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

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Abstract

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

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

RESULTS: The meta-analysis results showed that biological agents achieved better 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 profile, and infliximab had a better clinical effect than the other biological agents.

Key words: Biological agents; Drug safety; Efficacy; Meta-analysis; Ulcerative colitis

Core tip: Currently the selection of biological agents in ulcerative colitis (UC) therapy is 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 that all biological agents were superior to placebo for UC treatment in both induction and maintenance phases with a similar safety

profile, and infliximab had a better clinical effect than the other biological agents.

INTRODUCTION

Ulcerative colitis (UC) is a form of chronic inflammatory bowel disease (IBD) 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 include aminosalicylates, corticosteroids, immunosuppressive medications such as azathioprine and 6-mercaptopurine, and biological agents including tumor necrosis factor-α (TNF-α) 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 UC[4]. Patients who do not have an adequate response to 5-ASA are recommended to receive corticosteroid treatments[5]. Moreover, traditional immunosuppressive azathioprine (AZA) and 6-mercaptopurine are suggested to treat patients with moderate active UC 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-term disease control.

Anti-TNF-α agents including infliximab, adalimumab and golimumab have been approved by United States Food and Drug Administration for the treatment of moderate-to-severe UC. All the 3 anti-TNF-α 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 $\alpha 4\beta 7$ 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 in terms of clinical response and remission compared to placebo in both induction and maintenance phases[9].

Currently, the selection of biological agents in UC therapy is 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 articles from January 1996 to August 2014 for inclusion in this study. The key words "ulcerative colitis" and ("infliximab" or "adalimumab" or "golimumab" or "vedolizumab") were used to search relevant articles. We included those studies meeting the following two criteria: (1) the study evaluated the efficacy of biological treatments using a random case-control design; and (2) trials had to be placebo controlled.
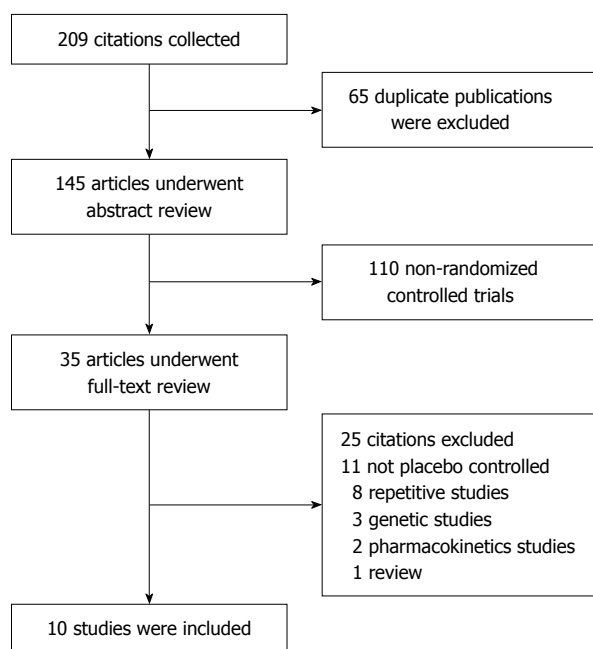
Data extraction and quality assessment
The following information was extracted from each study: the first author's name; the year of publication; the number of patients; the number of patients achieving clinical response; the number of patients achieving clinical remission; the number of patients achieving mucosal healing; the outcome of serious adverse events; endpoints; and study duration. The Jadad score was used to assess the quality of the included studies. Different doses of the same biological agent were regarded as separate interventions. Odds ratios (ORs) were used to measure the outcome of clinical response, clinical remission, mucosal healing and serious adverse events in induction and maintenance phases. Sandborn *et al*[12,13] and Feagan *et al*[14] presented induction phase results at week 6, and their studies were analyzed with trials presenting results at week 8[9]. Sandborn *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 biological agent, an 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 ORs 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. A fixed effects model was used when there was no evidence of heterogeneity, otherwise a random effects model was chosen. Data analysis was performed using WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom)

Table 1 Baseline characteristics of the included studies

Study	Age (yr)	Drug and dose	Case	Severity	Treatment	Duration (wk)
ACT 1	41.4 ± 13.7	Placebo	121	Moderate to-	Intravenous infusions at weeks 0, 2 and 6 and	54
(Rutgeerts *et al*[16],	42.4 ± 14.3	Infliximab 5 mg/kg	121	severe active UC	then every eight weeks or matching placebo	
Feagan *et al*[17],	41.8 ± 14.9	Infliximab 10 mg/kg	122			
Sandborn *et al*[18])						
ACT 2	39.3 ± 13.5	Placebo	123	Moderate-to-	Intravenous infusions at weeks 0, 2 and 6 and	30
(Rutgeerts *et al*[16],	40.5 ± 13.1	Infliximab 5 mg/kg	121	severe active UC	then every eight weeks or matching placebo	
Feagan *et al*[17],	40.3 ± 13.3	Infliximab 10 mg/kg	120			
Sandborn *et al*[18])						
Suzuki *et al*[19]	41.3 ± 13.6	Placebo	96	Moderate-to-	Subcutaneous injections 160/80 mg at week 0,	52
	44.4 ± 15.0	Adalimumab 80/40 mg	87	severe active UC	80/40 mg at week 2 and then 40 mg beginning	
	42.5 ± 14.6	Adalimumab 160/80 mg	90		at week 4 every other week or matching placebo	
ULTRA 2	41.3 ± 13.2	Placebo	246	Moderate-to-	Subcutaneous injections 160 mg at week 0, 80	52
(Sandborn *et al*[20])	39.6 ± 12.5	Adalimumab	248	severe active UC	mg at week 2 and then 40 mg beginning at week	8
					4 every other week or matching placebo	
Reinisch *et al*[21]	37.0 ± 9.0	Placebo	130	Moderate-to-	Subcutaneous injections 160/80 mg at week 0,	
	40.0 ± 9.5	Adalimumab 80/40 mg	130	severe active UC	80/40 mg at week 2 and then 40 mg beginning	
	36.5 ± 9.5	Adalimumab 160/80 mg	130		at week 4 every other week or matching placebo	6
PURSUIT-SC	39.0 ± 13.0	Placebo	331	Moderate-to-	Subcutaneous injections 400/200 mg at week 0	
(Sandborn *et al*[12])	40.0 ± 13.5	Golimumab 200/100 mg	331	severe active UC	and 200/100 at week 2 or matching placebo	
	40.7 ± 13.7	Golimumab 400/200 mg	331			54
PURSUIT-M	40.2 ± 14.1	Placebo	156	Moderate-to-	Subcutaneous injections 100/50 mg every 4 wk	
(Sandborn *et al*[13])	41.4 ± 13.8	Golimumab 50 mg	154	severe active UC	or matching placebo	
	39.1 ± 13.1	Golimumab 100 mg	154			52
GEMINI 1	41.2 ± 12.5	Placebo	149	Moderate-to-	Intravenous infusions every 4 wk or every 8 wk	
(Feagan *et al*[14], [9])	40.1 ± 13.2	Vedolizumab 300 mg	746	severe active UC	or matching placebo	

209 citations collected

65 duplicate publications were excluded

145 articles underwent abstract review

110 non-randomized controlled trials

35 articles underwent full-text review

25 citations excluded
11 not placebo controlled
 8 repetitive studies
 3 genetic studies
 2 pharmacokinetics studies
 1 review

10 studies were included

Figure 1 Flow diagram of the study selection.

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 articles 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 were involved. Among the UC patients, 484 were treated with infliximab; 685 with adalimumab; 970 with golimumab; 746 with vedolizumab; and 1352 with placebo. The information of these articles is summarized in Table 1.

Heterogeneity analysis
Before performing MTC meta-analysis, we analyzed the 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).
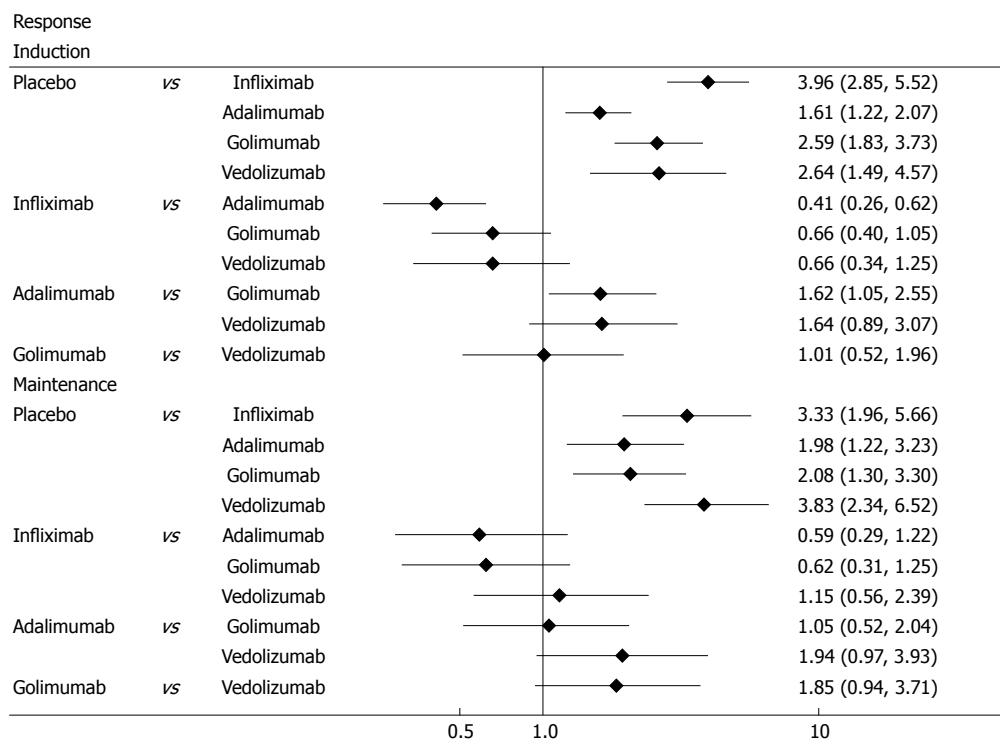
Clinical response
Clinical response was defined as a decrease from baseline in the total Mayo score of at least 3 points and by at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1. All biological agents 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 are summarized in Figure 3.

Table 2 Heterogeneity analysis of the biological agents compared to placebo (%)

	Response		Remission		Mucosal healing		Serious adverse events
	Induction	Maintenance	Induction	Maintenance	Induction	Maintenance	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	-

Placebo	OR = 3.33 (95%CI: 1.96-5.66)	OR = 1.98 (95%CI: 1.22-3.23)	OR = 2.08 (95%CI: 1.30-3.3)	OR = 3.83 (95%CI: 2.34-6.52)
OR = 3.96 (95%CI: 2.85-5.52)	**Infliximab**	OR = 0.59 (95%CI: 0.29-1.22)	OR = 0.62 (95%CI: 0.31-1.25)	OR = 1.15 (95%CI: 0.56-2.39)
OR = 1.61 (95%CI: 1.22-2.07)	OR = 0.41 (95%CI: 0.26-0.62)	**Adalimumab**	OR = 1.05 (95%CI: 0.52-2.04)	OR = 1.94 (95%CI: 0.97-3.93)
OR = 2.59 (95%CI: 1.83-3.73)	OR = 0.66 (95%CI: 0.4-1.05)	OR = 1.62 (95%CI: 1.05-2.55)	**Golimumab**	OR = 1.85 (95%CI: 0.94-3.71)
OR = 2.64 (95%CI: 1.49-4.57)	OR = 0.66 (95%CI: 0.34-1.25)	OR = 1.64 (95%CI: 0.89-3.07)	OR = 1.01 (95%CI: 0.52-1.96)	**Vedolizumab**

Induction (left axis) / *Maintenance* (right axis)

Figure 2 Comparison of biological agents for induction of clinical response in moderate to severe active ulcerative colitis.

Response
Induction

Placebo	*vs*	Infliximab	3.96 (2.85, 5.52)
		Adalimumab	1.61 (1.22, 2.07)
		Golimumab	2.59 (1.83, 3.73)
		Vedolizumab	2.64 (1.49, 4.57)
Infliximab	*vs*	Adalimumab	0.41 (0.26, 0.62)
		Golimumab	0.66 (0.40, 1.05)
		Vedolizumab	0.66 (0.34, 1.25)
Adalimumab	*vs*	Golimumab	1.62 (1.05, 2.55)
		Vedolizumab	1.64 (0.89, 3.07)
Golimumab	*vs*	Vedolizumab	1.01 (0.52, 1.96)

Maintenance

Placebo	*vs*	Infliximab	3.33 (1.96, 5.66)
		Adalimumab	1.98 (1.22, 3.23)
		Golimumab	2.08 (1.30, 3.30)
		Vedolizumab	3.83 (2.34, 6.52)
Infliximab	*vs*	Adalimumab	0.59 (0.29, 1.22)
		Golimumab	0.62 (0.31, 1.25)
		Vedolizumab	1.15 (0.56, 2.39)
Adalimumab	*vs*	Golimumab	1.05 (0.52, 2.04)
		Vedolizumab	1.94 (0.97, 3.93)
Golimumab	*vs*	Vedolizumab	1.85 (0.94, 3.71)

0.5   1.0   10

Figure 3 Forest plots of biological agents for induction of clinical response in moderate to severe active ulcerative colitis.

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 are summarized in Figure 5.

Mucosal healing

Mucosal healing was defined as an absolute subscore for endoscopy of 0 or 1. Biological agents were better than placebo for mucosal healing in induction and

Induction				Maintenance
Placebo	OR = 2.70 (95%CI: 0.86-8.43)	OR = 2.85 (95%CI: 0.93-9.47)	OR = 1.87 (95%CI: 0.59-5.79)	OR = 2.31 (95%CI: 0.71-7.04)
OR = 4.48 (95%CI: 2.85-7.54)	Infliximab	OR = 1.05 (95%CI: 0.22-5.68)	OR = 0.69 (95%CI: 0.14-3.44)	OR = 0.85 (95%CI: 0.16-4.25)
OR = 1.50 (95%CI: 0.93-2.37)	OR = 0.33 (95%CI: 0.16-0.62)	Adalimumab	OR = 0.66 (95%CI: 0.12-3.15)	OR = 0.81 (95%CI: 0.15-3.89)
OR = 3.24 (95%CI: 1.72-6.28)	OR = 0.72 (95%CI: 0.32-1.60)	OR = 2.15 (95%CI: 1.02-5.03)	Golimumab	OR = 1.24 (95%CI: 0.24-5.99)
OR = 3.72 (95%CI: 1.31-11.19)	OR = 0.83 (95%CI: 0.26-2.70)	OR = 2.49 (95%CI: 0.82-8.30)	OR = 1.15 (95%CI: 0.33-4.09)	Vedolizumab

Figure 4 Comparison of biological agents for induction of clinical remission in moderate to severe active ulcerative colitis.
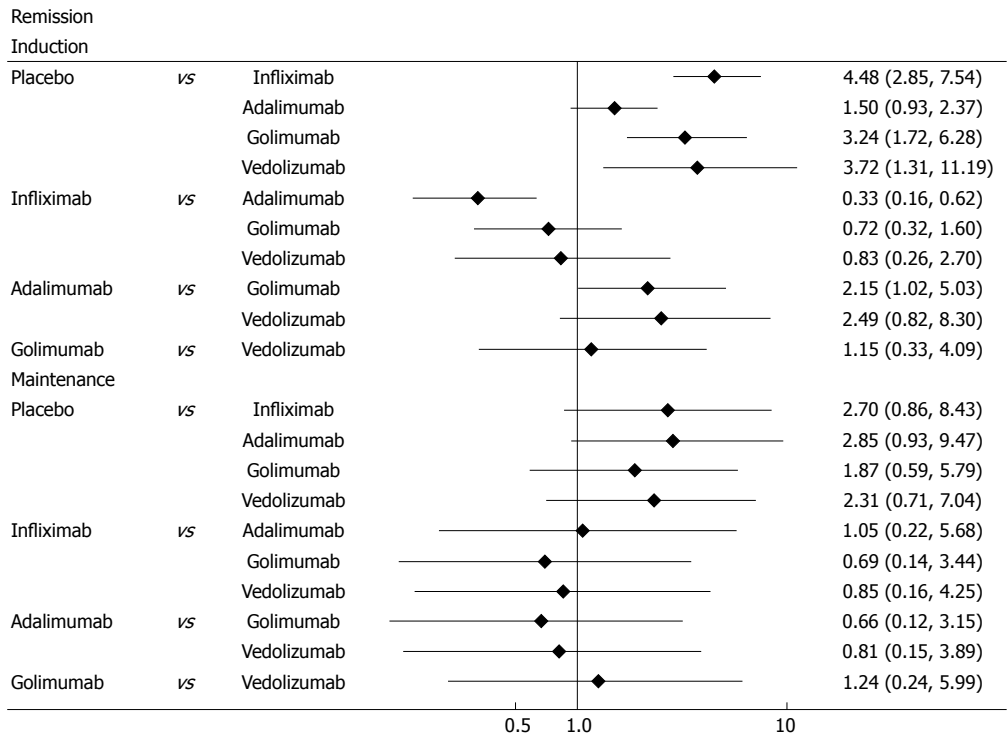

Figure 5 Forest plots of biological agents for induction of clinical remission in moderate to severe active ulcerative colitis.

Induction				Maintenance
Placebo	OR = 3.90 (95%CI: 1.29-12.17)	OR = 3.42 (95%CI: 1.18-11.03)	OR = 2.01 (95%CI: 0.67-5.96)	OR = 4.78 (95%CI: 1.56-14.47)
OR = 3.24 (95%CI: 2.39-4.44)	Infliximab	OR = 0.88 (95%CI: 0.19-4.53)	OR = 0.51 (95%CI: 0.10-2.49)	OR = 1.22 (95%CI: 0.25-5.91)
OR = 1.33 (95%CI: 1.02-1.74)	OR = 0.41 (95%CI: 0.27-0.62)	Adalimumab	OR = 0.59 (95%CI: 0.12-2.62)	OR = 1.40 (95%CI: 0.26-6.58)
OR = 1.94 (95%CI: 1.37-2.77)	OR = 0.60 (95%CI: 0.37-0.95)	OR = 1.45 (95%CI: 0.94-2.26)	Golimumab	OR = 2.37 (95%CI: 0.49-11.38)
OR = 2.10 (95%CI: 1.21-3.71)	OR = 0.65 (95%CI: 0.34-1.24)	OR = 1.58 (95%CI: 0.85-3.00)	OR = 1.09 (95%CI: 0.57-2.08)	Vedolizumab

Figure 6 Comparison of biological agents for induction of mucosal healing in moderate to severe active ulcerative colitis.

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 are summarized in Figure 7.

Safety
This analysis used random trial data on serious adverse events from maintenance phase. The MTC
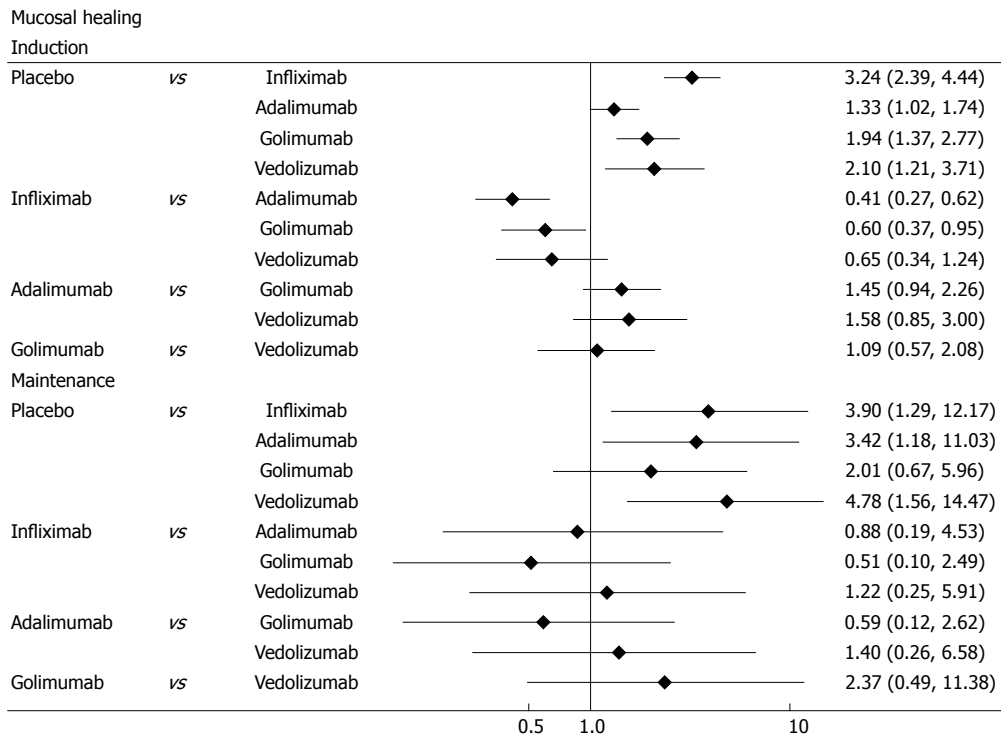
Mucosal healing

Induction

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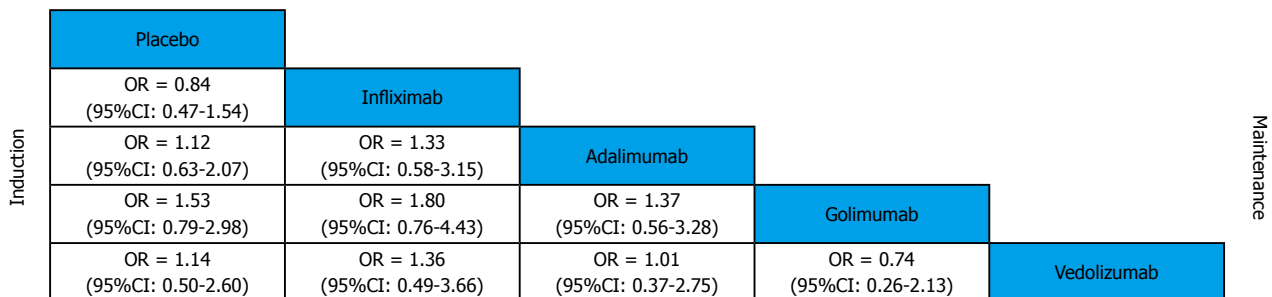

Figure 8 Comparison of serious adverse events of biological agents in moderate to severe active ulcerative colitis.

meta-analysis results showed that biological agents had a similar safety profile to placebo (Figure 8). Forest plots are summarized in Figure 9.

DISCUSSION

The appearance of biological agents dramatically changed the treatment landscape for UC. Biological agents have been 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*[3] 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-term efficacy and safety.

This meta-analysis assessing biological agents for the treatment of moderate to severe active UC included 9 RCTs, all of which were placebo controlled trials. No heterogeneity was found when assessing the effect of single biological agent. Meta-analysis results 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 more favorable clinical outcome than golimumab, vedolizumab and adalimumab, while adalimumab was less effective than the others. However, in maintenance phase, all biological agents had a similar effect without statistical difference. The incidence of serious adverse events was not different between the biological agents and placebo.

However, it should be noted that there were some limitations in our study. First, a potential weakness
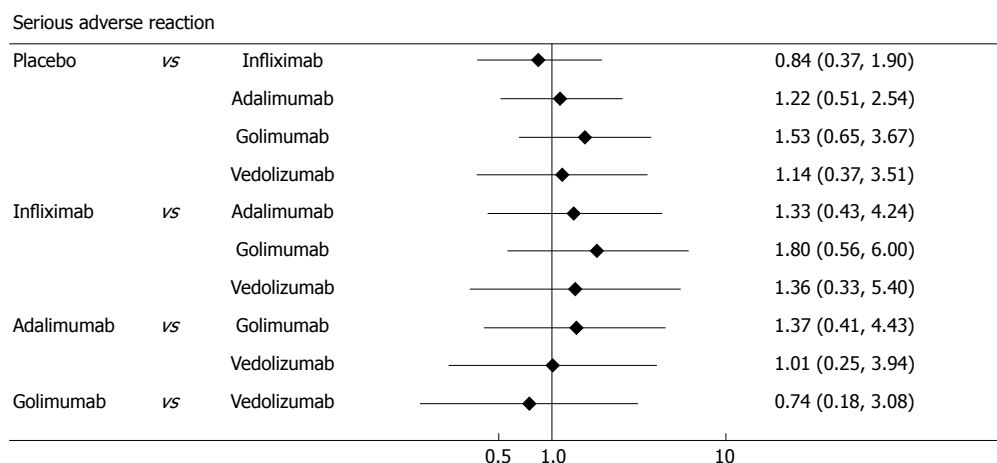
Serious adverse reaction

Placebo	*vs*	Infliximab		0.84 (0.37, 1.90)
		Adalimumab		1.22 (0.51, 2.54)
		Golimumab		1.53 (0.65, 3.67)
		Vedolizumab		1.14 (0.37, 3.51)
Infliximab	*vs*	Adalimumab		1.33 (0.43, 4.24)
		Golimumab		1.80 (0.56, 6.00)
		Vedolizumab		1.36 (0.33, 5.40)
Adalimumab	*vs*	Golimumab		1.37 (0.41, 4.43)
		Vedolizumab		1.01 (0.25, 3.94)
Golimumab	*vs*	Vedolizumab		0.74 (0.18, 3.08)

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

of this meta-analysis was caused by the fact that the included trials were likely different in study design. For example, the studies by Sandborn *et al*[12,13] and Feagan *et al*[14] reported efficacy and safety results at week 6 while the others at week 8[9]. Patient characteristics such as previous treatments also varied slightly across studies. Second, the small sample size and lack of head-to-head trials may increase the uncertainty of the results. Finally, we could not assess the publication bias. Despite these limitations, we believe 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 in terms of clinical effects in both induction and maintenance phases. It was also showed that infliximab had a better clinical effect than the other biological agents. By analyzing the incidence of serious adverse events, it was found that biological agents had a similar safety profile to placebo. However, head-to-head comparisons, continuous data collection and benefit-risk assessment are needed to confirm our findings.

COMMENTS

Background

Ulcerative colitis (UC) is a form of chronic inflammatory bowel disease (IBD) 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-term disease control.

Research frontiers

Biological agents include tumor necrosis factor-α (TNF-α) antibodies and integrin antagonists. Anti-TNF-α agents including infliximab, adalimumab and golimumab have been approved by United States Food and Drug Administration for the treatment of moderate-to-severe UC. All the 3 anti-TNF-α 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 in terms of 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 selection 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 the authors 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 profile, and infliximab had a better clinical effect than the other biological agents.

Terminology

UC is a form of chronic IBD characterized by recurrent rectal bleeding, increased stool frequency and urgency, abdominal cramps and pain, and systemic symptoms. Anti-TNF-α 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 a very interesting article.

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