Int J Clin Exp Med 2016;9(11):20668-20673
www.ijcem.com /ISSN:1940-5901/IJCEM0030743

Review Article

Anti-TNFα agents and interleukin-17A inhibitor Secukinmuab have similar effects in improvement of ASAS20, ASAS40, and safety: a meta-analysis

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Received April 18, 2016; Accepted September 17, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: Objective: The aim of this study was to indirectly compare the efficacy and safety of anti-tumor necrosis factor α (TNFα) agents and an interleukin (IL)-17A inhibitor Secukinmuab for the treatment of ankylosing spondylitis (AS). Methods: Literatures were searched in Pubmed, Medline, Embase and the Cochrane library to screen citations from January 1996 to December 2015. The mixed treatment comparison (MTC) meta-analysis within a Bayesian framework was performed by WinBUGS14 software. The proportion of patients reaching ASAS20 and ASAS40 improvement by the assessment of Spondyloarthritis International Society response criteria index at week 12 was used as efficacy end point. Results: There was no significant difference between the five anti-TNFα agents and Secukinmuab regarding their efficacy and safety. We found that infliximab may have a better effect in improving ASAS20 than the other drugs and ct-p13 may have a better effect in improving ASAS40 than the other drugs during 12 week therapy, although there were no statistical differences. Conclusion: Allsix agents have similar effects in improvement of ASAS20, ASAS40, and safety. However, infliximab and ct-p13 trended to be superior to the other four agents in terms of ASAS20 and ASAS40 during 12 week treatment. IL-17A can be a potential therapeutic target in spondyloarthritis.

Keywords: Ankylosing spondylitis, anti-TNFα agents, interleukin-17A inhibitor, meta-analysis, mixed treatment comparison

Introduction

Ankylosing spondylitis (AS) is one of the most common inflammatory rheumatic diseases characterized by new bone formation that progressively leads to ankylosis and functional disability [1]. To date, five tumor necrosis factor α (TNFα) blocker agentsadalimumab, etanercept, golimumab infliximab and infliximab-biosimilar (ct-p13) have been approved by the European Medicine Agency (EMA) for the treatment of adults AS. Previous randomized controlled trials (RCTs) have reported that the treatments with the anti-TNFα agents lead to improvement in function and reduction of disease activity. A meta-analysis has showed that anti-TNFα agents can improve disease activity and functional capacity in both AS and non-radiographic axial spondyloarthritis patients (nr-axSpA) [2]. Park et al has showed that there was no significant difference between the ct-13 and other anti-TNFα [3].

Secukinumab is a fully human, anti-interleukin-17A (IL-17A) monoclonal antibody, one phase II and two phase III trials have shown that secukinumab significantly suppressed the symptoms of ankylosing spondiylitis [4, 5].

As there were lack of head-to-head studies comparing anti-TNFα agents and IL-17A inhibitors, traditional methods cannot be applied for the comparison. Therefore, we used a mixed treatment comparison (MTC) to compare the efficacy and safety of anti-TNFα agents and the IL-17A inhibitor secukinumab, which is available for indirect comparisons between drugs with different comparators [6].

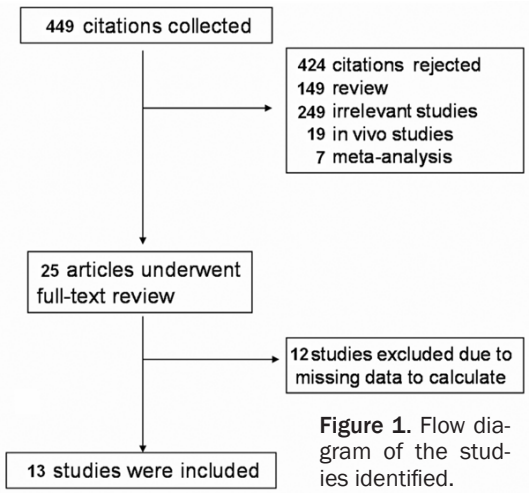

Figure 1. Flow diagram of the studies identified.

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 December 2015 for inclusion in this study. The key words ankylosing spondylitis and (infliximab or etanercept or adalimumab or golimumab or ct-p13 or Secukinumab) were used to find 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; (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 ASAS20 response; the number of patients achieving ASAS40 response; the outcome of adverse; endpoints and study duration. The Jadad score was used to assess the quality of included studies. The studies with score no less than 3 were regarded as high quality RCTs, while studies with score less than 3 were defined as low quality RCTs.

Data analysis

To evaluate the relative effectiveness of each biologics, a MTC meta-analysis within a Bayesian framework was performed. For all Bayesian analyses, Markov-chain-Monte-Carlo methods were used. A random effect model was used to estimate the odds ratios (OR) as the measure of relative treatment effect. We carried out 60,000 iterations. The first 10,000 iterations were discarded after the burn-in period and estimates were based on the subsequent 50,000 ones. Data analysis was performed by Stata 12 (Stata Corp, College Station, Texas, USA) and WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). Assessment of Spondyloarthritis International Society 20 response (ASAS20, improvement of ≥20% and absolute improvementof ≥1 unit [on a 10-unit scale] in atleast three of the four main ASAS domains, withno worsening by ≥20% in the remaining domain) and Assessment of Spondyloarthritis International Society 40 response (ASAS40, improvement of ≥40% and absoluteimprovement of ≥2 units [on a 10-unit scale] in atleast three of the four main ASAS domains, with no worsening in the remaining domain) were used to evaluate the effect of each agent.

Results

Search results and characteristics

A total of 449 citations were obtained via database searches; thirteen met the inclusion criteria for this study (**Figure 1**). A total of 2674 persons have been involved, in which 1550 subjects were AS patients and 803 subjects were health controls. Among the AS patients, 550 patients were treated with adalimumab, 337 patients with etanercept, 360 patients with infliximab, 138 patients with golimumab, 125 patients with ct-p13, and 197 patients with secukinumab. The information in these citations was summarized in **Table 1**. All 12 studies have been assessed by Jadad score system with score no less than 3 (**Table 1**).

The mix treatment comparison meta-analysis

ASAS20 at 12 week: Two studies presented ASAS20 results at week 14 and one study at week 16. These studies were analyzed with trials presenting results for week 12. The results of the pairwise comparison did not show any significant difference among anti-TNFα agents and IL-17A inhibitor secukinumab at week 12 (**Figure 2**). Compared with the other drugs, infliximab was likely having the higher ASAS20 response rate followed by ct-p13, although with no statistical difference.

Table 1. Characteristics of the included studies

Study	Age (mean)		Male sex		BASDAI score, mean		CRP level, mean (mg/dl)		Treatment	Sample size		Study duration (week)	Jadad score
	Case	Contorl	Case	Control	Case	Control	Case	Control		Case	Control		
Park (2014) [7]	38	38	99	103	6.8	6.6	1.1	1.4	CT-P13/INX	125	125	30	5
Huang (2014) [8]	30.1	29.6	185	95	6.0	6.2	0.2	0.2	ADA/PLA	229	115	24	5
Van der Heijde (2006) [9]	41.7	43.4	157	79	6.3	6.3	1.8	2.2	ADA/PLA	208	107	24	5
Sieper (2012) [10]	37.6	38.4	44	40	6.4	6.5	6.8	7.6	ADA/PLA	91	94	12	5
Haibel (2008) [11]	38	37	13	12	6.7	6.3	6.2	7.8	ADA/PLA	22	24	52	5
Dougadas (2010) [12]	46	48	37	39	6.4	5.8	2.5	1.7	ETA/PLA	39	43	12	5
Van der Heijde (2006) [13]	41.5	40.1	108	40	6.2	6.1	2.2	2.2	ETA/PLA	155	51	12	4
Calin (2004) [14]	45.3	40.7	80	77	6.1	5.9	15.4	9.7	ETA/PLA	45	39	12	5
Davis (2003) [15]	42.1	41.9	105	105	5.8	6	1.9	2.0	ETA/PLA	138	139	24	5
Braun (2002) [16]	40.6	39	23	22	-	-	-	-	INF/PLA	34	35	12	5
Van der Heijde (2005) [17]	40	41	157	68	6.6	6.5	1.5	1.7	INF/PLA	201	78	24	5
Inman (2008) [18]	38	41	102	55	6.6	6.6	1.1	1.2	GLM/PLA	138	78	24	5
Baeten (2015) [4]	40.8	43.3	218	141	6.3	6.6	8.1	7.4	SEC/PLA	321	196	16	5

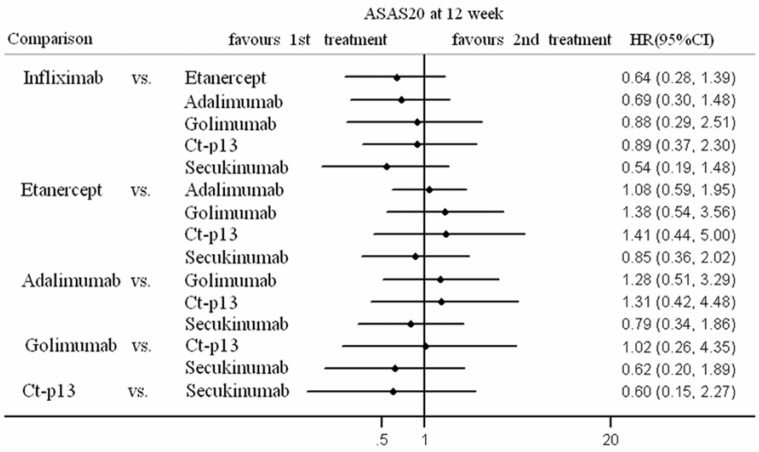

Figure 2. Efficacy of TNF-α blockers and IL-17A inhibitor on ASAS20 at 12 week, results of mixed treatment comparison.

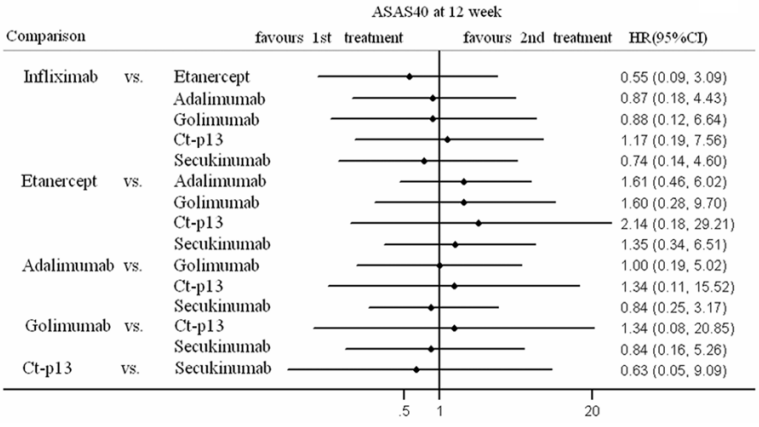

Figure 3. Efficacy of TNF-α blockers and IL-17A inhibitor on ASAS40 at 12 week, results of mixed treatment comparison.

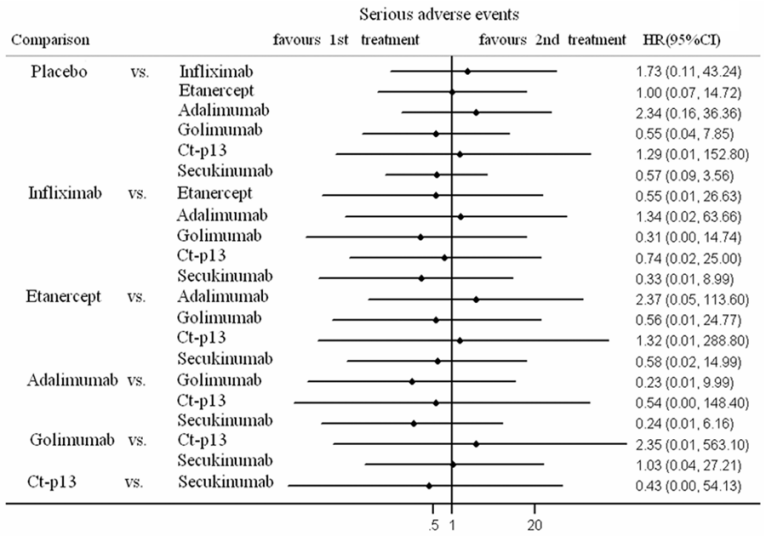

Figure 4. Safety of different TNF-α blockers, results of mixed treatment comparison.

ASAS40 at 12 week: Inman et al study and Park et al presented ASAS40 results at week 14. These studies were analyzed with trials presenting results for week 12. The results of the pairwise comparison did not show significant difference between the efficacy of the anti-TNFα agents and secukinumab in term of ASAS40 at week 12 (**Figure 3**). In these drugs, ct-p13 was likely having the higher ASAS40 response rate followed by infliximab without any statistical difference.

Safety

Serious adverse events were used to evaluate the safety of these drugs. The results of the pairwise comparison did not show significant difference in the safety of the agents (**Figure 4**).

Discussion

Previous studies have proven that anti-TNFα agents were superior to placebo. Machando et al in their meta-analysis compared the efficacy of infliximab, adalimumab, etanercept and golimumab. According to their results, all the four anti-TNFα agents can effectively reduce the signs and symptoms of the axial component of ankylosing spondylitis, but safety outcomes and withdraws did not indicate statistically significant differences between treatment and control groups after 12 or 30 weeks [19]. Mcleod et al evaluated the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab in AS. Their studies suggested that the three treatments were clinically effective in relation to

assessment of ASAS, BASDAI and BASFI, but indirect comparisons of treatments did not show a significant difference in effectiveness between the three agents [20]. Migliore et al compared the efficacy of biological therapies in AS at week 24 by mean of a mixed treatment comparison. In their meta-analysis, infliximab showed a 72% probability of being the best treatment, while adalimumab and etanercept showed probabilities of 13% and 15%, respectively. However, no significant differences were found between anti-TNFα agents by indirect comparison [21]. Shu et al compared the effectiveness of different doses of adalimumab, golimumab and infliximab in terms of ASAS20 response at week 12. The results suggested that infliximab 5 mg/kg at 0, 2, 6 weeks seems to be the best efficacious therapy [22]. However, both Migliore et al and Shu et al did not include the efficacy comparison of cpt-13.

Anti-TNFα agents were recommended for patients who were failed to response for conventional treatment. However, in some patients, such therapy fails to achieve adequate disease control or has unacceptable adverse events. Recent studies have identified the IL-17 pathway as a potential therapeutic target in spondyloarthritis [5]. Our study suggested that secukinumab has the similar effect and safety with anti-TNFα agents, and secukinumab could be chosen for those who was unable to use anti-TNFα agents.

We performed this MTC meta-analysis to further compare the effect of anti-TNFα agents and IL-17A inhibitor secukinumab. In our study, no significant difference was found between these treatments regarding their efficacy and safety. However, we found thatinfliximab may have a better effect in improving ASAS20 than the other drugs and ct-p13 may have a better effect in improving ASAS40 than the other drugs during 12 week therapy, although there were no statistical differences.

There are some limitations regarding the datasets used in our report. The sample size of the studies was small, and the duration of treatment was slightly different from each study. For example, some studies reported the efficacy and safety results at week 14 or 16, while the most studies reported them at week 12. However, except these limitations, we think our findings will be helpful for further evaluation of biological agents in AS treatment.

In conclusion, the results showed that all six agents have a similar effect on improvement of ASAS20, ASAS40 and safety. Infliximab and ct-p12 might be the potential optimal choice in AS treatment. Furthermore, secukinumab has the similar effect and safety with anti-TNFα agents and IL-17 could be a new therapeutic target in AS treatments. Large-size sample RCTs, head-to-head comparisons, continuous data collection and benefit-risk assessment are needed to confirm our findings.

Disclosure of conflict of interest

None.

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