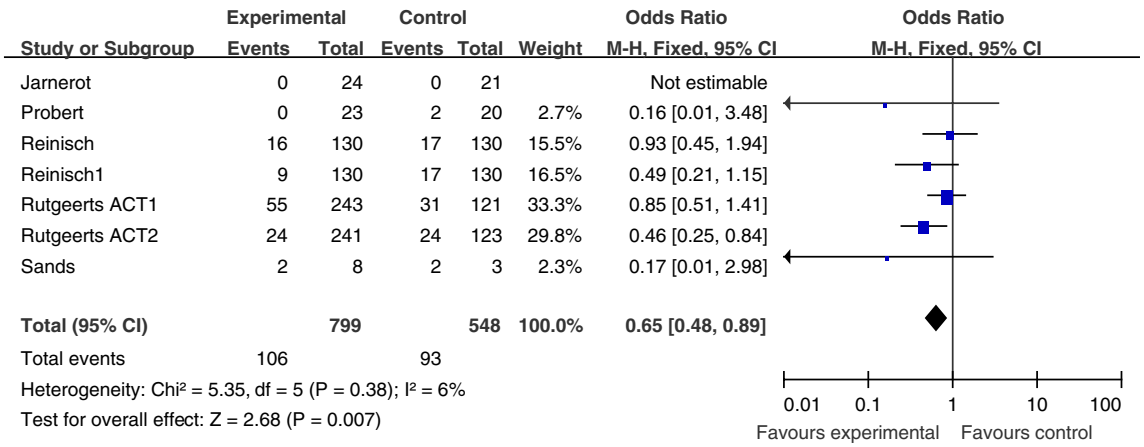

Fig. 8 The forest plot of severe adverse reactions with regard to the use of TNF-α blockers for the treatment of ulcerative colitis

95% CI: 1.91–4.16) were better in the TNF-α blocker group than in the control group. The clinical treatment goal for UC is to induce or maintain UC remission, and mucosal healing is considered to be the ideal goal of UC treatment. At present, it is believed that mucosal healing can reduce the incidence of cancer [27, 28]. Therefore, in this meta-analysis, mucosal healing was also considered, and TNF-α blockers failed to improve mucosal healing rate (OR: 1.59, 95% CI: 0.91–2.78), a result that is different from that of TNF-α blockers for CD treatment. This may be related to the heterogeneity of the selected studies and different pathogeneses between UC and CD. At present, although large dose adrenal corticosteroids or immunosuppressives are used for treatment of severe UC attack, the colectomy rate still reaches 38–47%, with 60% of patients with pancolitis requiring surgery within 3 months, and the operation rate is nearly 20% in cases of moderate or severe UC attack. Our meta-analysis indicated that infliximab decreased the colectomy rate (OR: 0.31, 95% CI: 0.20–0.48). In terms of side effects, the rates of adverse reactions were similar in the two groups, but the rate of severe adverse reactions was significantly lower in the TNF-α blocker group than in the control group. It has been reported that TNF-α blockers may induce lymphoma [29]. In our study, no lymphoma occurred, but four patients had malignant tumors in the TNF-α blocker group and three in the control group without statistical significance. Therefore, TNF-α blockers are safe and effective for UC treatment.

All papers selected for this study were high quality RCTs and had the same diagnostic criteria. In order to decrease publication bias, we collected papers widely through multiple approaches including computer searches, manual searches, and reference retrospection. Among repeated papers, short papers were excluded from this study to control repeated publication bias. In the nine papers, there was complete information including inclusion criteria, sex, age, pathogenetic condition, and medications, and the matched pairs were good between the treatment group and the control group. However, this meta-analysis still had some limitations. There was greater heterogeneity between papers because TNF-α blockers, TNF-α blocker doses, study design, drugs in the control group, and follow-up were different. There was also greater heterogeneity in short-term responses, short-term relief, mucosal healing, quality of life, and adverse reactions. These heterogeneities all affect results.

Conclusion

In summary, TNF-α blockers have better therapeutic effects on moderate or severe UC that shows little response to conventional therapy. They can induce short-term response and maintain long-term clinical response and relief, and decrease the colectomy rate and the severe adverse reaction rate, but they fail to improve quality of life and mucosal healing. A combination of biological and immunosuppressive agents is a promising therapy for UC [30]. It may be necessary to detect TNF-α gene polymorphism [31, 32]. Both TNF-α gene polymorphism detection and large sample randomized controlled trials will be conducive to further studies on UC.

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