Indirect comparison of anti-TNF-α agents for active ankylosing spondylitis: mixed treatment comparison of randomised controlled trials

T. Shu[1], G.H. Chen[2], L. Rong[1], F. Feng[1], B. Yang[1], R. Chen[1], J. Wang[3]

[1]Department of Orthopaedic Surgery, and [2]Department of Liver Transplantation Centre, The 3rd Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; [3]Department of Gynaecology, Sha Yang People's Hospital, Sha Yang, China.

Abstract

Objectives

We aimed to identify different anti-TNF-α agents for ankylosing spondylitis (AS) assessed in randomised controlled trials (RCTs) and to compare them within a single evidence synthesis framework.

Methods

A Bayesian network analysis method was used to generate direct and indirect comparisons while maintaining randomisation. The main outcomes were the proportion of ASAS20 patients at the follow-up of 12 weeks. The analysis was made based on an intention-to-treat basis.

Results

Data were combined from 14 (RCTs) that included 17833 patients randomised to 7 treatment strategies, including placebo. Except for 3mg/kg infliximab at 0, 2, 6 weeks, all other treatments were demonstrated to be more effective than placebo in the terms of clinical index ASAS20. Compared with 25 mg etanercept twice a week, 50 mg etanercept once a week, 50 mg golimumab, 100 mg golimumab every four weeks, 5mg/kg infliximab at 0, 2, 6 weeks and 40 mg adalimumab every other week for 12 weeks seemed to be more effective (odds ratios [OR] 1.38, 1.22, 1.26, 1.29, 1.38, and 1.25, respectively), while etanercept 50 mg twice a week have the similar efficacy (odds ratios [OR] 1.08), and infliximab 3 mg/kg at 0, 2, 6 weeks was less effective (odds ratios [OR] 0.69). However, all of these between-treatment comparisons detected no significant analysis. Finally, ranking analysis suggested that infliximab 5 mg/kg at 0, 2, 6 weeks may be the best efficacious therapy.

Conclusion

Our results suggested that infliximab 5 mg/kg at 0, 2, 6 weeks seems to be the best efficacious therapy, while infliximab 3 mg/kg at 0, 2, 6 weeks maybe could not be considered in the future studies. Future studies could pay more attention to the comparison of different anti-TNF agents, instead of comparison between anti-TNF agents and placebo.

Key words

Bayesian multiple treatment analysis, ankylosing spondylitis

Tao Shu, MD
Limin Rong, MD
Feng Feng, MD
Bu Yang, MD
Ruiqiang Chen, MD
GuiHua Chen, MD
Juan Wang, MD

Please address correspondence to:
Dr Limin Rong,
Department of Orthopaedic Surgery,
The 3rd Affiliated Hospital
of Sun Yat-sen University, Guangzhou,
510630 Guangdong, China.
E-mail: ronglm21@126.com

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disorder involving the sacroiliac joints (SIJs), spine and less frequently the peripheral joints. The disease usually starts at the third decade of life and males are affected more commonly compared to females with a ratio of 2 to 1 (1). AS may result in fusion of the spine, which leads to restriction in spinal mobility and overall function. Because of the early onset and chronicity of the disease, the lifetime costs and socioeconomic impairment in individual AS patients are high (2, 3).

Therapeutic options for AS have been limited during the past decades and the anti-rheumatic drugs, especially the NSAIDs, have been the cornerstone of medication. However, the effect of these drugs on disease progression is uncertain. The introduction of anti-TNF-α agents marked a turning point in the management of AS (4).

Tumour necrosis factor (TNF) appears to be key in the inflammatory response observed in AS and may play a part in the pathogenesis of ankylosing spondylitis. Increased expression of TNF-α has been reported in the serum, synovium, and sacroiliac joints in affected patients (5-7).

In 2002, the first two randomised controlled trials comparing anti-TNF-α agents with placebo were reported by Braun *et al*. and Gorman *et al*. (8, 9). Both infliximab and etanercept were found to be effective in the management of AS patients with rapid, significant, and sustained improvement. After that, there were more and more relevant trials conducted to assess the efficacy and safety of different anti-TNF-α agents in the management of AS (10-21).

However, most of these trials compared the anti-TNF-α agents with placebo, evidences of comparisons between different anti-TNF-α agents were lacking. Herein, a Bayesian network analysis of multiple treatments was conducted to comprehensively exploit the available evidence, especially for the indirect comparisons.

Methods

This systematic review was reported according to the guideline of PRISMA (22, 23).

Eligibility criteria

Types of participants: patients suffering from ankylosing spondylitis. Types of studies: randomised clinical trials reported in English and Chinese. No publication dates were imposed. Types of intervention: adalimumab, etanercept, infliximab, and golimumab. Types of outcome measures: the main outcome measure was the percentages of patients achieving the Assessments in Ankylosing Spondylitis 20% response (ASAS20) at weeks 12.

Information sources

Studies were identified by searching electronic databases, scanning reference lists of articles and consultation with experts in the field. This search was applied to PubMed (1980 to the present), and adapted for Embase (1980 to the present). Cochrane databases were also reviewed. The last search was run on November 2012.

Search strategy

A comprehensive literature search was performed to identify RCTs assessing efficacy of anti-TNF-α agents (adalimumab, etanercept, infliximab, and golimumab) for treating patients suffering from ankylosing spondylitis. Pubmed, CENTRAL library, and EMBASE databases were searched with the strategy of a combination of free-text and thesaurus terms relevant to anti-TNF-α agents and ankylosing spondylitis. Searching terms for anti-TNF-α agents and ankylosing spondylitis were as follows: anti-TNF-α agents, adalimumab, etanercept, infliximab, golimumab, anti-TNF(α), TNFR-Fc fusion protein, and 'Tumor Necrosis Factor-alpha/antagonists and inhibitors' [MeSH]; spondylarthropathies, ankylosing spondylitis, 'spondylarthropathies' [MeSH].

Study selection

Eligibility assessment was performed independently in an unblended standardised manner by 2 reviewers. Disagreements between reviewers were resolved by consensus.

Data collection process

We developed a data extraction sheet (based on the Cochrane Consumers and

Communication Review Group's data extraction template), pilot-tested it on ten randomly selected included studies, and refined it accordingly. One review author extracted the following data from included studies and the second author checked the extracted data. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, it was planned a third author would decide. We contacted eleven authors for further information. All responded and none provided valuable data.

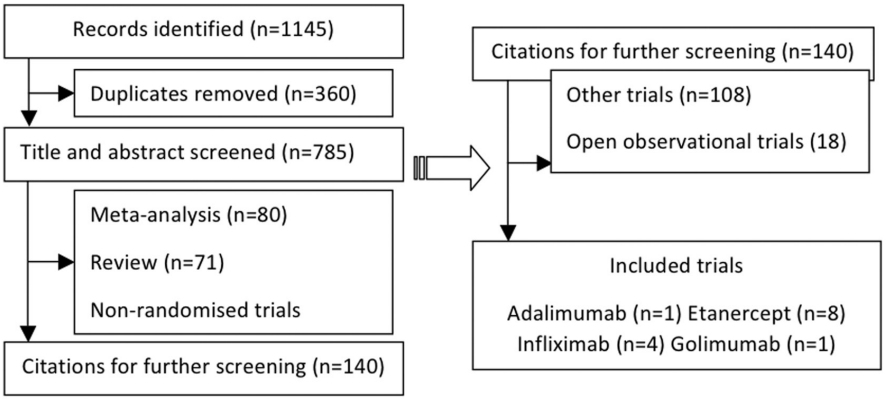

Fig. 1. Study selection flow.

Data items

Information was extracted from each included trial on characteristics of trial (including country, age, sample size, sex, mean weight, duration of surgery).

Risk of bias in individual studies

To ascertain the validity of eligible randomised trials, pairs of reviewers working independently and with adequate reliability determined the adequacy of randomisation and concealment of allocation, blinding of patients, health care providers, data collectors, and outcome assessors; and extent of loss to follow-up.

Synthesis of results

A Bayesian analysis using Markov chain Monte Carlo (MCMC) simulation was applied in our network analysis. Meanwhile, a generalised linear model (GLM) framework for the synthesis of data from randomised controlled trials (RCTs) were applied, which allows us to present a unified account of how models can be compared using the Deviance Information Criterion (DIC), and how goodness of fit can be assessed using the residual deviance (24). Use of the GLM framework WinBUGS code for model critique is provided. These methods are a generalisation of meta-analysis methods because they allow comparisons of agents not addressed within any of the individual primary trials. In addition to analysing the direct within-trial comparisons between 2 treatments (*e.g.* A *vs.* C), the mixed-treatment comparisons framework enabled us to incorporate the indirect comparisons constructed from 2 trials that have 1 treatment in common (*e.g.* A *vs.* B, B *vs.* C) (25, 26). Analysis was conducted in free software of WinBUGS 1.4.3 MCMC package (27), which takes full advantage of the modularity afforded by a GLM approach to synthesis. Random effects model for meta-analysis were applied to combine the binary outcome. Both placebo and 25 mg etanercept twice a week were chosen to be the reference treatment.

Results

Figure 1 presented the process of study selection. Finally, fourteen trials were included in our study (8 etanercept trials [9-12, 15, 19-21]; 4 infliximab trials [8, 13, 14, 18]; one golimumab trial [17]; and one adalimumab trial [16]). Of those etanercept trials, four studies compared 25 mg twice a week etanercept with placebo (9-12), and two studies compared 50 mg etanercept once a week with placebo (19, 20), while in the remaining two trials, different dosage and regimes of etanercept were compared (25 mg twice a week compared with 50 mg once a week in van der Heijde's study [15], and 50 mg once a week compared with 50 mg twice a week in the study of Navarro-Sarabia *et al.* study [21]). Of those infliximab trials, three studies compared 5 mg/kg at 0, 2, 6 weeks infliximab with placebo (8, 13, 14), and one trial compared low dosage of 3 mg/kg infliximab at 0, 2, 6 weeks with placebo (10). In the golimumab trial, there were three arms compared (50 mg golimumab, 100 mg golimumab, placebo). Etanercept, golimumab and adalimumab were administrated subcutaneously, while infliximab was administrated by infusion. Other characteristics were described in Table I. Our study mainly focused on the outcome of ASAS20, which was reported in all included trials, and considered to be the primary endpoint in most trials.

All of included trials was considered to be of high methodological quality, except one (20). All trials were randomised adequately, and most trials were double-blinding designed. Our analysis was based on intention-to-treat principle.

Results of multiple treatment meta-analysis

Twenty-five mg etanercept twice a week were chosen as reference treatment. The detail of direct and indirect comparison was described in the Table II. First of all, compared with placebo, all treatments were more effective with regard to the outcome of ASAS20, except for 3 mg/kg infliximab at 0, 2, 6 weeks. Furthermore, comparisons among those treatments detect no significant difference.

According to the ranking analysis (Fig. 2), 5 mg/kg infliximab at 0, 2, 6 weeks was considered to be the most effective therapy, 50 mg etanercept once a week was demonstrated to be second most effective therapy, while 50 mg golimumab once a week, 100 mg golimumab once a week and 40 mg adalimumab every other week for 12 weeks had a similar efficacy, which were better than 25 mg or 50 mg etanercept twice a week.

Additionally, placebo was also chosen to be the reference treatment, and analysis generated almost the same result (Table II). The detailed ranking analysis results are presented in Figure 2.

Table I. Main characteristics of included trials.

Reference	Year	Location	Sample	Age (year)	Male (%)	Patients	Follow-up
van der Heijde	2006	US and Europe	155/150/51	42/40/40	70/76/78	active ankylosing spondylitis	12
Navarro-Sarabia	2011	Spanish	54/54	42/40	80/80	active ankylosing spondylitis	12
Huang	2011	China	300/100	29/28	83/84	active ankylosing spondylitis	12
Dougados	2011	Europe	43/39	46/48	95/91	active ankylosing spondylitis	12
Calin	2004	Europe	45/39	45/41	80/77	active ankylosing spondylitis	12
Davis	2003	US and Europe	138/139	42/41	76/76	active ankylosing spondylitis	12
Brandt	2003	Germany	14/16	40/32	71/75	active ankylosing spondylitis	12
Gorman	2002	US	20/20	38/39	65/90	active ankylosing spondylitis	12
Braun	2002	Germany	34/35	40/39	68/63	active ankylosing spondylitis	12
Marzo-Ortega	2006	UK	28/14	41/39	82/79	active ankylosing spondylitis	10
van der Heijde	2005	US,Canada, Europe	78/201	40/41	78/87	active ankylosing spondylitis	12
Inman	2010	Canada	39/37	42/39	82/78	active ankylosing spondylitis	12
van der Heijde	2006	US and Europe	208/107	43/41	76/74	active ankylosing spondylitis	12
Inman	2008	US, Canada, Europe, Asia	138/140/78	38/38/41	74/70/71	active ankylosing spondylitis	14

Regimen	
van der Heijde	etanercept 50 mg once a week (qw), or etanercept 25 mg twice a week (biw) for 12 weeks/placebo
Navarro-Sarabia	etanercept 50 mg twice a week (biw), or etanercept 50 mg once a week (qw) for 12 weeks
Huang	etanercept 50 mg once a week for 6 weeks/placebo
Dougados	etanercept 50 mg once a week for 12 weeks/placebo
Calin	etanercept 25 mg twice a week (biw) for 12 weeks/placebo
Davis	etanercept 25 mg twice a week (biw) for 12 weeks/placebo
Brandt	etanercept 25 mg twice a week (biw) for 6 weeks/placebo
Gorman	etanercept 25 mg twice a week (biw) for 12 weeks/placebo
Braun	intravenous infliximab (5 mg/kg) at weeks 0, 2, and 6/placebo
Marzo-Ortega	intravenous infliximab (5 mg/kg) at weeks 0, 2, and 6/placebo, combined with MTX
van der Heijde	intravenous infliximab (5 mg/kg) at weeks 0, 2, and 6/placebo
Inman	intravenous infliximab (3 mg/kg) at weeks 0, 2, and 6/placebo
van der Heijde	adalimumab, 40 mg every other week for 12 weeks/placebo
Inman	golimumab (50 mg or 100 mg) every 4 weeks for 14 weeks/placebo

Discussion

NSAIDs and physical therapy are still recommended to be the first-line therapy for ankylosing spondylitis (AS) (28). When NSAIDs fail to control the progression of ankylosing spondylitis, anti-TNF agents, including infliximab, etanercept, golimumab, and adalimumab, were suggested to be effective in the management of active ankylosing spondylitis in dozens of randomised trials. However, there were just trials designed to compare anti-TNF agents to placebo, and almost no comparisons among these active treatments were conducted to assess the relative efficacy.

Fortunately, over the years methodological and software advances in meta-analytic techniques, more powerful mixed treatment analysis, also known as network meta-analysis, made the indirect comparison from available evidences being possible. In our present study, this new method was applied to generate both direct and indirect comparisons, trying to explore the relative efficacy between those anti-TNF agents.

Network meta-analysis makes similar assumptions to standard meta-analysis of direct within-trial comparisons, but requires that these assumptions hold over the entire set of trials in the network, including the assumption that relative treatment effects comparing two interventions in different trials are from the same common distribution. The smaller the heterogeneity between trials, the more likely relative treatment effects originate from the same distribution. Additional assumptions are that the model fits the data and that the network of trials is consistent.

The clinical response to anti-TNF agents was evaluated chiefly on the basis of response criteria recommended by the ASAS Working Group, which covered four domains to assess disease activity – that is, spinal inflammation, back pain, patient global assessment. And our study mainly focused on the outcome of percentage of ASAS 20 responders after 12 weeks of treatment, which were patients who reported improvements of at least 20% and absolute improvement of at least 10 units in at least three of the four symptom domains, with no worsening in the remaining domain. Other relevant outcomes, such as ASAS 50 or 70 responders, BASDAI index, were not referred to.

Both placebo and 25 mg etanercept twice a week were chosen to be the reference treatment, because they were the treatments most compared against in most trials, and were located in the central of network. Meanwhile, we could assess the effect of different choice of the reference treatment on the estimates of parameters of interest. Ranking results were almost same with each other, demonstrating that 5 mg/kg infliximab at 0, 2, 6 weeks was the most effective therapy, while 3 mg/kg infliximab at 0, 2, 6 weeks perhaps should not be taken into our consideration for choice because this therapy was not superior to placebo. In addition, the 50 mg etanercept once a week was demonstrated to be second most effective therapy, while 50 mg golimumab once a week, 100 mg golimumab once a week and 40 mg adalimumab had a similar efficacy, which were better than 25 mg or 50 mg etanercept twice a week. However, there were no significant differences detected in the between-treatment comparisons, which meant that although 5 mg/kg in-

Table II. The direct and indirect comparisions of all treatments, using etanercept 20 mg twice a week and placebo as reference treatments, respectively (ORs were significant differences in yellow. More than 1 favours the treatments).

	25 mg twice a week etanercept		Placebo	
Comparisons	OR	(95%CI)		OR (95%CI)
25 mg twice a week etanercept			*placebo*	
Placebo	0.21	(0.13, 0.31)	25 mg twice a week etanercept	5.05 (3.28, 7.91)
50 mg etanercept once a week	1.22	(0.63, 1.99)	50 mg etanercept once a week	5.98 (3.62, 9.29)
50 mg etanercept twice a week	1.06	(0.28, 2.70)	50 mg etanercept twice a week	5.31 (1.54, 13.04)
50 mg golimumab	1.25	(0.40, 2.91)	50 mg golimumab	5.94 (2.29, 12.66)
100 mg golimumab	1.29	(0.41, 3.07)	100 mg golimumab	6.09 (2.32, 12.95)
5 mg/kg infliximab	1.38	(0.58, 2.73)	5 mg/kg infliximab	6.53 (3.35, 11.61)
3 mg/kg infliximab	0.69	(0.18, 1.89)	3 mg/kg infliximab	3.31 (0.95, 8.68)
40 mg adalimumab	1.25	(0.44, 2.76)	40 mg adalimumab	5.92 (2.51, 12.23)
Placebo			*25 mg twice a week etanercept*	
50 mg etanercept once a week	5.94	(3.55, 9.27)	50 mg etanercept once a week	1.23 (0.64, 2.00)
50 mg etanercept twice a week	5.20	(1.49, 13.25)	50 mg etanercept twice a week	1.09 (0.29, 2.68)
50 mg golimumab	6.04	(2.29, 13.04)	50 mg golimumab	1.24 (0.40, 2.80)
100 mg golimumab	6.22	(2.34, 13.6)	100 mg golimumab	1.27 (0.41, 2.86)
5 mg/kg infliximab	6.65	(3.36, 11.97)	5 mg/kg infliximab	1.35 (0.58, 2.67)
3 mg/kg infliximab	3.33	(0.96, 8.72)	3 mg/kg infliximab	0.69 (0.18, 1.89)
40 mg adalimumab	6.03	(2.52, 12.56)	40 mg adalimumab	1.23 (0.44, 2.69)
50 mg etanercept once a week			*50 mg etanercept once a week*	
50 mg etanercept twice a week	0.88	(0.29, 2.05)	50 mg etanercept twice a week	0.89 (0.29, 2.03)
50 mg golimumab	1.08	(0.36, 2.63)	50 mg golimumab	1.06 (0.35, 2.48)
100 mg golimumab	1.13	(0.36, 2.72)	100 mg golimumab	1.08 (0.36, 2.56)
5 mg/kg infliximab	1.19	(0.50, 2.45)	5 mg/kg infliximab	1.16 (0.50, 2.33)
3 mg/kg infliximab	0.60	(0.15, 1.69)	3 mg/kg infliximab	0.59 (0.15, 1.64)
40 mg adalimumab	1.09	(0.38, 2.54)	40 mg adalimumab	1.05 (0.38, 2.42)
50 mg etanercept twice a week			*50 mg etanercept twice a week*	
50 mg golimumab	1.62	(0.30, 5.25)	50 mg golimumab	1.54 (0.28, 4.65)
100 mg golimumab	1.67	(0.31, 5.38)	100 mg golimumab	1.57 (0.30, 4.75)
5 mg/kg infliximab	1.77	(0.40, 3.17)	5 mg/kg infliximab	1.68 (0.40, 4.72)
3 mg/kg infliximab	0.90	(0.14, 3.17)	3 mg/kg infliximab	0.86 (0.14, 3.02)
40 mg adalimumab	1.63	(0.32, 4.917)	40 mg adalimumab	1.53 (0.32, 4.70)
50 mg golimumab			*50 mg golimumab*	
100 mg golimumab	1.13	(0.48, 2.19)	100 mg golimumab	1.10 (0.48, 2.16)
5 mg/kg infliximab	1.37	(0.40, 3.43)	5 mg/kg infliximab	1.34 (0.41, 3.33)
3 mg/kg infliximab	0.69	(0.13, 2.24)	3 mg/kg infliximab	0.69 (0.13, 2.15)
40 mg adalimumab	1.25	(0.32, 3.31)	40 mg adalimumab	1.22 (0.33, 3.27)
100 mg golimumab			*100 mg golimumab*	
5 mg/kg infliximab	1.32	(0.38, 3.35)	5 mg/kg infliximab	1.31 (0.39, 3.29)
3 mg/kg infliximab	0.66	(0.12, 2.15)	3 mg/kg infliximab	068 (0.13, 2.12)
40 mg adalimumab	1.20	(0.30, 3.24)	40 mg adalimumab	1.20 (0.32, 3.23)
5 mg/kg infliximab			*5 mg/kg infliximab*	
3 mg/kg infliximab	0.56	(0.13, 1.62)	3 mg/kg infliximab	0.57 (0.13, 1.63)
40 mg adalimumab	1.01	(0.32, 2.47)	40 mg adalimumab	1.01 (0.33, 2.46)
3 mg/kg infliximab			*3 mg/kg infliximab*	
40 mg adalimumab	2.55	(0.51, 7.56)	40 mg adalimumab	2.48 (0.51, 7.36)

fliximab at 0, 2, 6 weeks seems to be the most efficacious therapy, yet more direct evidences need to further assess the relative efficacy between different treatments. Furthermore, the feasibility and cost-effectiveness of treatments also needs to be assessed.

The test for goodness of model fit suggested that the model was appropriate according to the assessment methods which was recommended by NICE committee (24). Since there was no independent loop of evidence, there was no test performed to check the consistency between the direct and indirect evidence. The two points were important for mixed treatment meta-analysis. Several limitations existed in our present study. First, not all of included trials applied the ASAS response criteria as the primary end points, which may introduce some bias into our estimates. Second, other relevant outcomes were not discussed in our study, due to just part of included trials reporting these outcomes.

Conclusion

Generally, our present study suggested that compared with placebo, all anti-TNF agents were effective in the management of acute ankylosing spondylitis refractory to NSAIDs in the aspects of clinical response index ASAS20, and 5 mg/kg infliximab at 0, 2, 6 weeks maybe was the most effective. Future studies could pay more attention to the comparison of different anti-TNF agents, instead of comparison between anti-TNF agents and placebo.

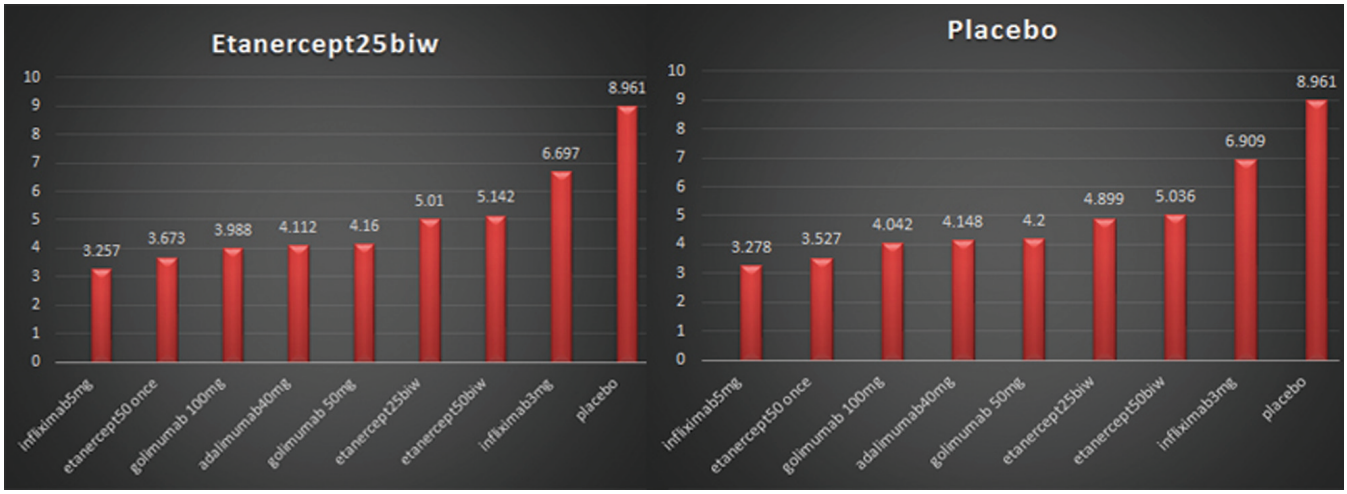

Fig. 2. The ranking analysis results, using etanercept 25 mg twice a week and placebo as reference treatment respectively, both demonstrated that infliximab 5 mg/kg was the best effective therapy. The larger the values were in the figure, the less effective they were.

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