Original Article
The efficacy and safety of certolizumab pegol (CZP) in the treatment of active rheumatoid arthritis (RA): a meta-analysis from nine randomized controlled trials

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Abstract: Objective: Certolizumab pegol (CZP) is a novel anti-TNF agent that is used for patients with moderate to severe active rheumatoid arthritis (RA). However, the efficacy of CZP in RA remains controversial. Thus, we performed this meta-analysis to assess the efficacy and safety of CZP in the treatment of RA patients. Methods: Eligible studies were randomized controlled trials (RCTs) that evaluated the efficacy and safe of CZP in the patients with active RA. The primary outcome was American College of Rheumatology 20% (ACR20), and secondary outcome were ACR50, ACR70, disease activity, patient-reported outcomes (PROs), and adverse events. A fixed-effect model or random-effect model was used to pool the estimates, depending on the absence or presence of heterogeneity among the included studies. Results: Nine RCTs with a total of 5228 patients were included in this meta-analysis, and all of the patients were administered CZP or placebo. The pooled results showed that CZP significantly improved the ACR20, ACR50, ACR70 response rates, and physical function. CZP was associated with a statistically significant reduction in Disease Activity Score in 28 joints-Erythrocyte sedimentation rate, arthritis pain, and fatigue. Patients who received CZP treatment did not have a higher incidence of treatment-related adverse events, no matter in any intensity. Conclusions: CZP 200 or 400mg in the treatment of active RA significantly reduced the RA signs and symptoms, and improved physical function as compared with the placebo. More large-scale RCTs are needed to evaluate the long-term efficacy and safety of CZP in the treatment of active RA.

Keywords: Certolizumab pegol, rheumatoid arthritis, meta-analysis

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease characterized by synovial lining of joints, tendons, and periarticular structures [1]. The joint inflammation leads to tenderness and pain, which reduces the quality of life of patients. Proinflammatory cytokine, produced by a variety of immune cells, would prolong the joint inflammation if patients were untreated. Among these cytokines, tumor necrosis factor-α (TNFα) plays an important role in the inflammatory process, which can activate the immune cell and cause chronic inflammation [2]. Thus, TNFα became a fundamental target of anti-RA therapy. TNF inhibitors, which were first developed at the begging of the 2000s, have shown significant benefits in the treatment of RA. These agents can significantly improve the signs and symptoms of RA [3, 4], inhibit the progression of joint destruction [5, 6], and improve physical function and health-related quality of life (HEQ-oL) [5, 6], when used in combination with methotrexate (MTX).

Certolizumab pegol (CZP) is a relatively new member of the TNFα inhibitor family, which composed of a humanized Fab' fragment combined with polyethylene glycol (PEG) to increase its half-life [7]. As a Fc-free TNFα inhibitor, CZP does not lead to the formation of immune complexes, activation of complement, and the produce of antibody-dependent cytotoxicity [7]. The efficacy and safety of CZP in the treatment of active RA have been demonstrated in several studies [8, 9]. CZP, is clinically used in combination with MTX for the treatment of patients with

active RA, who failed to response to disease-modifying antirheumatic drug (DMARD). CZP can also be given as monotherapy in those who cannot tolerate MTX [10].

An early meta-analysis published in 2010 [11] compared the clinical efficacy of CZP with that of other anti-cytokine agents for the treatment of RA, and the authors found that CZP had a highest OR for ACR20 response, among these anti-cytokines agents. This meta-analysis confirmed the effects of CZP in the treatment of RA, however, the efficacy assessment of CZP was performed based on only two randomized controlled trials (RCTs), which gave a less statistical power to pool the estimates. And with the widely used of CZP around the world, more and more large-scale RCTs that evaluating the efficacy and safety of CZP have been conducted, thus, it is necessary to update the meta-analysis and provide a quantitative assessment of CZP in the treatment of RA. Moreover, in this updated meta-analysis, we also assess the effect of CZP in disease activity and patient-reported outcomes (PROs), as well as treatment-related adverse events, which had not been discussed in previous meta-analysis.

Methods

Literature search

Pubmed, Embase, and Web of Science databases (up to June 14, 2014) were searched to identify relevant studies, which assessed the efficacy and safety of CZP in the treatment of RA patients. The search items were generated as: ("certolizumab pegol" [Supplementary Concept] or "certolizumab pegol" [All Fields]) and ("arthritis, rheumatoid" [MeSH Terms] or ("arthritis" [All Fields] and "rheumatoid" [All Fields]) or "rheumatoid arthritis" [All Fields] or ("rheumatoid" [All Fields] and "arthritis" [All Fields]). The search was limited to human and RCTs, and no language limitation was imposed. We also reviewed the references cited in the included studies, to identify additional articles. When several trials with the same population were reported, we only chose the study with most informative or the latest data.

Study inclusion and exclusive criteria

All the published studies were included if they met the following inclusion criteria: (1) used a randomized controlled study design; (2) patients were ≥ 18 years old, and had a diagnosis of RA; (3) patients in the study arm were administered CZP or CZP-based therapy, while those in the control arm were administered placebo therapy; (4) evaluated the efficacy and safety of CZP in the treatment of AS; (5) provided interest data of American College of Rheumatology 20% (ACR20), ACR50, ACR70 response rates, disease activity and PROs, and the adverse events. Any studies that met the following exclusion criteria were excluded: (1) non-RCTs; (2) patients in the study group did not receive CZP or CZP-based therapy; (3) patients were aged less than 18 years old, or diagnosed with any other disease; (4) the study did not provide data of interest.

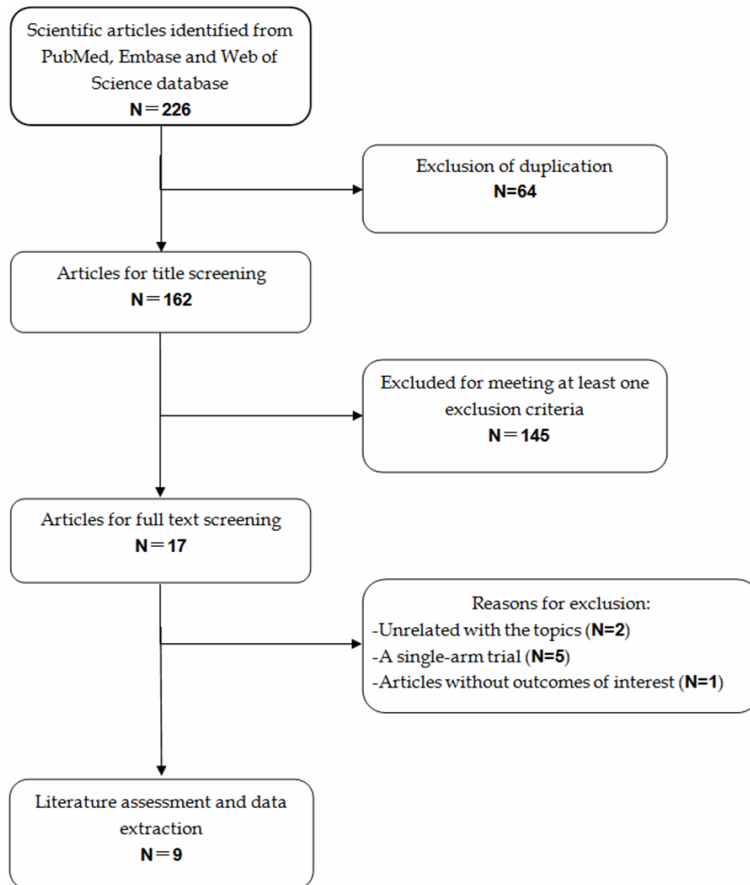### Data extraction and quality assessment

Two investigators (Qing Zhou and Yaodong Zhou) independently reviewed the eligible study and extracted the information as follows: the first author's name, year of publication, mean age, sample size (number of patients in the study arm and control arm), treatment regimen, ACR20/ACR50/ACR70 response rate, Health Assessment Questionnaire disability index (HAQ-DI) rate, mean and SE of Disease Activity Score in 28 joints-Erythrocyte sedimentation (DAS28-ESR) rate, and adverse events. The disagreements between two investigators were resolved by discussion and consensus.

To assess the methodological quality of each study, Jadad scale [12] was used in this meta-analysis. This scale consists of three items, including randomization (0-2 points), blinding (0-2 points), and dropouts and withdraws (0-1 point) to describe the quality of a RCT [12]. The full score is 5 and high score indicates better reporting. Studies with a score ≥ 3 points are considered as high quality [13].

Statistical analysis

We assessed the efficacy and safety of CZP in the treatment of AS based on the data from included studies. Cochran's Q statistic and the I^2 statistic were used to test the heterogeneity among the included studies, in which $I^2 > 50\%$ or chi-squared test $P < 0.1$ were considered as the existence of substantial heterogeneity. The meta-analysis was carried out to pool the estimates of the risk ratio (RR), or Weighted Mean

Figure 1. Identification of eligible randomized-controlled trials.

145 were excluded after the abstract and title review, leaving 17 for full text review. Among the remaining 17 studies, 8 were excluded for the following reasons: five studies were single-arm study design [18-22]; two studies reported outcomes unrelated with our topics [23, 24]; one study were excluded for no data available [25]. Finally, nine studies with a total of 5228 patients were included in this meta-analysis [8, 9, 26-32] (**Figure 1**). Of these included studies, the RA Prevention of Structural Damage 1 (RAPID1) [8, 30] trial and RAPID2 [9, 31] trial present two publications, respectively. However, both of the two publications reported different variables, thus, we included both of these publications.

Characteristics of eligible studies and quality assessment

Table 1 illustrated the baseline characteristics of the included studies. All studies for inclusion were selected strictly according to prior inclusion criteria. The sample size of included studies ranged from 194 to 1063. There were no statistical differences in the patients' baseline characteristics or disease activity status between the study group and control group. Among the 5228 eligible patients, 4122 (78.8%) of them were female, and 1106 (21.2%) were male. Patients in three trials [27, 29, 32] were administered CZP 400mg plus MTX or placebo, while patients in the remaining six trials [8, 9, 26, 28, 30, 31] received additional treatment regimens of CZP 200 mg plus MTX. Rheumatoid factor (RF) (≥ 14 IU/ml) positive were diagnosed in approximately 77.7% of the patients. According to the quality criteria, all of the nine studies had a high quality, and the median Jadad score was 4 (range from 4 to 5).

Primary endpoint: ACR20

Seven studies reported the data of ACR20 response rate [8, 9, 26-29, 32]. The aggregat-

Difference (WMD) and 95% confidence intervals (CIs), using a fixed-effect model [14] when there is no existence of substantial heterogeneity. Otherwise, a random-effect model [15] was used to calculate the estimates. We also intended to perform subgroup analysis according to the dosage of CZP. Publication bias was assessed by using the Begg [16] and Egger test [17]. A *P* value less than 0.05 was judged as statistically significant. All statistical analyses were conducted by using of STATA software version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Identification of eligible studies

A total of 226 studies were identified in the literature search, including 145 articles in Pubmed, 65 articles in Embase, and 16 articles in Web of Science. After a check for duplicates, 64 articles were removed, leaving 162 articles for abstract/title and full-text review. Of these,

Table 1. Baseline characteristics of the trials included in the meta-analysis

Study	Treatment	No. of patients	Age (mean ± SD, year)	Male/Female	Duration of disease (mean ± SD, year)	RF positive (%) (≥ 14 IU/ml)	HAQ-DI, mean ± SD	DAS28-ESR, mean ± SD	Jadad scale
Keystone E [8]	Placebo + MTX	199	52.2 ± 11.2	32/167	6.2 ± 4.4	82.8	1.7 ± 0.6	7.0 (4.9, 8.7)*	5
	CZP 200 mg + MTX	393	51.4 ± 11.6	69/324	6.1 ± 4.2	79.6	1.7 ± 0.6	6.9 (4.3, 8.9)*	
	CZP 400 mg +MTX	390	52.4 ± 11.7	64/326	6.2 ± 4.4	83.6	1.7 ± 0.6	6.9 (4.8, 9.1)*	
Yamamoto K [26]	Placebo + MTX	77	51.9 ± 11.1	11/66	5.8 ± 4.1	85.7	1.2 ± 0.7	6.5 ± 0.9	5
	CZP 200 mg +MTX	82	50.6 ± 11.4	13/69	5.6 ± 4.2	86.6	1.1 ± 0.7	6.2 ± 0.8	
	CZP 400 mg + MTX	85	55.4 ± 10.3	16/69	6.0 ± 3.9	89.4	1.1 ± 0.6	6.3 ± 0.8	
Fleischmann R [27]	Placebo	109	54.9 ± 11.6	12/97	10.4 ± 9.6	100.0	1.6 ± 0.65	6.3 ± 0.9	4
	CZP 400 mg	111	52.7 ± 12.7	24/87	8.7 ± 8.2	100.0	1.4 ± 0.63	6.3 ± 1.1	
Smolen J [9]	Placebo + MTX	127	51.5 ± 11.8	20/107	5.6 ± 3.9	78.2	1.6 ± 0.6	6.83 ± 0.87	4
	CZP 200 mg + MTX	246	52.2 ± 11.1	40/206	6.1 ± 4.1	77.5	1.6 ± 0.6	6.85 ± 0.84	
	CZP 400 mg + MTX	246	51.9 ± 11.8	54/192	6.5 ± 4.3	75.5	1.6 ± 0.6	6.80 ± 0.79	
Landewé R [28]	Placebo + MTX	107	39.9 ± 12.4	65/42	7.7 (0.3-50.9)*	NR	NR	NR	4
	CZP 200 mg + MTX	111	39.1 ± 11.9	67/44	6.9 (0.3-34.2)*	NR	NR	NR	
	CZP 400 mg + MTX	107	39.8 ± 11.3	68/39	7.9 (0.3-44.8)*	NR	NR	NR	
Smolen JS [29]	Placebo	98	54 ± 12.4	23/75	4.7 ± 3.3	67.3	1.0 ± 0.6	NR	5
	CZP 400 mg	96	53.6 ± 11.9	15/81	4.5 ± 3.5	74.0	1.1 ± 0.6	NR	
Strand V [30]	CZP 200 mg + MTX	393	51.4 ± 11.6	69/324	6.1 ± 4.2	79.6	1.7 ± 0.6	6.9 (4.3, 8.9)*	5
	CZP 400 mg + MTX	390	52.4 ± 11.7	64/326	6.2 ± 4.4	83.6	1.7 ± 0.6	6.9 (4.8, 9.1)*	
	Placebo + MTX	199	52.2 ± 11.2	32/167	6.2 ± 4.4	82.8	1.7 ± 0.6	7.0 (4.9, 8.7)*	
Strand V [31]	Placebo + MTX	127	51.5 ± 11.8	20/107	5.6 ± 3.9	78.2	1.6 ± 0.6	6.83 ± 0.87	4
	CZP 200 mg + MTX	246	52.2 ± 11.1	40/206	6.1 ± 4.1	77.5	1.6 ± 0.6	6.85 ± 0.84	
	CZP 400 mg + MTX	246	51.9 ± 11.8	54/192	6.5 ± 4.3	75.5	1.6 ± 0.6	6.80 ± 0.79	
Weinblatt ME [32]	Placebo	212	53.9 ± 12.7	43/169	8.9 ± 9.1	76.5	1.6 ± 0.6	5.7 ± 0.9	4
	CZP 400 mg	851	55.4 ± 12.4	191/660	8.6 ± 8.8	73.9	1.5 ± 0.6	5.7 ± 0.9	

*data are expressed with median (minimum, maximum). MTX, methotrexate; CZP, certolizumab pegol; RF, rheumatoid factor; HAQ, Health Assessment Questionnaire; DI, disability index; DAS28, Disease Activity Score 28-joint assessment; ESR, erythrocyte sedimentation rate.
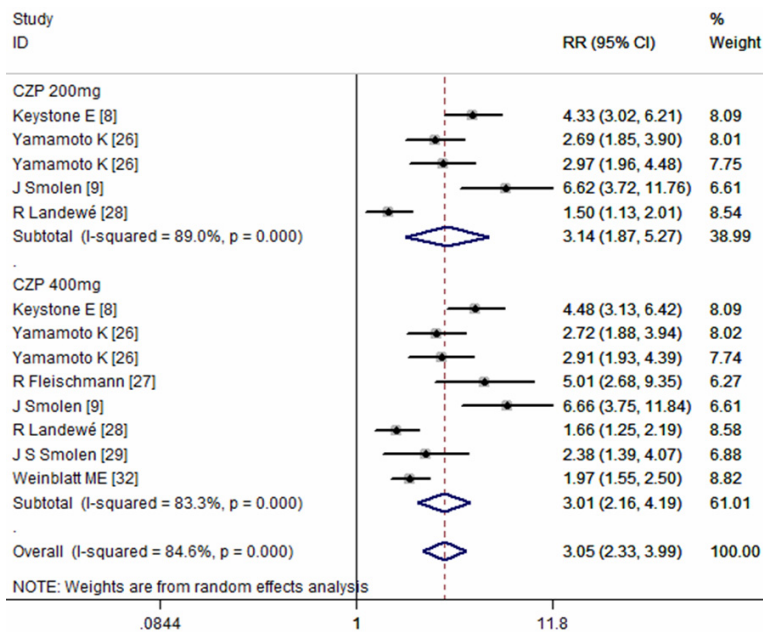
Figure 2. Comparison of certolizumab pegol (CZP) with placebo for active ankylosing spondylitis (AS) patients in terms of ACR20 response rate.
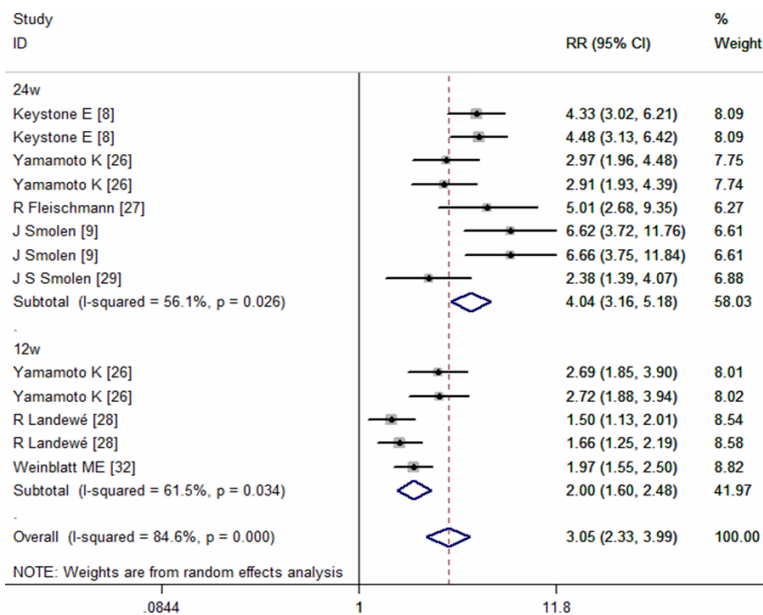
Figure 3. Subgroup analysis of ACR20 response rate for the treatment of certolizumab pegol (CZP) versus placebo.
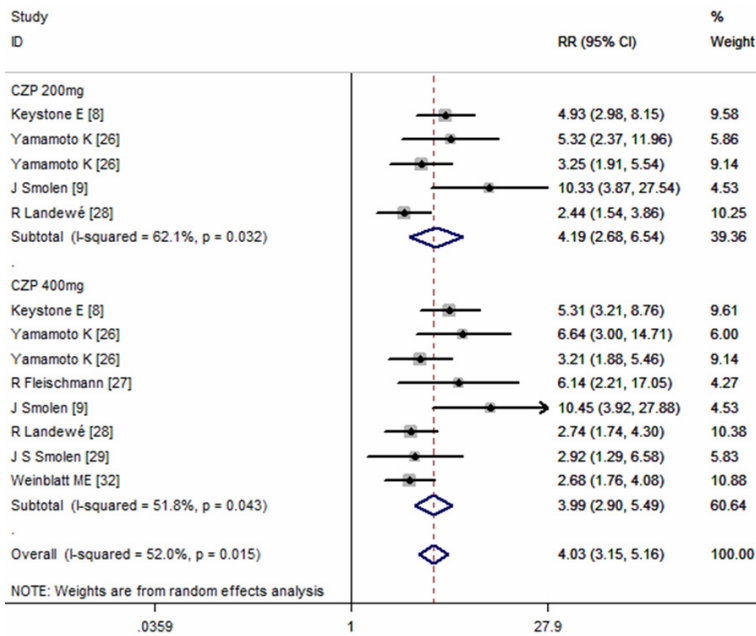
Subgroup analysis based on CZP dosage showed that, RA patients who were treated with 200 mg or 400 mg of CZP plus MTX had a higher ACR20 response rate, compared with those treated with placebo (for CZP 200 mg: RR = 3.14, 95% CI: 1.87, 5.27, P = 0.000; for CZP 400 mg: RR = 3.01, 95% CI: 2.16, 4.19, P = 0.000) (**Figure 2**).

Subgroup analysis based on the different time-endpoints suggested that ACR20 response rates at either week 12 or 24 were superior in the CZP plus MTX group than that in the placebo group (at week 12: RR = 2.00, 95% CI: 1.60, 2.48, P = 0.000; at week 24: RR = 4.04, 95% CI: 3.16, 5.18, P = 0.000) (**Figure 3**). The Begg's and Egger's test suggested that there were no publication bias (for Begg's test, Z = 0.99, P = 0.322; for Egger's test, t = 0.12, P = 0.907).

Secondary endpoints: ACR50, ACR70

Seven of the included studies provided data of ACR50 response rate [8, 9, 26-29, 32]. The pooled estimates using random-effect model showed that CZP plus MTX significantly increase ACR50 response rate in the treatment of active RA patients (RR=4.03, 95% CI: 3.15, 5.16; P = 0.000) (**Figure 4**). According to the subgroup analysis based on different CZP dosage and time end-points, we found that, at any time point examined, ACR50 response rates for those receiving 200 mg or 400 mg of CZP plus MTX were significant higher than those treated with placebo alone (for CZP 200 mg: RR = 4.19, 95% CI: 2.68, 6.54, P = 0.000; for CZP 400 mg: RR = 3.99, 95% CI: 2.90, 5.49, P = 0.000; at week 12: RR = 3.13,

ed results showed that CZP plus MTX significantly improved ACR20 response rate in the treatment of RA (RR = 3.05, 95% CI: 2.33, 3.99; P = 0.000) (**Figure 2**). The test for heterogeneity was significant (P = 0.000, I^2 =84.6%). Thus, we performed subgroup analysis to identify the potential sources of heterogeneity.

Figure 4. Comparison of certolizumab pegol (CZP) with placebo for active ankylosing spondylitis (AS) patients in terms of ACR50 response rate.
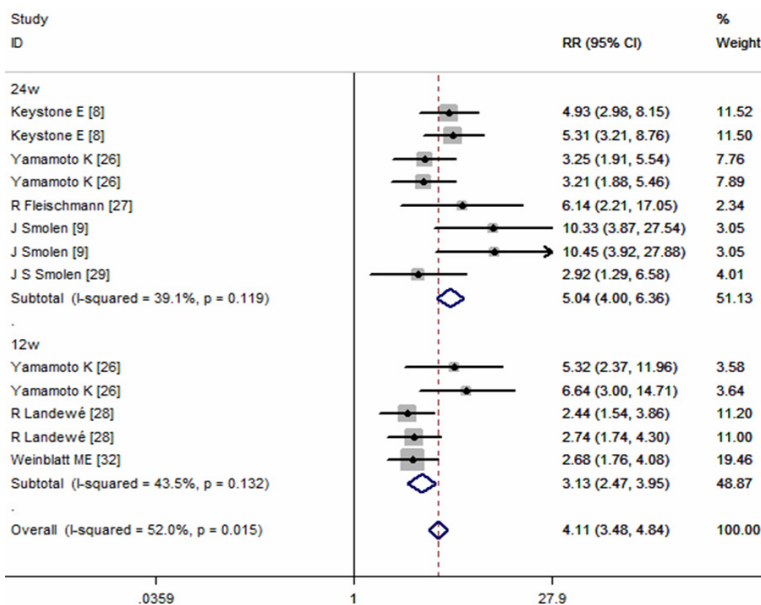
Figure 5. Subgroup analysis of ACR50 response rate for the treatment of certolizumab pegol (CZP) versus placebo.

95% CI: 2.47, 3.95, P = 0.000; at week 24: RR = 5.04, 95% CI: 4.00, 6.36, P = 0.000) (**Figures 4, 5**).

Six studies reported the data in ACR70 [8, 9, 26, 27, 29, 32]. The pooled results using a fixed-effect model indicated that, RA patients

treated with CZP plus MTX had benefit in ACR70, compared to those treated with placebo (RR = 8.66, 95% CI: 5.93, 12.65; P = 0.000) (**Figure 6**). Subgroup analysis based on different CZP dosage and time end-points were performed, and the results showed that, CZP plus MTX significantly improved ACR70 response rate in the treatment of RA patients, irrespective of the CZP dosage or time point examined (for CZP 200 mg: RR = 10.08, 95% CI: 5.11, 19.89, P = 0.000; for CZP 400 mg: RR = 6.52, 95% CI: 3.90, 10.88, P = 0.000; at week 12: RR = 7.76, 95% CI: 3.85, 15.65, P = 0.000; at week 24: RR = 9.06, 95% CI: 5.77, 14.22, P = 0.000) (**Figures 6, 7**).

We performed the Begg's and Egger's test for ACR50 and ACR70 to assess the presence of any publication bias. No evidence of obvious publication bias was found (for ACR50: Begg's test, Z = 1.50, P = 0.133, Egger's test, t = 1.22, P = 0.276; for ACR70: Begg's test, Z = 0.75, P = 0.452, Egger's test, t = 2.31, P = 0.082).

*Disease activity and patient-reported outcomes*

Four studies reported the results of DAS28-ESR [8, 9, 27, 32]. The pooled analysis using random-effect model showed a significantly reduction in DAS28-ESR (WMD = -1.25, 95% CI:-1.60, -0.89; P = 0.000) (**Figure 8**), with significant heterogeneity between the studies (I^2 = 97.8%, P = 0.000).

Four studies provided the data of PROs, including HAQ-DI, arthritis pain, and fatigue. The pooled results showed that CZP plus MTX significantly reduced the incidence of arthritis
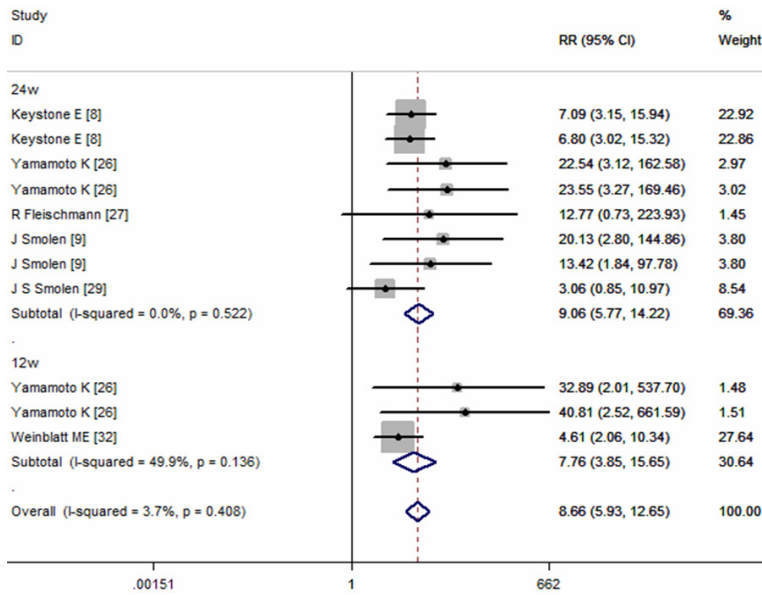
Figure 6. Comparison of certolizumab pegol (CZP) with placebo for active ankylosing spondylitis (AS) patients in terms of ACR70 response rate.
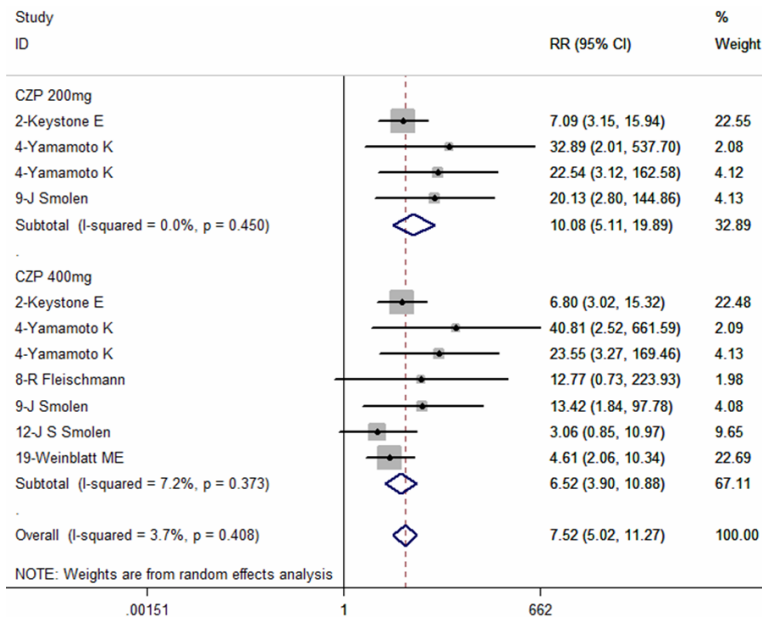
Figure 7. Subgroup analysis of ACR70 response rate for the treatment of certolizumab pegol (CZP) versus placebo.

pain (RR = 4.00, 95% CI: 3.14, 5.09; P = 0.000), fatigue (RR = 3.79, 95% CI: 2.90, 4.95; P = 0.000) and improved the physical function (RR = 4.57, 95% CI: 3.84, 5.44; P = 0.000), compared with controls (**Figure 9**).

Adverse events

Six studies reported the data of adverse events (AEs) [8, 9, 26-28, 32]. The most frequent non-

infectious treatment-related AEs were headache, hypertension, and back pain. And the most frequent reported infectious AEs were urinary tract infections, nasopharyngitis, and upper respiratory tract infections. The pooled analysis using a random-effect model suggested that, the incidence of AEs in the CZP plus MTX group and control group was not statistically significant differences, no matter in mild adverse events (RR = 1.12, 95% CI: 0.81, 1.55; P = 0.000), moderate adverse events (RR = 1.01, 95% CI: 0.82, 1.25; P = 0.000), or severe adverse events (RR = 0.93, 95% CI: 0.70, 1.25; P = 0.000) (**Figure 10**).

Discussion

This meta-analysis demonstrated that CZP (200 or 400 mg) combined with MTX was associated with significantly higher ACR20, ACR50 and ACR70 response rates at week 12 and 24, and had amelioration in PROs, including HAQ-DI, arthritis pain, and fatigue, in the treatment of patients with active RA. The incidence of AEs (any intensity) between the CZP group and control group was not statistically significant difference. This study confirmed the clinical benefits of CZP in the treatment of active RA, with rapid, significant and clinical meaningful improvements in multiple PROs, and ACR20/ ACR50/ACR70 response rates, which was observed at week 12, and maintained until at week 24.

In a previously published meta-analysis [11], another three licensed anti-TNF agents, including adaliumab, infliximab, and etanercept, showed significantly efficacy in the treatment of RA, when compared with placebo. Interestingly, all these agents contain an immunoglobulin G
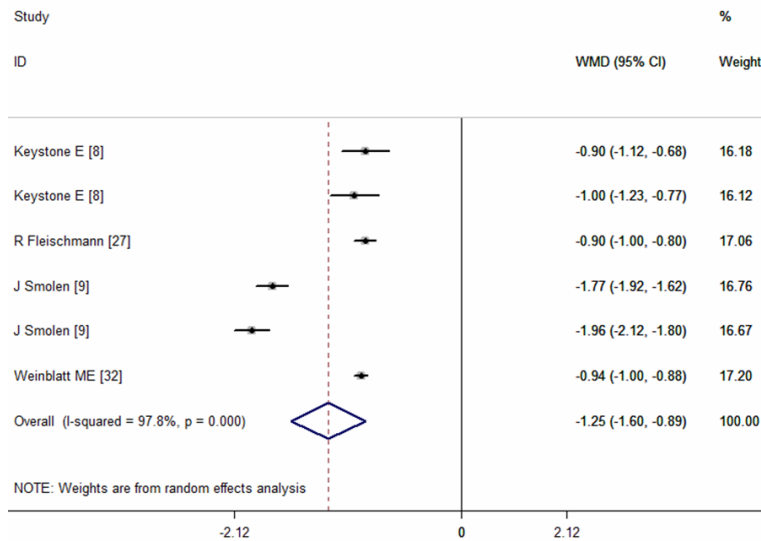
Figure 8. Disease Activity Score 28-joint assessment erythrocyte sedimentation rate (DAS28-ESR) for the treatment of certolizumab pegol (CZP) versus placebo.
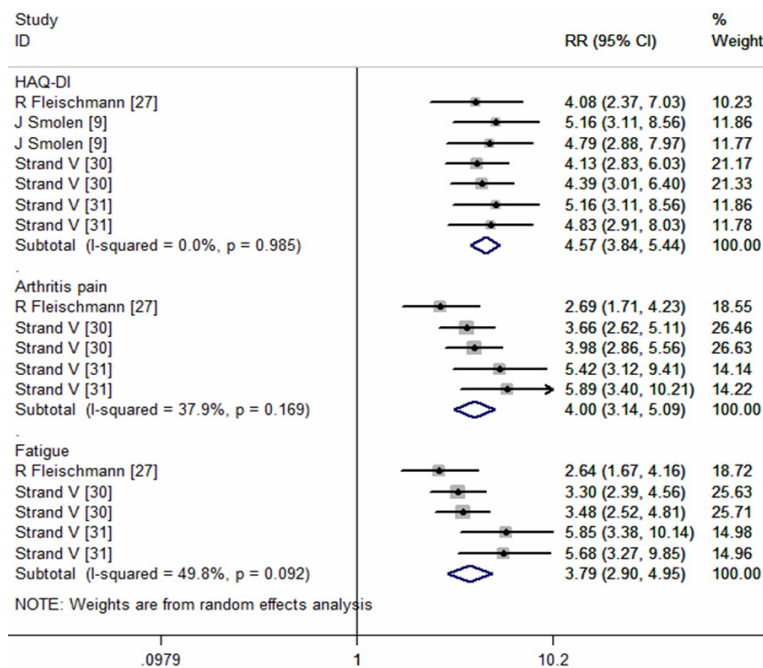
Figure 9. Patients-reported outcomes (PROs) for the treatment of certolizumab pegol (CZP) versus placebo.

signaling [33, 34]. This meditation process could also be activated by Fc free Fab' molecule such as CZP.

According to this meta-analysis, we found that the combination treatment of CZP with MTX significantly improved the ACR20/50/70 response rates in RA patients. And these clinical benefits were observed from 12 week until 24 week. Moreover, we also found that both dose of CZP significantly inhibited the progression of joint damage, increased physical function and quality of life, compared with placebo, which suggested that CZP 200 mg every 2 week could be recommended as an optimal treatment.

The treatment of CZP had an acceptable safety profile in that the incidence of adverse events (any intensity) was not significantly difference between the CZP and placebo group. However, more serious adverse events were observed in the RAPID2 [9], JRAPID [26], FAST4WARD [27], and REALISTIC [32] trials. A possible explanation is that the patients in the CZP group had longer treatment exposure compared with that in the control group, since those patients in the latter withdrew from the trials because of inefficacy treatment. In our study, the safety profile assessment was based on a short-term analysis with the event end-point at 24 week. Thus, whether CZP would bring additional treatment-related events after a few years' administration remains unclear. In a recently published integrated analysis study, Bykerk VP et al. [35] assessed the long-term safety profile of CZP, in which a total of 4049 patients were exposed to the CZP treatment up to 7.6 years [35]. He found no new safety events reported in the

Fc portion, which is lacking in CZP. This suggests that the immunoglobulin G Fc portion may not be necessary for TNF inhibitors to be active in the treatment of RA. Therefore, the primary mode of action of TNF inhibitors in RA may not be associated with Fc mediated effects, but the blockage of TNF by reversing
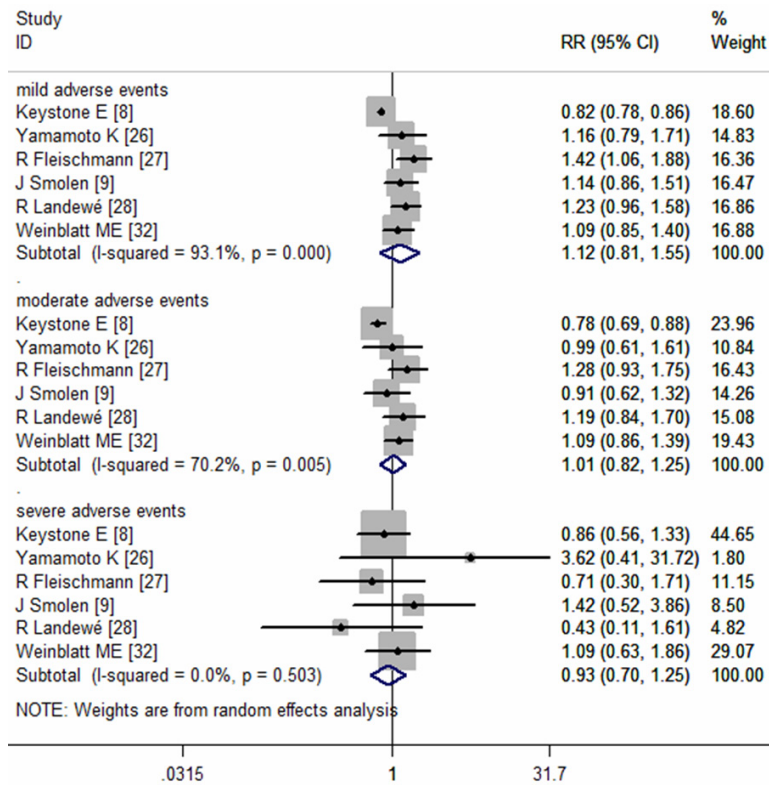
Figure 10. The risk ratio of treatment-related adverse events (AEs) in AS patients with certolizumab pegol (CZP) versus placebo.

long-term data. And the incidence of adverse events in the CZP group was similar to that in the control group.

Our meta-analysis has several strengths and limitations which should be considered when interpreting our results. First, a major strength of our study is that all of the available data were obtained from RCTs, and most of the studies were well performed, high-quality (Jadad scale ≥ 3). Second, all the included studies have enlarged sample size, which enhanced statistical power to provide reliable effect estimates. Although our meta-analysis represents a complete summary of the efficacy of CZP for RA patients, it also serves to note the potential limitations. First, the variety of criteria was used to define RA. In the majority of the studies, the definition of RA was based on American College of Rheumatology (ACR) 1987 criteria. Second, there was considerable heterogeneity among the included studies, including different population, duration of disease, disease activity status, prior disease-modifying antirheumatic drug (DMARDs). These factors would have

potential impacts on our results. Third, in this meta-analysis, we only assessed the efficacy and safety of CZP at week 12 and 24. And we also tried to assess the long-term effect and safety of CZP in the treatment of RA. However, there was insufficient data for us to pool the estimates. Thus, a further long-term evaluation for the effect of CZP is urgently needed.

In summary, this meta-analysis demonstrated that CZP 200 or 400 mg was clinically effective in the treatment of active RA patients, with an improvement in ACR20/ACR-50/ACR70 response rates, and amelioration in PROs. The incidence of AEs in the CZP group was not statistically significant different with that in the control group. However, considering the heterogeneity among the included studies, more large-scale, well-designed RCTs are urgently needed.

Disclosure of conflict of interest

None.

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