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DOSAGE AND DURATION OF ETANERCEPT THERAPY FOR ANKYLOSING SPONDYLITIS: A META-ANALYSIS

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Objectives: We conducted a meta-analysis of recently published randomized controlled trials (RCTs) to identify the most effective and safe etanercept dosing regimen and duration of therapy for the treatment of patients with ankylosing spondylitis (AS).
Methods: We systematically reviewed PubMed, Embase, Cochrane Library, and Web of Science databases for RCTs. The proportion of patients attaining 20 percent improvement (according to the Spondyloarthritis International Society response criteria [ASAS 20]) was evaluated as a primary outcome. Secondary outcomes included 50 percent increase in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50) used for evaluating efficacy, as well as the BASDAI/Bath Ankylosing Spondylitis Functional Index (BASFI) scores and adverse events.
Results: ASAS 20 indicated that the efficacy of etanercept did not differ amongst dosing regimens (25 mg twice-weekly versus 50 mg once-weekly: relative risk [RR], 2.18, 95 percent confidence interval [CI], 1.78–2.67 versus RR, 2.00, 95 percent CI, 1.70–2.37). The ASAS 20 reported subgroup differences among treatment durations of less than 12 weeks (RR, 2.70; 95 percent CI, 2.09–3.49); 12 weeks (RR, 1.74; 95 percent CI, 1.37–2.22); and more than 12 weeks (RR, 2.56; 95 percent CI, 1.88–3.48). Other outcomes included BASDAI, BASDAI 50, and BASFI. Drug safety differed according to the treatment regimen and duration.
Conclusion: Our meta-analysis found that there was no significant efficacy difference between 50 mg once-weekly and 25 mg twice-weekly dosing for the treatment of AS, and a dosing duration of less than 12 weeks was more effective for treating AS patients.

Keywords: Meta-analysis, Etanercept, Ankylosing spondylitis, Dosing regimen, Duration of therapy

Ankylosing spondylitis (AS) is a prototype, subtype, or clinical outcome of spondyloarthritis (SpA), especially axial SpA (1). Among the available options for AS treatment, anti-tumor necrosis factor (TNF) therapy has become increasingly popular. However, several studies have reported high remission rates in AS patients following treatment (2). In addition, the United States Food and Drug Administration (FDA) has approved a number of TNF blockers for AS and indicate 50 mg of etanercept to be administered once weekly. Etanercept is a recombinant protein of p75 TNF receptor as a competitive inhibitor binding of TNF-alpha to cell-surface TNF receptors (3). However, there is a discrepancy between the approved dosing regimen and that used in a related clinical trial (4), which demonstrated that a 25 mg twice-weekly regimen of etanercept was effective for the treatment of AS. Such discrepancies could cause confusion in the future selection of an appropriate dosing regimen (5).

Discrepancies in etanercept dosing regimen and duration of therapy for the treatment of AS patients also existed in prior studies. For example, McCormack et al. (6) recommended a twice-weekly dosage of 25 mg, but a clinical trial with active rheumatoid arthritis patients showed comparable efficacy and safety results between 50 mg once-weekly and 25 mg twice-weekly treatments (6). Additionally, several meta-analyses have been conducted to evaluate the efficacy and safety of anti-TNFs, especially etanercept treatment for ankylosing spondylitis (7–9). Some recent systematic reviews have tried to determine the optimal dosing regimen and duration of therapy for etanercept use (8;9) However, the findings of these studies were somewhat less robust, owing to the lack of updated

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clinical trials, analysis issues, and not providing outcome measures commonly recommended for evaluating efficacy of treatment for ankylosing spondylitis by experts (10).

There is still a need to verify the ideal dosing regimens and therapy duration for etanercept in the treatment of AS patients. To do this, using multifocal indices, we conducted a meta-analysis of recently published randomized controlled trials (RCTs).

METHODS

This review was conducted according to the Cochrane Collaboration Handbook (11) and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines (12).

Data Sources and Search Parameters

The following major medical databases were searched: PubMed, Embase, Cochrane Library, and Web of Science. We designed and applied a search strategy using sensitivity criteria filtering for RCTs for etanercept including patients with AS. The search strategy is described in Supplementary Table 1. References of related articles were hand-searched, and the "Related Article" feature was used to discover additional articles while excluding unpublished dissertations or theses. Language was not restricted during the article search.

Study Selection

Two examiners independently screened the titles, abstracts, and full texts of articles to identify relevant studies for inclusion in the meta-analysis. Discrepancies in results were resolved by discussion. The efficacy and toxicity outcomes of interest in the RCTs were searched for by two independent investigators. Only trials that used randomized controlled study designs to compare the efficacy or safety between etanercept and a placebo were included. Studies included patients with radiographic axial SpA, which was defined as that satisfied the definition of the modified New York criteria, and nonradiographic AS, also termed early AS and defined by a score of 4 or more on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (1). Studies with less than 10 participants were excluded.

Data Extraction and Outcomes of Interest

Two reviewers separately collected the following relevant data: publication year, study design, study population, number of patients, previous or simultaneous use of disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs and/or glucocorticoids, intervention, and outcomes. The primary outcome was measured by a population-pooled odds ratio (OR) showing the Assessment of SpondyloArthritis International Society 20 (ASAS 20) response, which was defined as a decrease of at least 20 percent and 10 units (on an illustrated analog scale from 0 to 100) in at least three of the following categories: patient global assessment, lumbar pain, physical function, and inflammation (without exacerbation >20 percent and 10 units in the remaining fourth category).

The ASAS 20 response represents the efficacy of the treatment (1). The secondary endpoints were assessed from BASDAI and BASDAI 50 responses. The BASDAI is widely used and was designed by medical professionals in conjunction with patients. The BASDAI gathers the patient's response to a self-administered questionnaire containing six questions regarding the symptoms of AS. The BASDAI 50 is a 50 percent improvement in the BASDAI score, and it represented the proportion of patients with improvements of at least 50 percent from the baseline value of the BASDAI. The Bath Ankylosing Spondylitis Functional Index (BASFI) (1) reflects the degree of disability in patients with AS. Other secondary outcomes that were evaluated included safety and adverse reactions.

Assessment of Bias Risk

The risk of bias in the clinical trials was assessed using the Cochrane Risk of Bias tool (11) with respect to randomization allocation, double blinding, and description of withdrawals. Every domain was categorized as having a low, high, or unclear risk of bias. If the explanation in the report could not be classified as high or low, it was considered "unclear." Two independent reviewers evaluated the methodological quality of the studies and resolved disparities by discussion. The methodological quality was examined according to the Jadad scale (13), which assigns a study score ranging from 0 to 6, with 6 denoting the highest quality.

Data Synthesis and Analysis

Data from the eligible studies were entered into the Review Manager 5.1 software (version 5.1.2, The Nordic Cochrane Center, The Cochrane Collaboration, 2011). Concerning continuous data, the mean difference was calculated to perform the analysis. The mean difference was used for continuous data with 95 percent confidence intervals (CIs). The results were expressed as risk ratios (RRs) with CIs for dichotomous outcomes. Higgins' I^2 statistic and the chi-square-based Q-test were used to assess heterogeneity among studies and subgroup differences. The heterogeneity was denoted by $p < .10$ and/or $I^2 > 40$ percent. Factors that affected heterogeneity were investigated in positive cases (11).

A random-effects model (the DerSimonian and Laird method) was used to analyze pooled data according to heterogeneity; otherwise, a fixed-effects model was used (the Mantel–Haenszel method) (11). The statistical significance ($p < .05$) of the pooled ORs was determined by the Z-test. Publication bias in the literature was assessed by Egger's linear regression test, and visual inspection of asymmetry was performed in funnel plots. If a publication bias was present, p-values examined by Egger's test would have resulted in less than .05 (14). The "trim

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Table 1. Characteristics of the RCTs Included in the Analysis

Study	Patients (*N*)	Country	Intervention (dosing regimen)	Therapy duration	Follow-up (evaluation time)
Dougados 2011 (13)	82	FR, DE, AN, HUN	ETN 50 mg qw Placebo	12 weeks	12 weeks (RCT: at weeks 2, 4, 8, and 12)
Dougados 2014 (14)	106	EU, Asia, Latin America	ETN 50mg qw Placebo	12 weeks	24 weeks (RCT: 12 weeks, OLE: following 12 weeks)
Calin 2004 (15)	84	BE, FI, FR, DE, AN, IT, ES, US	ETN 25 mg biw Placebo	12 weeks	12 weeks (RCT: at weeks 2, 4, 8, and 12)
Pang 2008 (16)	40	CN	ETN 50 mg qw Placebo	6 weeks	6 weeks (RCT: at weeks 2 and 6)
Davis 2003 (17)	277	US, CA, FR, AN, DE	ETN 25 mg biw Placebo	24 weeks	24 weeks (RCT: at weeks 12 and 24)
Lin 2010 (18)	39	CN	ETN 50 mg qw Placebo	6 weeks	12 weeks (RCT: at week 6 OLE: following week 6)
Heijde 2006 (19)	356	BE, FR, DE, GR, HUN, IT, AN, PL, PT, ES, UK	ETN 25 mg biw Placebo	12 weeks	12 weeks (RCT: at weeks 2, 4, 8, and 12)
Gorman 2002 (20)	40	US	ETN 25 mg biw Placebo	16 weeks	16 weeks (RCT: at day 1 and weeks 4, 8, 12, and 16)
Brandt 2003 (21)	30	DE	ETN 25 mg biw Placebo	6 weeks	24 weeks (RCT: at weeks 3 and 6 Observation: after week 6 and every 3 weeks thereafter)
Barkham 2010 (22)	40	UK	ETN 25 mg biw Placebo	12 weeks	12 weeks (RCT: at week 12)
Huang 2010 (23)	397	CN	ETN 50 mg qw Placebo	6 weeks	12 weeks (RCT: at weeks 2 and 6 OLE: at week 12)

ETN, etanercept; RCT, randomized controlled trial; OLE, open-label trial; Belgium, BE; Canada, CA; CN, China; DE, Germany; FR, France; FI, Finland; GR, Greece; AN, Netherlands; PL, Poland; PT, Portugal; HUN, Hungary; US, United States; IT, Italy; ES, Spain; United Kingdom, UK; qw, once weekly; biw, twice weekly

and fill" method was used to correct publication bias, which was made to correct the funnel plot by imputing where the missing studies would be likely to occur (15). The correction for missing studies could lead to relevant changes regarding the weighted mean effect, so the influence of the publication bias for the statistical significance in the overall effects was also evaluated (15).

RESULTS

Studies and Their Main Characteristics

A flow diagram of the clinical trial selection process is shown in Figure 1. A total of 2,079 articles were identified through a database literature search, and manual searching revealed additional reports. After eliminating duplicates, 2,067 records were retrieved. Ultimately, eleven RCTs that evaluated the efficacy and safety of etanercept in comparison with a placebo were included in the meta-analysis. The main characteristics of the RCTs included in this analysis are shown in Table 1. The total number of patients included in the meta-analysis was 1640, and the trials were performed in Europe, Asia, the United States, and South America.

Clinical outcomes that demonstrated the efficacy and safety of etanercept in the treatment of AS were evaluated in the RCT phase in all studies (16–26). To determine the differences in the efficacy and safety of etanercept, we analyzed the results obtained in the randomized controlled phase: four studies (19; 21;24;26) continued therapy for 6 weeks; five studies (16–18;22;25) maintained treatment for 12 weeks, and two trials (20; 23) offered drug treatment for more than 12 weeks. Five trials (16;17;19;21;26) used a dosage of 50 mg administered once weekly to AS patients, whereas in other studies (18;20;22–25) etanercept was administered at a dosage of 25 mg twice-weekly. The methodological quality assessment is described in Table 2.

Efficacy

A greater number patients who received etanercept had a positive ASAS 20 response than those who received the placebo. There was an RR of 2.18 with a 95 percent CI of 1.78–2.67 for the 25 mg twice-weekly etanercept regimen without significant heterogeneity ($I^2 = 0$ percent; $p = .80$). For the 50 mg once-weekly regimen, the RR was 2.00 (95 percent CI, 1.70–2.37). The RR was 2.70 (95 percent CI, 2.09–3.49) when the drug was used for less than 12 weeks, versus 1.74 (95 percent CI, 1.37–2.22) for the 12-week treatment without heterogeneity. With a treatment duration of greater than 12 weeks, the RR was 2.56 (95 percent CI, 1.88–3.48).

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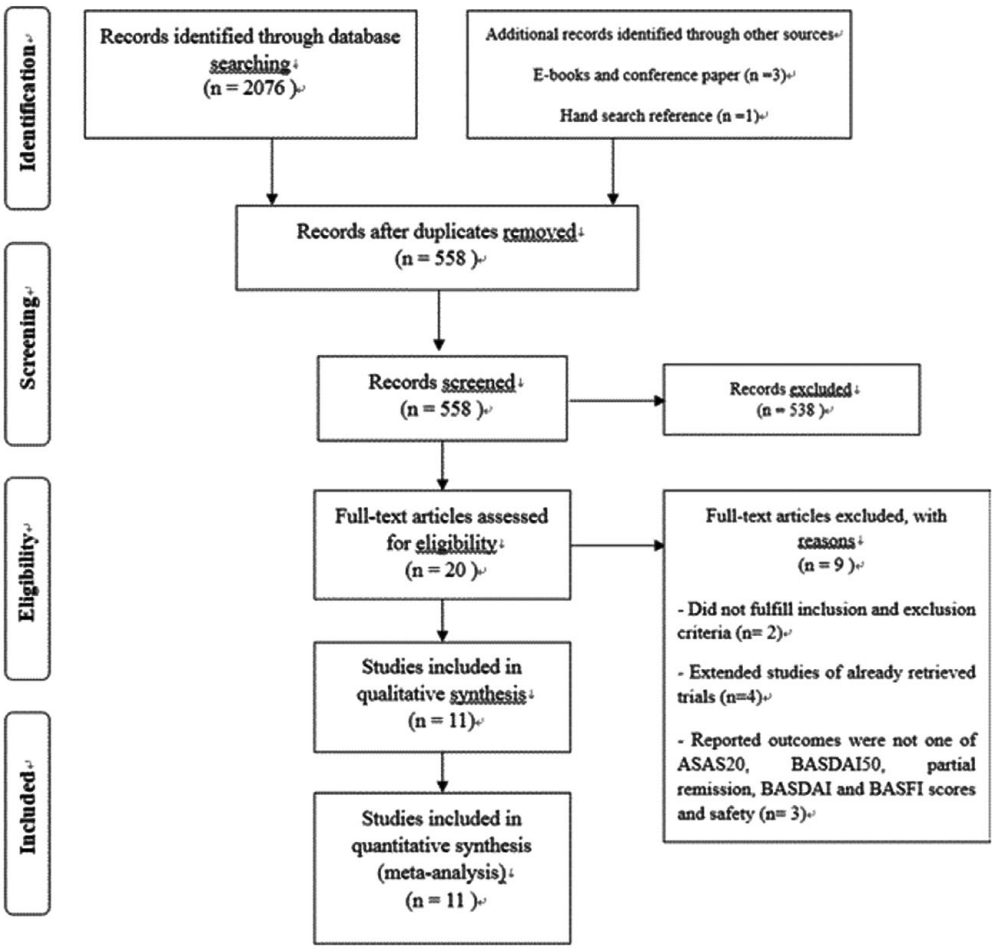

Figure 1. Flow diagram of the selection process for the included studies.

The subgroup differences for ASAS 20 according to therapy duration showed that less than 12 weeks of treatment was more beneficial than treating for 12 weeks ($p = .01$, $I^2 = 83$ percent). Moreover, dosing more than 12 weeks of etanercept was evaluated and found to be more effective than the 12 week duration ($p = .06$, $I^2 = 72.6$ percent). The RR for the BASDAI 50 response was 2.20 (95 percent CI, 1.66–2.93) for 50 mg of etanercept administered once weekly, versus 3.41 (95 percent CI, 2.01–5.80) for 25 mg of etanercept administered twice-weekly with insignificant heterogeneity. The RR was 5.73 (95 percent CI, 1.85–17.72) when treatment lasted less than 12 weeks without heterogeneity, versus 1.95 (95 percent CI, 1.39, 2.72) for 12-week therapy without heterogeneity (Figure 2). The BASFI and BASDAI results are presented in Supplementary Table 2. The RR was more favorable for etanercept, although significant heterogeneity was observed among the trials.

Safety

The only significant adverse reactions included were injection site reactions (Supplementary Table 3). The RR was 2.75 (95 percent CI, 1.84–4.09) for studies using the 25 mg twice-weekly treatment, versus 2.05 (95 percent CI, 0.95–4.43) for 50 mg administered once weekly. The use of etanercept was associated with a greater number of injection site reactions, as evidenced by an RR of 2.62 (95 percent CI, 1.84–3.71) without heterogeneity (Supplementary Figure 1). Other adverse reactions had insignificant disparities between the two dose groups that were consistent with the different dosing regimens and treatment durations (Supplementary Table 3).

Publication Bias

Publication bias was assessed using funnel plots and Egger's test. Asymmetric plots were observed in several responses such as ASAS 20 and BASDAI 50, suggesting a possible publication bias. However, with the small number of studies included in the analysis, it was possible that the statistical power was too low to distinguish real asymmetry; therefore, Egger's test was also used. In the present study, the analyzed ASAS 20 response outcomes showed a p-value = .03, while the p-value was 0.04 for BASDAI 50 response; p-values were calculated by Egger's test, and they indicated a publication bias. However, BASFI and injection site reaction results did not show a publication bias.

After the trim and fill procedure, we found that three studies were missing for each, and relevant changes in the overall

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Table 2. Methodological Assessment of the RCTs Included in the Analysis (Jadad Score)

Study	Randomization	Double blinding	Withdrawals and dropouts	Total score
Dougados 2011 (13)	1	1	1	3
Dougados 2014 (14)	2	1	1	4
Calin 2004 (15)	1	1	1	3
Pang 2008 (16)	1	1	1	3
Davis 2003 (17)	2	2	1	5
Lin 2010 (18)	2	2	0	4
Heijde 2006 (19)	1	1	1	3
Gorman 2002 (20)	1	1	1	3
Brandt 2003 (21)	1	2	1	4
Barkham 2010 (22)	1	1	1	3
Huang 2010 (23)	2	2	1	5

pooled estimates (RRs) for each response outcome showed a publication bias. For the ASAS 20 response, the overall effect of the unadjusted RR was 2.07 (95 percent CI, 1.82–2.36) and the overall effect-adjusted RR was 1.99 (95 percent CI, 1.76–2.25). The outcomes of BASDAI 50 showed the unadjusted RR of the overall effect to be 2.43 (95 percent CI, 1.89–3.12), and the adjusted RR of the overall effect was 2.28 (95 percent CI, 1.79–2.91).

DISCUSSION

We conducted a meta-analysis to evaluate the safety and efficacy of etanercept to identify the most appropriate dose and duration of treatment in AS patients.

In the present study, no differences were observed between AS patients receiving etanercept 25 mg twice-weekly and those receiving 50 mg once-weekly. In addition, an etanercept dosing period of less than 12 weeks was more beneficial than other durations of therapy.

According to ASAS 20 responses, no differences were observed between 50 mg once-weekly and 25 mg twice-weekly dosing regimens, both of which demonstrated improvement of symptoms and physical limitations. BASDAI 50 outcomes indicated that the 25 mg twice-weekly etanercept regimen was more beneficial than the 50 mg once-weekly regimen in the present study. However, for the evaluation of AS symptoms, one group of international SpA experts currently recommends the use of ASAS 20 criteria to measure TNF blocker efficacy (10). AS disease activity is believed to be underdetermined by BASDAI (27). A previous analysis indicated etanercept 50 mg once-weekly dosing showed more effective for treating AS patients, but the study less focused on the outcome of etanercept thereby containing several other TNF-blockers during the indirect analysis (28). Moreover, a current systematic review evaluated the efficacy of etanercept treatment for AS patients using a different outcome measure, the ASAS 40 response, which also showed no discrepancies between these two dosing regimens (9).

Systematical evaluation of optimal durations for etanercept therapy to treat AS patients has been performed previously (8;29). However, these studies still had several limitations for analyzing data from the included trials. To provide more confident and specific outcomes, we categorized the treatment period into durations of less than 12 weeks, 12 weeks, and more than 12 weeks. We found that patients' symptoms relatively improved with a treatment duration of less than 12 weeks. According to the ASAS 20 outcomes, we could not say significant efficacy differences existed between the less than 12 weeks and more than 12 weeks treatment duration groups. However, subgroup differences in the ASAS 20 responses demonstrated that etanercept treatment for less than 12 weeks showed benefit than treatment for exactly 12 weeks. This evaluation was confirmed by the BASDAI 50 response.

On the other hand, we could not demonstrate that dosing etanercept for more than 12 weeks was more beneficial than treatment for exactly 12 weeks, since this pooled ASAS 20 result could not be supported by another outcome such as BASDAI 50. Furthermore, a recent review reported that the ASAS 20 responses were not different between two durations of etanercept therapy, 12 and 24 weeks (8). As such, we can only suggest that AS patients should be treated with etanercept for less than 12 weeks.

However, some of these response measures evaluated were patient self-administered questionnaires, which may not correlate well with external indicators of disease activity (27). Questionnaire responses at the beginning of the treatment were usually more optimistic than later on, when patients had adjusted to the new health status. Considering the range of CIs in the present study for etanercept treatment duration of less than 12 weeks and the limitations of patient self-administered questionnaires, clinician decisions for etanercept therapy duration should be valuably considered, even though the analytic data showed that AS patients received the most benefit from less than 12 weeks of treatment.

According to the trial of Brandt et al. (30), the most efficacious end-points were reached at week 6, and were then maintained for 54 weeks after starting to dose etanercept for AS patients, and they therefore suggested that dosing etanercept at regular intervals with periodic interruptions should be used d for treating AS patients. The cyclic discontinuation of etanercept could also reduce the economic burden on AS patients (30), and prevent them from producing auto-antibodies (31). However, the outcome of the present analysis indicates that more supporting evidence is needed before suggesting that discontinuing etanercept therapy in AS patients might have an effect on response and/or remission after short-term treatment. Primary data corrected from RCTs or patient registries would

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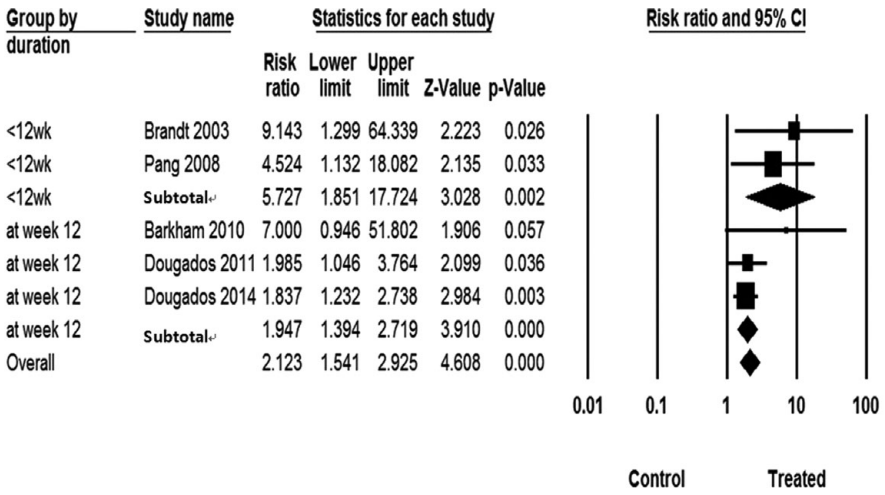

Figure 2. Forest plots of etanercept efficacy compared with placebo evaluated by BASDAI 50 according to the duration of therapy.

be helpful in finding clear evidence in the future. BASFI and BASDAI scores were also consistent with the results of prior meta-analyses (7;9;29).

The most frequent adverse reactions reported in previous studies were headaches, upper respiratory infections, and injection site reactions (2). Although the incidence was not significant, serious adverse events were reported (29). According to the present analysis, the incidence of injection site reactions was significantly higher in the treatment group than the placebo group. In the subgroup analysis, injection site reactions were more common with the 25 mg twice-weekly dosing regimen. Other adverse reactions were not significantly different between the treatment and placebo groups.

In this study, we specified inclusion criteria for AS patients, dividing them into radiographic axial SpA and non-radiographic SpA (nr-axSpA) categories because of a recent attempt to diagnose AS according to the disease stage. However, there still have been many controversial efforts to clearly separate the stages of the disease (31). In addition, one study (17) included in the present study included nr-axSpA patients showing a BASDAI score of 4 or more, which means these types of patients were good candidates to receive biological therapy. However, this study did not significantly influence the conclusion of our meta-analysis.

Conclusively, the present study showed it is more beneficial to use etanercept for less than 12 weeks, and two dosing regimens, 50 mg once-weekly and 25 mg twice-weekly, were equally effective for treating AS patients. However, if the patients present significant injection site reactions, we recommended 50 mg once-weekly dosing because that may require desensitization (32)

There were several limitations to this study. It did not differentiate results according to ethnic groups. A prior meta-analysis analyzed the efficacy of etanercept in AS patients according to ethnicity (7). However, studies included in that meta-analysis did not provide efficacy results according to race, and the analysis showed discrepancies in the number of patients in the trial groups compared with the original articles. The recommendations of international SpA experts for the measurement of TNF blocker efficacy have changed over time, leading to difficulty regarding the direct comparison of results among studies (10).

To evaluate the efficacy of etanercept treatment in AS patients, this analysis compared multifocal indexes. Studies included for this analysis used somewhat different outcome measures, so the models used in the present study may not provide fully comparable results. However, during the meta-analysis procedure, parts of outcome measures from an included study could be extracted and merged for pooling estimates (33). In the present study, included studies also provided outcomes of interests such as ASAS 20, and BASDAI 50. This study was the first meta-analysis to evaluate the efficacy and safety of etanercept in AS patients according to the dosing regimen and duration of therapy, using the most updated RCTs.

CONCLUSIONS

This meta-analysis analyzed the safety and efficacy of etanercept for the treatment of AS including recently published data. There was no significant efficacy difference between 50 mg once-weekly and 25 mg twice-weekly dosages, and etanercept dosing of a shorter duration than 12 weeks was more beneficial for AS patients. The safety of etanercept did not significantly differ between the dosing regimens, with the exclusion of injection site reactions.

SUPPLEMENTARY MATERIAL

Supplementary Table 1: https://doi.org/10.1017/S0266462317000150

Supplementary Table 2: https://doi.org/10.1017/S0266462317000150

Supplementary Table 3: https://doi.org/10.1017/S0266462317000150
Supplementary Figure 1: https://doi.org/10.1017/S0266462317000150

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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