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**Infliximab is superior to the other biological agents for the treatment of active ulcerative colitis: A meta-analysis**

Mei WQ *et al*. Meta-analysis of biological agents in UC

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**Author contributions:** Wang WG designed the study; Mei WQ and Hu HZ screened the citations; Mei WQ and Liu Y did the data analyses; Li ZC wrote the paper.

**Conflict-of-interest:** The authors declare that there is no conflict of interest.

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**Abstract**

**AIM:** To compare the efficacy and safety of biological agents for the treatment of active ulcerative colitis (UC).

**METHODS:** Literatures were searched in PubMed, MEDLINE, EMBASE and the Cochrane library to screen citations from January 1996 to August 2014 in this study. The mixed treatment comparison meta-analysis within a Bayesian framework was performed by WinBUGS14 software. The proportions of patients reaching clinical response, clinical remission and mucosal healingin induction and maintenance phases were analyzed as efficacy indicators. Serious adverse events in maintenance phase were analyzed as safety indicator.

**RESULTS:** The meta-analysis results showed that biological agents achieved more clinical response, clinical remission and mucosal healing than placebo. Indirect comparison indicated that in induction phase, infliximab was more effective than adalimumab in inducing clinical response (OR = 0.41, 95%CI: 0.29-0.57), clinical remission (OR = 0.33, 95%CI: 0.19-0.56) and mucosal healing (OR = 0.33, 95%CI: 0.19-0.56), and golimumab in inducing clinical response (OR = 0.66, 95%CI: 0.39-2.33) and mucosal healing (OR = 2.15, 95%CI: 1.18-4.22). No significant difference was found between placebo and biological agents regarding their safety.

**Conclusion:** All biological agents were superior to placebo for UC treatment in both induction and maintenance phases with a similar safety, and infliximab had a better clinical effect than the other biological agents.

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**Key words:** Biological agents; Efficacy; Meta-analysis; Safety; Ulcerative colitis

**Core tip:** Currently the option of biological agents in ulcerative colitis (UC) therapy was still controversial. We performed this meta-analysis to compare the efficacy and safety of biological agents for the treatment of active UC, and finally found all biological agents were superior to placebo for UC treatment in both induction and maintenance phases with a similar safety, and infliximab had a better clinical effect than the other biological agents.

Mei WQ, Hu HZ, Liu Y, Li ZC, Wang WG. Infliximab is superior to the other biological agents for the treatment of active ulcerative colitis: A meta-analysis. *World J Gastroenterol* 2015; In press

**INTRODUCTION**

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) of colon characterized by recurrent rectal bleeding, increased stool frequency and urgency, abdominal cramps and pain, and systemic symptoms (such as fever, anemia and weight loss)[1,2]. It is reported that the incidence of UC is 1.2-20.3 per 100000 person-years and its prevalence is 7.6-246.0 per 100000 persons[3]. Current options of treatment includeaminosalicylates, corticosteroids, immunosuppressive medications such as azathioprine, 6-mercaptopurine and biological agents including antitumor necrosis factor α (TNFα) antibodies and integrin antagonists.

5-aminosalicylic acid (5-ASA) is the first line medication used to induce and maintain remission in patients with mild-to-moderate active ulcerative colitis[4]. Patients who do not have adequate response to 5-ASA are recommended to receive corticosteroids treatments[5]. Moreover, traditional immunosuppressive azathioprine (AZA) and 6-mercaptopurine are suggested to treat patients with moderate active ulcerative colitis who are not responsive to oral corticosteroids[6]. However, conventional treatments often lead to a series of adverse events and have a limited effect in long time disease control.

Anti-TNFα agents including infliximab, adalimumab and golimumab have been approved by United States Food and Drug Administration for the treatment of moderate-to-severe ulcerative colitis. All the 3 anti-TNFα agents are demonstrated to be effective for the induction and maintenance of remission in moderate or severe UC. In addition, these agents can also induce mucosal healing and reduce glucocorticoid dependence[7]. Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody to α4β7 integrin[8]. A phase 3 study investigating the efficacy and safety of vedolizumab in patients with moderate to severe active UC indicated that vedolizumab was significantly more effective on clinical response and remission compared to placebo in both induction and maintenance phases[9].

Currently, the option of biological agents in UC therapy was still controversial. Traditional methods cannot be applied for the comparison for lack of head-to-head studies comparing different biological agents. Therefore we used a mixed treatment comparison (MTC) to compare the efficacy of biological agents, as MTC was available for indirect comparisons between drugs with different comparators[10,11].

**MATERIALS AND METHODS**

***Search strategy and inclusion criteria***

Four databases (PubMed, EMBASE, MEDLINE and the Cochrane library) were screened to obtain citations from January 1996 to August 2014 for inclusion in this study. The key words Ulcerative Colitis and (infliximabor adalimumab or golimumab orvedolizumab) were used to search relevant citations. We included those studies meeting the two criteria: (1) the study evaluated the efficacy of biological treatments by a random case-control design; and (2) trials had to be placebo controlled.

***Data extraction and*** ***quality assessment***

The following information was extracted from each study: the first author name; the year of publication; the number of patients; the number of patients achieving clinical response; the number of patients achieving clinical remission; the number of patients achieving mucosal healing; the outcome of serious adverse events; endpoints and study duration. The Jadad score was used to assess the quality of included studies. Different doses of the same biological agent were regarded as different separate interventions. Odds rates were used to measure the outcome of clinical response, clinical remission, mucosal healing and serious adverse events in induction and maintenance phases. Sanborn *et al*[12,13]study and Feagan *et al*[9,14] study presented induction phase results at week 6, and their studies were analyzed with trials presenting results at week 8. Sanborn *et al*[12,13] presented maintenance phase results at week 54, and this study was analyzed with trials presenting results at week 52.

***Statistical analysis***

To evaluate the relative effectiveness of each biologics, a mixed treatment comparison (MTC) meta-analysis within a Bayesian framework was performed. For all Bayesian analyses, Markov-chain-Monte-Carlo methods were used[15]. A random effect model was used to estimate the odds ratios (OR) as the measurement of relative treatment effect. We carried out 60000 iterations. The first 10000 iterations were discarded after the burn-in period and estimates were based on the subsequent 50000 ones. Heterogeneity between studies was assessed by Cochrane *Q* statistics and *I*2 test. A significant level of no less than 50% for *I*2 test was considered as evidence of heterogeneity. Fix effect model was used when there was no evidence of heterogeneity, otherwise random effect model was chosen. Data analysis was performed by WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom) and STATA12 (Stata Corp, College Station, Texas, United States). The statistical methods of this study were reviewed by Shanghai 2med Biotechnology Co., Ltd (Shanghai, China).

**RESULTS**

***Search results and characteristics***

A total of 209 citations were obtained via database searches; ten met the inclusion criteria for this study (Figure 1). A total of 4237 patients with moderate-to-severe active UC have been involved. Among the UC patients, 484 patients were treated with infliximab; 685 patients were treated with adalimumab; 970 patients were treated with golimumab; 746 patients were treated with vedolizumab; 1352 patients were treated with placebo. The information in these citations was summarized in Table 1.

***Heterogeneity analysis***

Before performing MTC meta-analysis, we analyzed effect of single biological agent on response, remission, mucosal healing and serious adverse events compared to placebo.No heterogeneity was found between studies (Table 2).

***Clinical response***

Clinical response was defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolutesubscore for rectal bleeding of 0 or 1. All biological agents were superior to placebo in both induction and maintenance phases (Figure 2). The results of MTC meta-analysis showed that in induction phase infliximab was more effective than adalimumab (OR = 0.41, 95%CI: 0.29-0.57) and golimumab (OR = 0.66, 95%CI: 0.44-0.97), while golimumab had a better effect than adalimumab (OR = 1.62, 95%CI: 1.13-2.33). In maintenance phase, vedolizumab was more effective than adalimumab (OR = 1.94, 95%CI: 1.11-3.44) and golimumab (OR = 1.85, 95%CI: 1.08-3.2). Forest plots were summarized in supplementary Figure 3.

***Clinical remission***

Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. All biological agents were better than placebo for clinical remission in induction and maintenance phases (Figure 4). In induction phase, adalimumab was less effective than infliximab (OR = 0.33, 95%CI: 0.19-0.56), golimumab (OR = 2.15, 95%CI: 1.18-4.22) and vedolizumab (OR = 2.49, 95%CI: 0.99-6.64). However, there was no significant difference between the biological agents in maintenance phase. Forest plots were summarized in supplementary Figure 5.

***Mucosal healing***

Mucosal healing was defined as absolute subscore for endoscopy of 0 or 1. Biological agents were better than placebo for mucosal healing in induction and maintenance phases (Figure 6). In induction phase, infliximab was more effective than adalimumab (OR = 0.41, 95%CI: 0.29-0.57) and golimumab (OR = 0.6, 95%CI: 0.41-0.87), while golimumab had a better effect than adalimumab (OR = 1.45, 95%CI: 1.02-2.09). However, no significant difference was found between the biological agents in maintenance phase. Forest plots were summarized in supplementary Figure 7.

***Safety***

This analysis used random trials data on serious adverse events from maintenance phase. The MTC meta-analysis results showed that biological agents had a similar safety with placebo (Figure 8). Forest plots were summarized in supplementary Figure 9.

**DISCUSSION**

The appearance of biological agents dramatically changed the treatment landscape for UC. Biological agents were used for the treatment of moderate to severe UC patients failing conventional treatment. Previous randomized controlled trials (RCTs) proved that biological agents were effective and safe for the treatment of UC in both induction and maintenance phases. Danese et al. compared the biological agents by performing a multiple-treatment meta-analysis. They illustrated that infliximab is more effective to induce clinical response and mucosal healing than adalimumab in induction phase[3]. However, there was still lack of head to head RCTs to compare the different treatment options for long time efficacy and safety.

This meta-analysis assessing biological agents for the treatment of moderate to severe active ulcerative colitis included 9 RCTs, all of which were placebo controlled trials. No heterogeneity was found when assessing the effect of single biological agent. Meta-analysis showed that all biological agents were effective for UC treatment in induction and maintenance phases. Indirect comparisons of induction studies indicated that infliximab had a favorable clinical outcome than golimumab, vedolizumaband adalimumab, while adalimumabwas less effective than the others. However, at maintenance phase, all biological agents had a similar effect without statistical difference. The occurrence of serious adverse events was not different between the biological agents and placebo.

However, it should be noted that there are some limitations in our study. Firstly, a potential weakness of this meta-analysis was caused by the fact that the included trials were likely different in study design. For example, Sanborn *et al*[12,13] study and Feagan *et al*[9,14] study reported effect and safety results at week 6 while the others at week 8. Patient characteristics such as previous treatments also varied slightly across studies. Secondly, the small sample size and lack of head-to-head trials may increase the uncertainty of the results. Thirdly, we could not assess the publication bias. Despite these limitations, we believed that our analysis could contribute to the evaluation of biological agents that might support clinical decision making.

In conclusion, the results of our meta-analysis suggested that all biological agents were superior to placebo for clinical effect in both induction and maintenance phases. It was also showed that infliximab had a better clinical effect than the other biological agents. By analyzing incidence of serious adverse events, biological agents had a similar safety with placebo. However, head-to-head comparisons, continuous data collection and benefit-risk assessment are needed to indentify our findings.

**COMMENTS**

***Background***

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) of colon characterized by recurrent rectal bleeding, increased stool frequency and urgency, abdominal cramps and pain, and systemic symptoms (such as fever, anemia and weight loss). Current options of treatment include aminosalicylates, corticosteroids, immunosuppressive medications and biological agents. However, conventional treatments often lead to a series of adverse events and have a limited effect in long time disease control.

***Research frontiers***

Biological agents include antitumor necrosis factor α (TNFα) antibodies and integrin antagonists. Anti-TNFα agents including infliximab, adalimumab and golimumabhave been approved by United States Food and Drug Administration for the treatment of moderate-to-severe UC. All the 3 anti-TNFα agents are demonstrated to be effective for the induction and maintenance of remission in moderate or severe UC. In addition, these agents can also induce mucosal healing and reduce glucocorticoid dependence. Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody to α4β7 integrin. A phase 3 study investigating the efficacy and safety of vedolizumab in patients with moderate to severe active UC indicated that vedolizumab was significantly more effective on clinical response and remission compared to placebo in both induction and maintenance phases.

***Innovations and breakthroughs***

Previous studies have shown that biological agents were effective in treatment of UC. However, the option of biological agents in UC therapy was still controversial. Traditional methods cannot be applied for the comparison for lack of head-to-head studies comparing different biological agents. Therefore we used a mixed treatment comparison (MTC) to compare the efficacy of biological agents, as MTC was available for indirect comparisons between drugs with different comparators.

***Applications***

The study results suggest that all biological agents were superior to placebo for UC treatment in both induction and maintenance phases with a similar safety, and infliximab had a better clinical effect than the other biological agents.

***Terminology***

UC is a chronic IBD of colon characterized by recurrent rectal bleeding, increased stool frequency and urgency, abdominal cramps and pain, and systemic symptoms.Anti-TNFα agents including infliximab, adalimumab and golimumab are monoclonal antibodies that bind to TNF-α with high affinity and specificity. Vedolizumab, a representative for integrin antagonists, is a humanized immunoglobulin G1 monoclonal antibody to α4β7 integrin.

***Peer review***

This manuscript is very interesting article.

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**P-Reviewer:** Kawalec P **S-Editor:** Qi Y **L-Editor: E-Editor:**

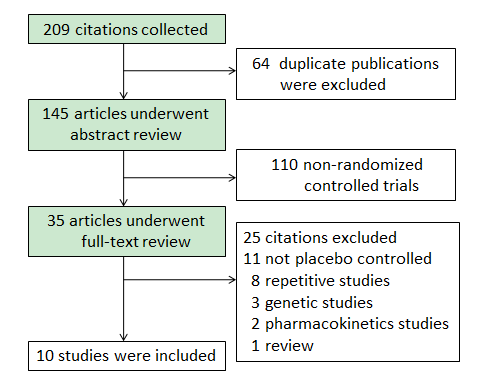
**Table 1 Baseline characteristics of the included studies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Age (yr) | Durg and dose | Case | Patients | treatment | Duration(week) |
| ACT 1  (Rutgeerts *et al*[16], Feagan *et al*[17], Sandborn *et al*[18] ) | 41.4 ± 13.7  42.4 ± 14.3  41.8 ± 14.9 | Placebo  Infliximab 5 mg/kg  Infliximab 10 mg/kg | 121  121  122 | Moderate to-severe active UC | Intravenous infusions at weeks 0, 2 and 6 and then every eight weeks or matching placebo. | 54 |
| ACT 2  (Rutgeerts *et al*[16],Feagan *et al*[17], Sandborn *et al*[18] ) | 39.3 ± 13.5  40.5 ± 13.1  40.3 ± 13.3 | Placebo  Infliximab 5 mg/kg  Infliximab 10 mg/kg | 123  121  120 | moderate-to-severe active UC | Intravenous infusions at weeks 0, 2 and 6 and then every eight weeks or matching placebo. | 30 |
| Suzuki *et al*[19] | 41.3 ± 13.6  44.4 ± 15.0  42.5 ± 14.6 | Placebo  Adalimumab 80/40mg  Adalimumab 160/80mg | 96  87  90 | moderate-to-severe active UC | Subcutaneous injections 160/80 mg at wk 0, 80/40 mg at week 2 and then 40 mg beginning at week 4 every other week or match placebo. | 52 |
| ULTRA 2  (Sandborn *et al*[20] ) | 41.3 ± 13.2  39.6 ± 12.5 | Placebo  Adalimumab | 246  248 | moderate-to-severe active UC | Subcutaneous injections 160 mg at week 0, 80 mg at week 2 and then 40 mg beginning at week 4 every other week or matching placebo. | 52 |
| Reinisch *et al*[21] | 37 ± 9  40 ± 9.5  36.5 ± 9.5 | Placebo  Adalimumab 80/40mg  Adalimumab 160/80mg | 130  130  130 | moderate-to-severe active UC | Subcutaneous injections 160/80 mg at week 0, 80/40 mg at week 2 and then 40 mg beginning at week 4 every other week or matching placebo. | 8 |
| PURSUIT-SC  (Sandborn *et al*[12]) | 39.0 ± 13.0  40.0 ± 13.5  40.7 ± 13.7 | Placebo  Golimumab 200/100mg  Golimumab 400/200mg | 331  331  331 | moderate-to-severe active UC | Subcutaneous injections 400/200 mg at week 0 and 200/100 at week 2 or matching placebo. | 6 |
| PURSUIT-M  (Sandborn *et al*[13]) | 40.2 ± 14.1  41.4 ± 13.8  39.1 ± 13.1 | Placebo  Golimumab 50 mg  Golimumab 100 mg | 156  154  154 | moderate-to-severe active UC | Subcutaneous injections 100/50 mg every 4 wk or matching placebo. | 54 |
| GEMINI 1  (Feagan *et al*[14], *et al*[9]) | 41.2 ± 12.5  40.1 ± 13.2 | Placebo  Vedolizumab 300mg | 149  746 | moderate-to-severe active UC | Intravenous infusions every 4 wk or every 8 wk or matching placebo. | 52 |

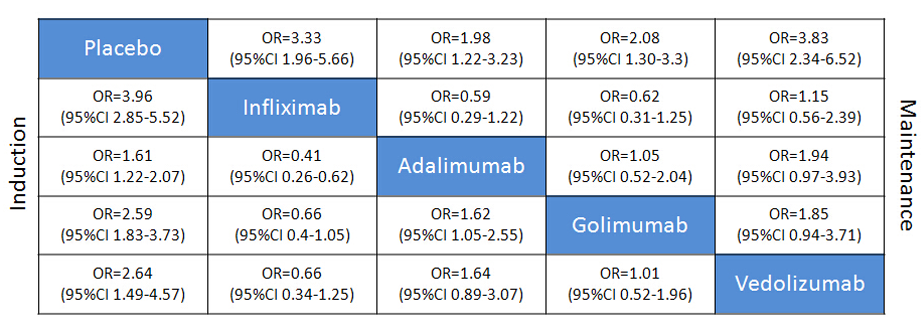
**Table 2 Heterogeneity analysis of the biological agents compared to placebo**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Response  induction maintenance | | Remission  induction maintenance | | Mucosal healing  induction maintenance | | Serious adverse  maintenance |
| Infliximab | 0 | 0 | 47.4% | 0 | 0 | 0 | 0 |
| Adalimumab | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Golimumab | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vedolizumab | - | 0 | - | 0 | - | 0 | - |

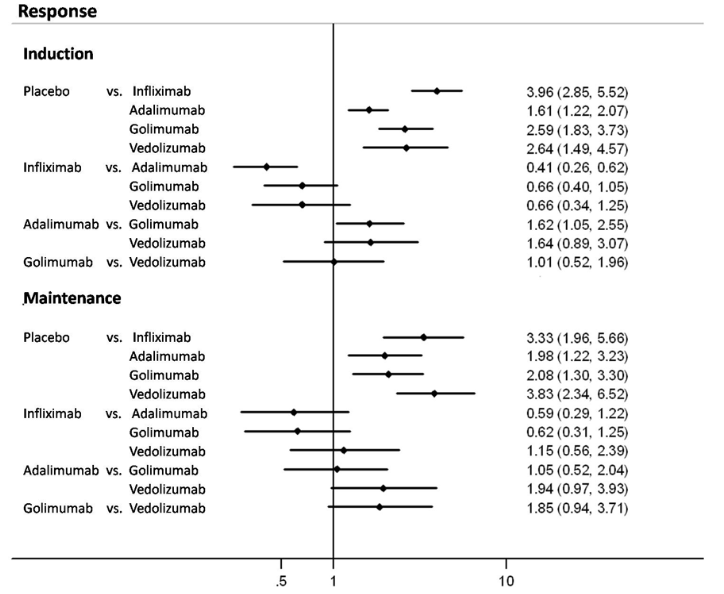
**Figure 1 Flow diagram of the studies identified.**



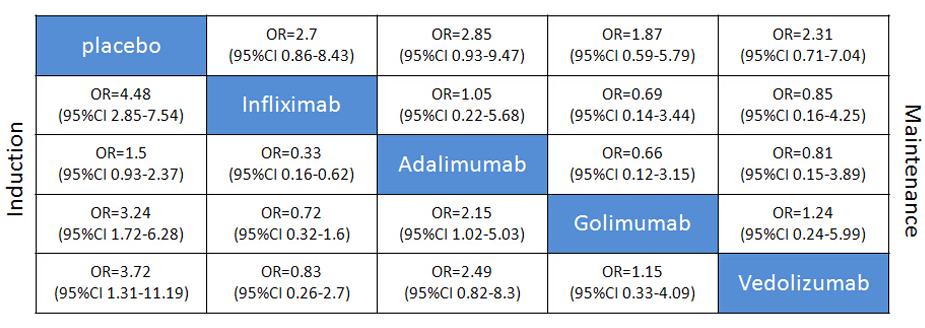
**Figure 2 Comparative clinical response of biological agents therapy for moderate to severe active ulcerative colitis.**



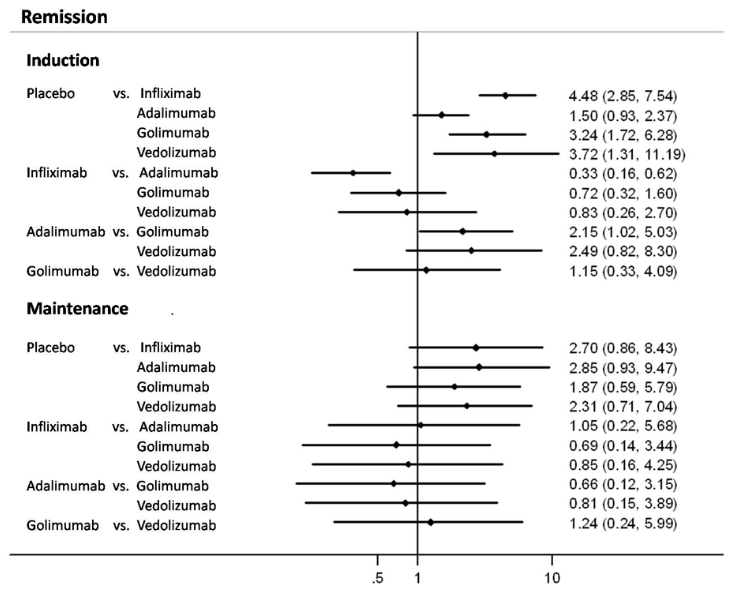
**Figure 3 Forest plots of biological agents therapy clinical reponse for moderate to severe active ulcerative colitis.**



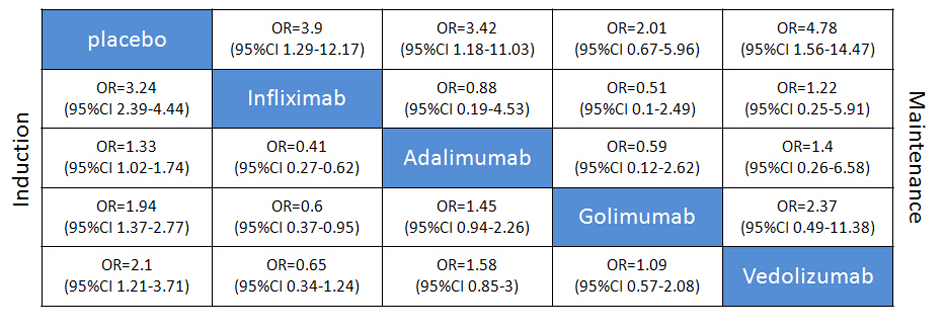
**Figure 4 Comparative clinical remission of biological agents therapy for moderate to severe active ulcerative colitis.**



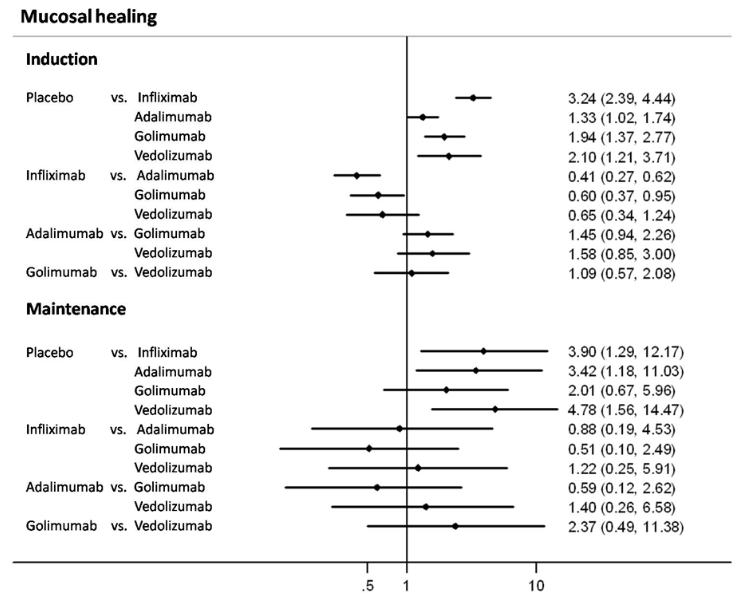
**Figure 5 Forest plots of biological agents therapy clinical remission for moderate to severe active ulcerative colitis.**



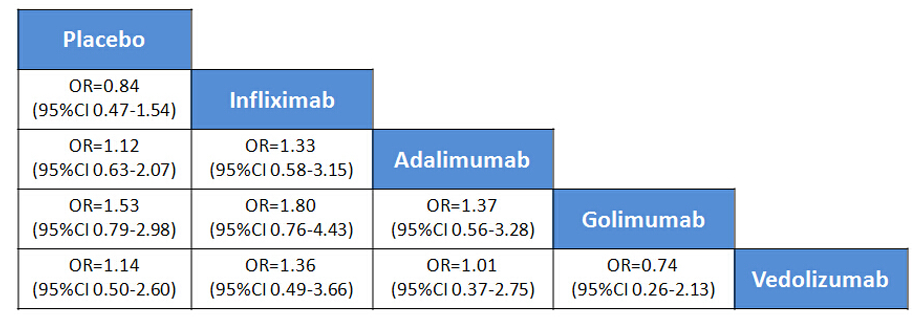
**Figure 6 Comparative****mucosal healing of biological agents therapy for moderate to severe active ulcerative colitis.**



**Figure 7 Forest plots of biological agents therapy mucosal healing for moderate to severe active ulcerative colitis.**



**Figure 8 Comparative** **serious adverse events of biological agents therapy for moderate to severe active ulcerative colitis.**



**Figure 9 Forest plots of biological agents therapy serious adverse events for moderate to severe active ulcerative colitis.**

