Review Article

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

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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: All six 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) blockers (adalimumab, 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 spondylitis [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].
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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 improvement of ≥1 unit [on a 10-unit scale] in at least three of the four main ASAS domains, with no worsening by ≥20% in the remaining domain) and Assessment of Spondyloarthritis International Society 40 response (ASAS40, improvement of ≥40% and absolute improvement of ≥2 units [on a 10-unit scale] in at least 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.
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Table 1. Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (mean)</th>
<th>Male sex</th>
<th>BASDAI score, mean</th>
<th>CRP level, mean (mg/dl)</th>
<th>Treatment</th>
<th>Sample size</th>
<th>Study duration (week)</th>
<th>Jadad score</th>
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</table>
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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...
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