Systematic Review and Meta-Analysis

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A systematic review and meta-analysis of rituximab combined with methotrexate versus methotrexate alone in the treatment of rheumatoid arthritis

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Abstract

Background: This meta-analysis aimed to explore the efficacy and safety of rituximab combined with methotrexate (MTX) versus MTX alone in the treatment of rheumatoid arthritis (RA).

Methods: We performed an electronic search of PubMed (1950–January 2018), EMBASE (1974–January 2018), the Cochrane Library (January 2018 Issue 3), the Google database (1950–January 2018), and the Chinese Wanfang database (1950–January 2018). Only randomized controlled trials (RCTs) were included. The American College of Rheumatology 20% improvement criteria (ACR20), ACR50, ACR70, total complication rate, and infection rate were the outcomes. A fixed/random effects model was used according to the heterogeneity assessed by the I^2 statistic. Data analysis was performed using Stata 12.0 software.

Results: A total of five RCTs with 3299 patients (rituximab combined with MTX group = 1787, MTX only group = 1512) were included in the meta-analysis. The pooled risk ratio showed that the administration of rituximab combined with MTX was associated with more ACR20, ACR50, and ACR70 than the administration of MTX only ($P < .05$). There were no significant differences between the two groups in terms of the total complication rate and the infection rate ($P > .05$).

Conclusion: The administration of rituximab combined with MTX was effective and safe for RA patients. Additional high-quality RCTs with long-term follow-ups should be conducted in the future to identify the potential complications in the long term.

Abbreviations: ACR20 = American College of Rheumatology 20% improvement criteria, CI = confidence interval, MTX = methotrexate, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RA = rheumatoid arthritis, RCTs = randomized controlled trials, RR = risk ratio.

Keywords: meta-analysis, rheumatoid arthritis, rituximab

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by symmetric inflammation in the affected joints.[1,2] RA affects nearly 1% of the population and is considered a significant cause of disability.[3–5] Thus, RA causes a heavy economic burden on individuals and the society as a whole. The etiology and pathogenesis of RA is still unclear. It is well known that immune cells, such as T lymphocytes and B lymphocytes, participate in the development of RA.[6]

Rituximab is a genetically engineered chimeric monoclonal antibody that targets CD20+ B cells.[7]

The efficacy and safety of rituximab combined with methotrexate (MTX) in the treatment of RA was disputed and requires further analyses. To further investigate the efficacy and safety of rituximab when administered in combination with MTX, we conducted a meta-analysis and attempted to identify the efficacy and safety of rituximab combined with MTX versus MTX alone in the treatment of RA patients.

2. Materials and methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] No ethical approval was necessary for this article because this study type was systematic review.

2.1. Search strategies

The following databases were searched in October 2017 without restrictions on the language or publication type: PubMed (1950–January 2018), EMBASE (1974–January 2018), the Cochrane Library (January 2018 Issue 3), the Google database (1950–January 2018), and the Chinese Wanfang database (1950–January 2018). The following MeSH terms and their combinations were used in the search: "rituximab" OR ""Rituximab"[Mesh]"

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OR "CD20 Antibody", "Rituximab CD20 Antibody", "Mabthera", "IDEC-C2B8 Antibody", "IDEC C2B8 Antibody", "IDEC-C2B8", "IDEC C2B8" "GP2013", and "Rituxan" AND "rheumatoid arthritis" OR ""Arthritis, Rheumatoid"[Mesh]". The reference lists of the related review articles and original studies were searched for any relevant studies, including randomized controlled trials (RCTs) involving adult humans. There was no restriction on the language or publication date. When multiple reports describing the same sample were published, the most recent or most complete report was used.

2.2. Inclusion criteria and study selection

The inclusion criteria were as follows: patients, patients diagnosed with RA according to the according to the American College of Rheumatology (ACR) 1987 revised criteria; intervention, the use of rituximab combined with MTX; comparison, MTX as the control; outcomes, the American College of Rheumatology 20% improvement criteria (ACR20), ACR50, ACR70, total complication rate, and the occurrence of infections; and study design, RCT.

Two independent reviewers screened the titles and abstracts of the identified studies after removing duplicates from the search results. Any disagreements about the inclusion or exclusion of a study were solved by discussion or consultation with an expert. The reliability of the study selection process was determined by Cohen kappa test, and the acceptable threshold value was set at 0.61.[6,7]

2.3. Data abstraction and quality assessment

A specific extraction process was conducted to collect data in a predefined standard Microsoft Excel (Microsoft Corporation, Redmond, WA) file. The items extracted from relevant studies were as follows: first author and publication year; sample size; mean age of the intervention group and control groups; dose of rituximab and MTX and the follow-up duration. Outcomes, such as the ACR20, ACR50, ACR70, total complication rate, and the occurrence of infections, were abstracted and recorded in the spreadsheet. Data that was presented in other formats (i.e., median, interquartile range, and mean ± 95% confidence interval [CI]) were converted to the mean ± standard deviation according to the Cochrane Handbook.[9] If the data were not reported numerically, we extracted them from the published figures using "GetData Graph Digitizer" software. All data were extracted by two independent reviewers, and disagreements were resolved by discussion.

The quality of all included trials was independently assessed by two reviewers on the basis of the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://www.cochrane-handbook.org/).[9] A total of seven domains were used to assess the overall quality: random sequence generation; allocation concealment; blinding of the participants and personnel; blinding of the outcome assessors; incomplete outcome data; selective reporting and other biases. Each domain was measured as low bias, unclear bias, or high bias.

2.4. Outcome measures and statistical analysis

Discontinuous outcomes (the ACR20, ACR50, ACR70, total complication rate, and occurrence of infections) were expressed as risk ratios (RRs) with 95% CIs. The level of statistical significance was set to be $P < .05$ to summarize the findings across the trials. Variables in the meta-analysis were calculated using Stata software, version 12.0 (Stata Corp., College Station, TX). Statistical heterogeneity was evaluated using the chi-squared test and the I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .1$), a fixed effects model was adopted; otherwise, a random effects model was used. Publication bias was tested and visually assessed using funnel plots and quantitatively assessed using Begg test. We considered there to be no publication bias if the funnel plot was symmetrical and the P-value was $> .05$.

3. Results

3.1. Search results and general characteristics

A study flow diagram of the included studies can be seen in Figure 1. In the initial search, 194 studies were identified from the electronic databases, and no additional records were identified through other sources. All papers were then inputted into

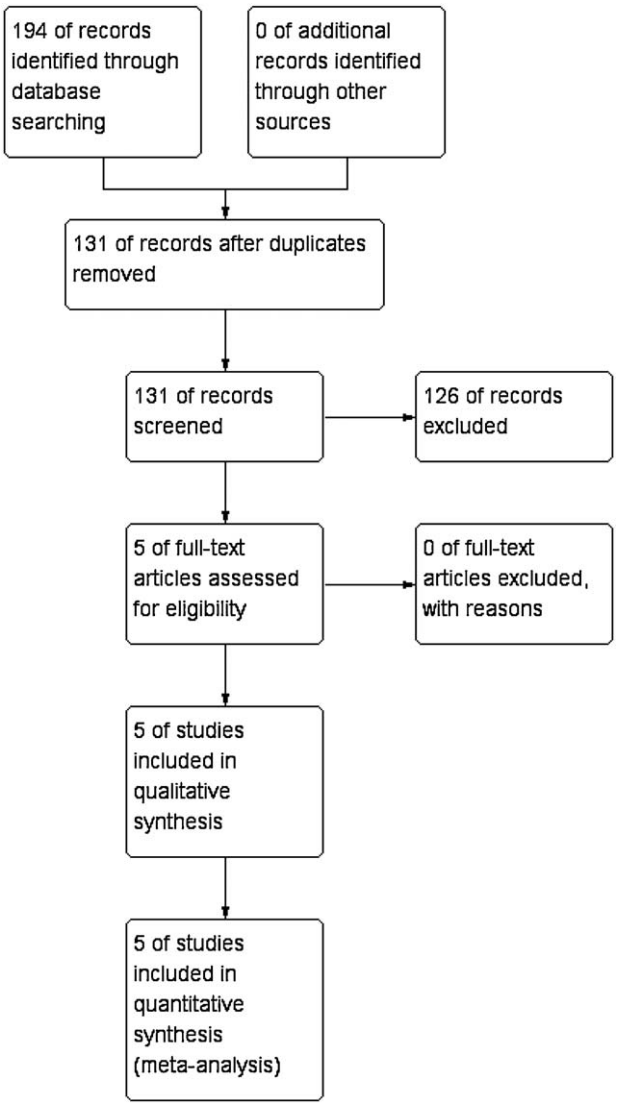

Figure 1. PRISMA flow chart of the retrieved studies. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

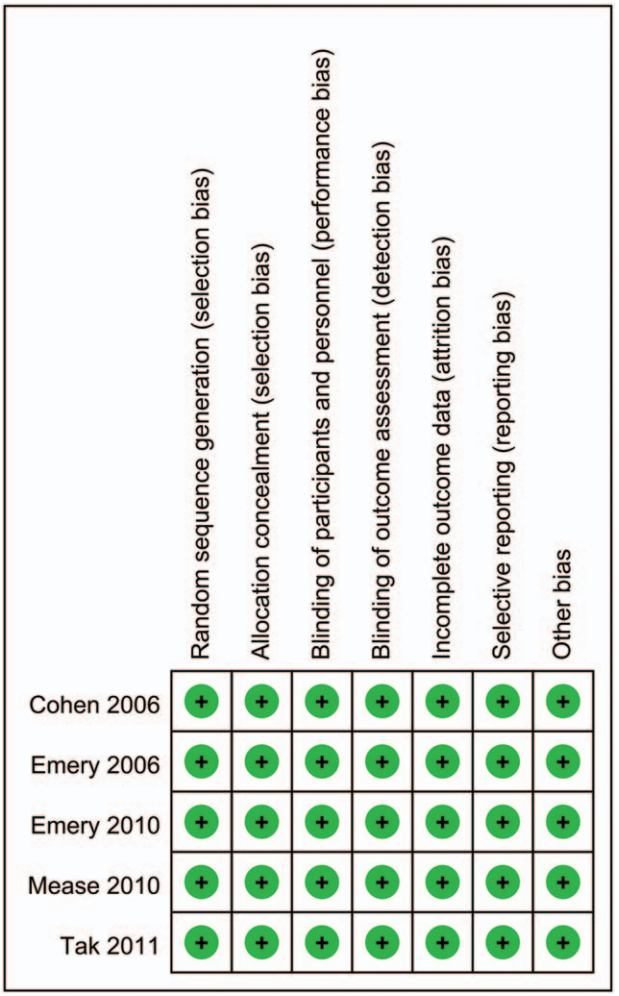

Figure 2. Risk of bias summary of the included studies.

Endnote X7 (Thomson Reuters Corp., USA) software for the removal of duplicate papers. A total of 131 papers were reviewed, and 126 were removed according to the inclusion criteria at the abstract and title levels. Since, four studies involved different doses of rituximab and one was divided into two separate studies, ultimately, five RCTs with 3299 patients (rituximab combined with MTX group = 1787, MTX only group = 1512) were included in this meta-analysis.[10–14]

The general characteristics of the included studies are shown in Table 1. There were two multicenter RCTs, and the remaining three RCTs were single-center RCTs. The mean age of the patients ranged from 47.9 to 54.0 years. The follow-up duration ranged from 24 to 52 weeks.

3.2. Quality of the included studies

The risk of bias summary and risk of bias graph are shown in Figure 2. All five included RCTs were reported using appropriate randomization techniques and were rated as having a low risk of bias. Other biases (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias) were all associated with a low risk of bias.

4. Results of the meta-analysis

4.1. ACR20

A total of eight included studies (3033 patients) reported data on the ACR20 after treatment. The pooled meta-analysis indicated that there was large statistical heterogeneity between the included studies ($I^2 = 97.2\%$, $P = .000$), so a random effects model was adopted to determine the effect size. The pooled RR showed that the administration of rituximab combined with MTX was associated with more ACR20 than the administration of MTX alone (RR = 1.44, 95% CI: 1.34–1.54, $P = .000$, Fig. 3).

A subgroup analysis was performed according to the dose of rituximab (1000 or 500 mg). Both 1000 mg rituximab and 500 mg rituximab can increase the ACR20 compared to the control group (1000 mg, RR = 1.59, 95% CI: 1.45–1.75, $P = .000$; 500 mg, RR = 1.21, 95% CI: 1.10–1.34, $P = .000$, Fig. 3).

4.2. ACR50

A total of eight included studies (3480 patients) reported data on the ACR50 after treatment. The pooled meta-analysis indicated that there was large statistical heterogeneity between the included studies ($I^2 = 86.3\%$, $P = .000$), so a random effects model was adopted to determine the effect size. The pooled RR showed that the administration of rituximab combined with MTX was associated with more ACR50 than the administration of MTX alone (RR = 1.73, 95% CI: 1.56–1.92, $P = .000$, Fig. 4).

A subgroup analysis was performed according to the dose of rituximab (1000 or 500 mg). Both 1000 mg rituximab and 500 mg rituximab can increase the ACR50 compared to the control group (1000 mg, RR = 1.79, 95% CI: 1.58–2.03, $P = .000$; 500 mg, RR = 1.63, 95% CI: 1.37–1.93, $P = .000$, Fig. 4).

4.3. ACR70

A total of eight included studies (2937 patients) reported data on the ACR70 after treatment. The pooled meta-analysis indicated that there was large statistical heterogeneity between the included

Table 1

The general characteristic of the included studies.

Author	Country	Mean age (years)	Intervention	Controls	Study	Follow-up
Cohen 2006	USA	52.2 vs 52.8	1000 mg or 500 mg rituximab plus methotrexate	Methotrexate	Multicenter RCTs	24 weeks
Emery 2010	USA	51.9 vs 52.1	1000 mg or 500 mg rituximab plus methotrexate	Methotrexate	Multicenter RCTs	24 weeks
Emery 2006	USA	51.4 vs 51.1	1000 mg or 500 mg rituximab plus methotrexate	Methotrexate	RCTs	24 weeks
Mease 2010	USA	54.0 vs 54.0	1000 mg rituximab plus methotrexate	Methotrexate	RCTs	24 weeks
Tak 2011	Europe	47.9 vs 48.1	1000 mg or 500 mg rituximab plus methotrexate	Methotrexate	RCTs	52 weeks

RCTs = randomized controlled trials.

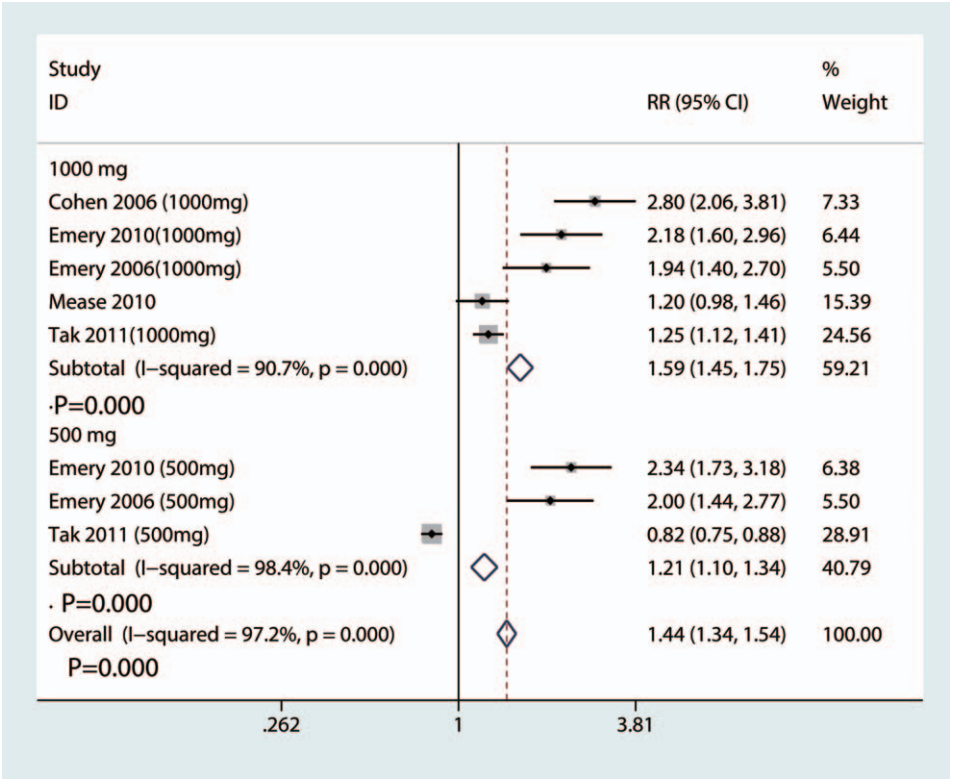

Figure 3. Forest plot comparing the ACR20 between the rituximab combined with methotrexate and methotrexate only groups. ACR20 = American College of Rheumatology 20% improvement criteria.

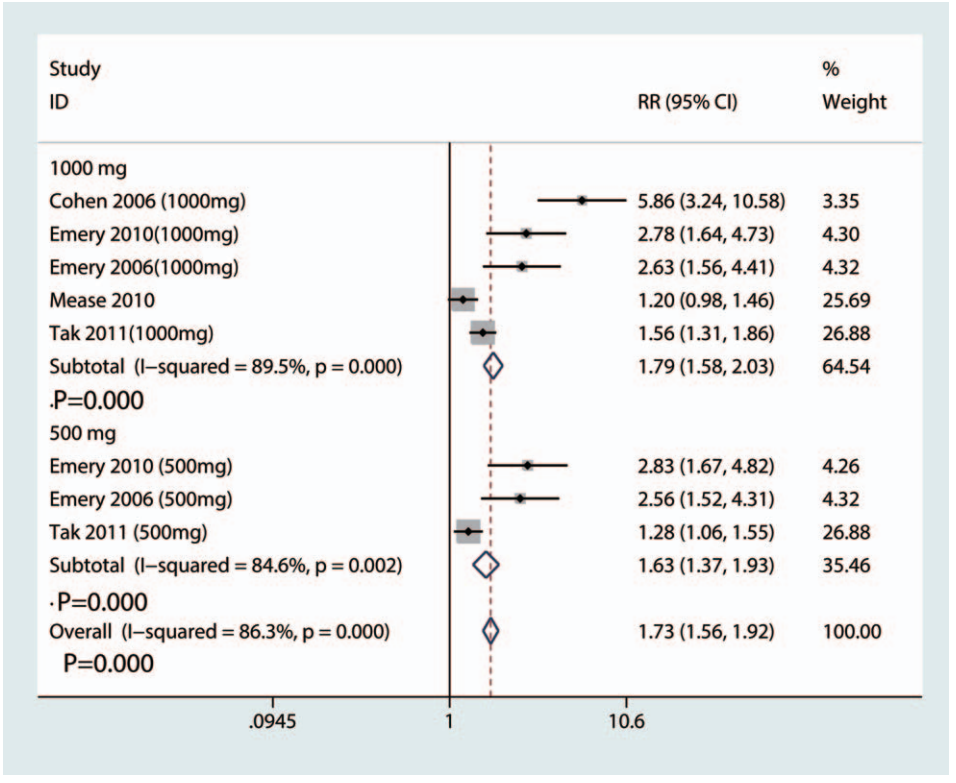

Figure 4. Forest plot comparing the ACR50 between the rituximab combined with methotrexate and methotrexate only groups. ACR50 = American College of Rheumatology 50% improvement criteria.

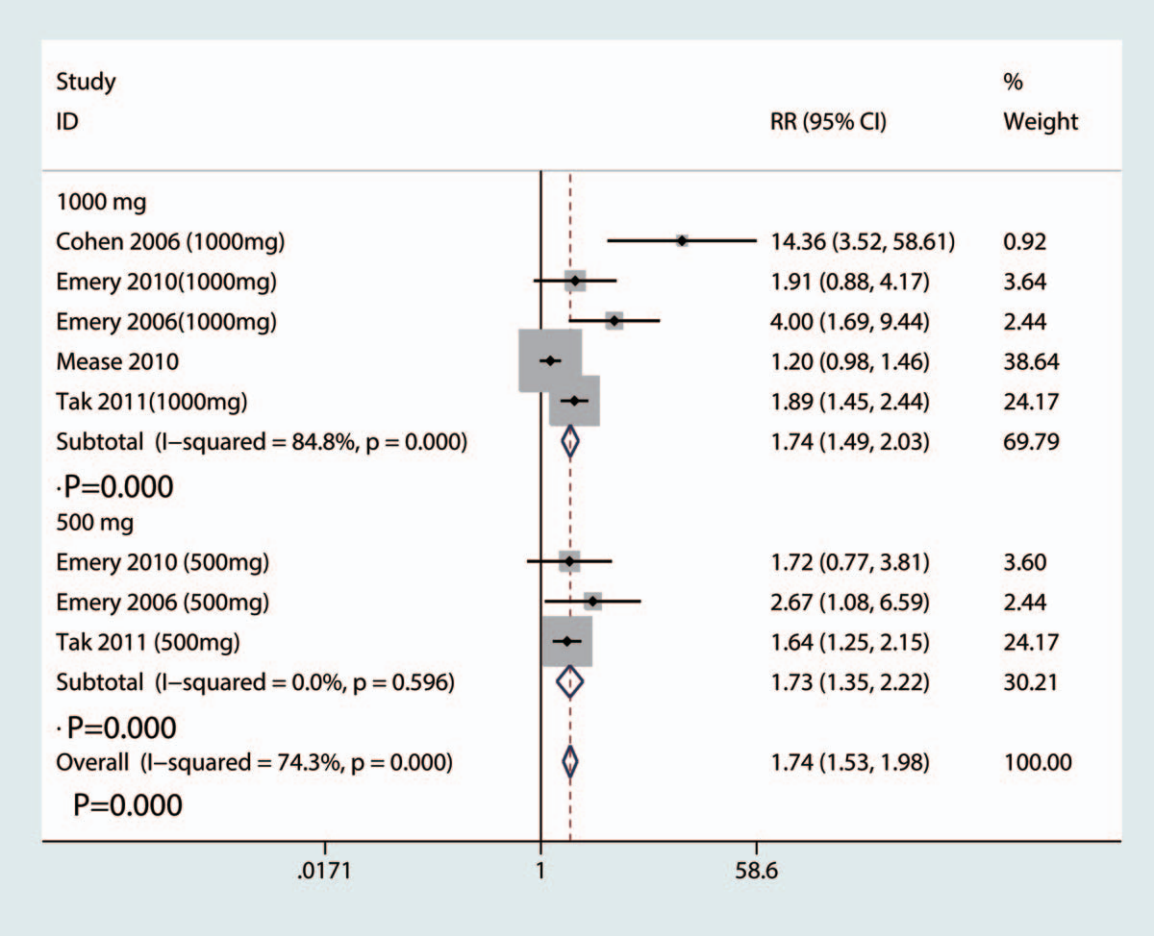

Figure 5. Forest plot comparing the ACR70 between the rituximab combined with methotrexate and methotrexate only groups. ACR70 = American College of Rheumatology 70% improvement criteria.

studies (I^2 = 74.3%, P = .000), so a random effects model was adopted to determine the effect size. The pooled RR showed that the administration of rituximab combined with MTX was associated with more ACR70 than the administration of MTX alone (RR = 1.74, 95% CI: 1.53–1.98, P = .000, Fig. 5). A subgroup analysis was performed according to the dose of rituximab (1000 or 500 mg). Both 1000 mg rituximab and 500 mg rituximab can increase the ACR70 compared to the control group (1000 mg, RR = 1.74, 95% CI: 1.49–2.03, P = .000; 500 mg, RR = 1.73, 95% CI: 1.35–2.22, P = .000, Fig. 5).

4.4. Total complications

A total of seven included studies (3299 patients) reported data on the patients who needed transfusion after scoliosis surgery. The pooled meta-analysis indicated that there was large statistical heterogeneity between the included studies (I^2 = 66.6%, P = .004), so a random effects model was adopted to determine the effect size. The pooled RR showed no significant difference between rituximab combined with MTX and MTX alone in terms of the total complication rate (RR = 1.00, 95% CI: 0.96–1.03, P = .786, Fig. 6).

There was no significant difference in the occurrence of complications between different doses of rituximab (1000 mg, RR = 1.00, 95% CI: 0.96–1.04, P = .967; 500 mg, RR = 0.99, 95% CI: 0.94–1.04, P = .640, Fig. 6).

4.5. The occurrence of infections

A total of seven included studies (3480 patients) reported data on the occurrence of infections. The pooled meta-analysis indicated that there was large statistical heterogeneity between the included studies (I^2 = 50.0%, P = .051), so a random effects model was adopted to determine the effect size. The pooled RR showed no significant difference between rituximab combined with MTX and MTX alone in terms of the occurrence of infections (RR = 1.00, 95% CI: 0.91–1.10, P = .973, Fig. 7). A subgroup analysis was performed according to the dose of rituximab (1000 or 500 mg). The results are shown in Fig. 7, and there was no significant difference in the occurrence of infections between different doses of rituximab (1000 mg, RR = 1.00, 95% CI: 0.91–1.10, P = .592; 500 mg, RR = 1.00, 95% CI: 0.91–1.10, P = .538, Fig. 7).

5. Discussion

This is the first meta-analysis comparing rituximab combined with MTX versus MTX alone for the treatment of RA. The final results indicated that rituximab combined with MTX obtained

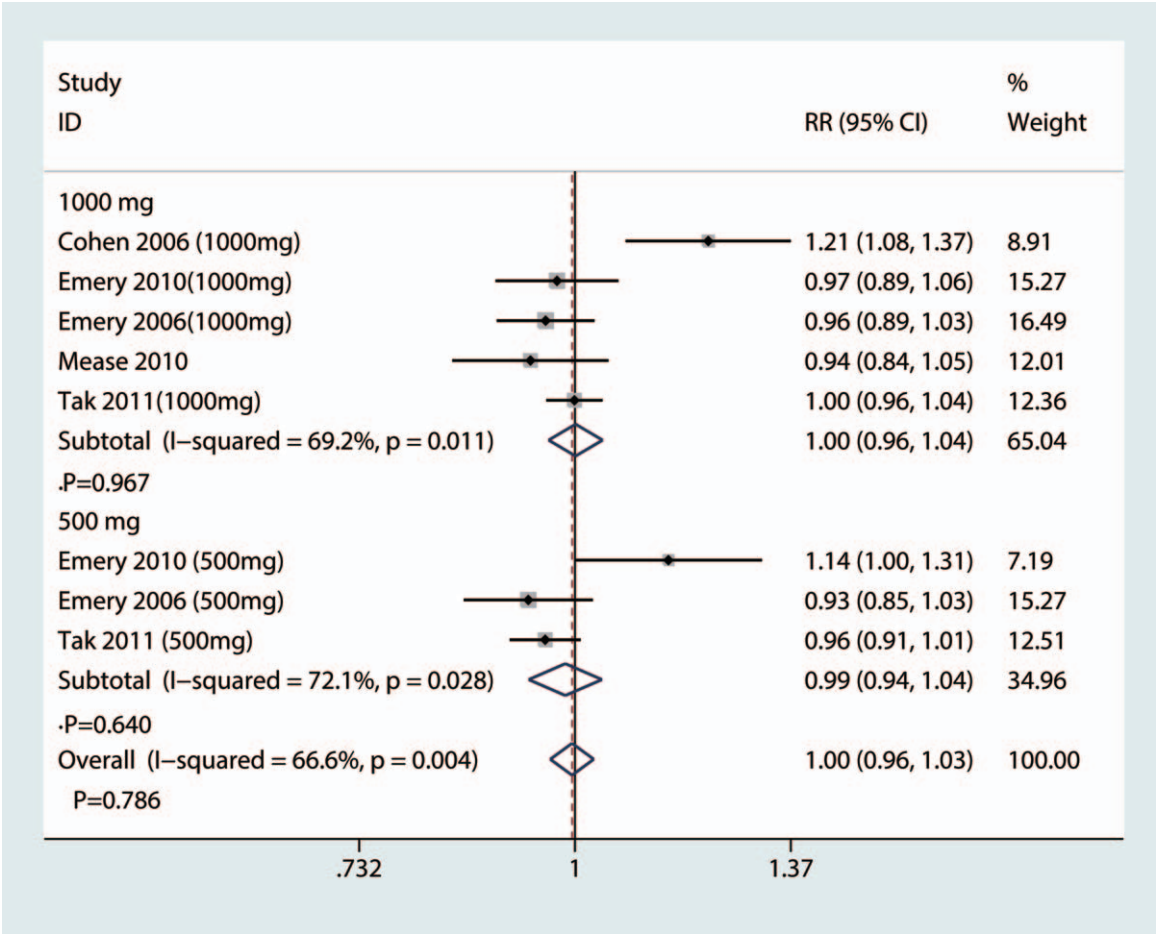

Figure 6. Forest plot comparing the total complication rate between the rituximab combined with methotrexate and methotrexate only groups.

better clinical outcomes than MTX alone. The clinical outcomes reflecting more ACR20, ACR50, and ACR70 are clinically significant. Furthermore, there was no significant difference between groups in the complication rate and the occurrence of infections. In addition, a high dose of rituximab combined with MTX was superior to MTX alone in terms of the ACR20 only.

Rituximab is a monoclonal antibody directed to CD20 molecules and has been used for many years. Singh et al[15] conducted a meta-analysis on the biologics of tofacitinib for people with RA naive to MTX. The final results showed that biologics with MTX used in MTX-naive populations are beneficial and that there is little/inconclusive evidence of harm.

There was no significant difference in the total complication rate in this meta-analysis. Common complications include headache, nausea, and diarrhea. We synthesized these results and found no significant difference between rituximab combined with MTX and MTX alone ($P > .05$). A subgroup analysis was performed according to the doses of rituximab. There was no difference between the doses of rituximab in terms of the total complication rate.

Infections remain a major concern with all biological treatments for RA. Rituximab causes a rapid depletion of pre-B and mature B cells and several other mechanisms that cause immunosuppression when it is administered for long periods. The current meta-analysis did not reveal any significant difference between the combination of rituximab and MTX and MTX alone in terms of the occurrence of infections. Tank et al[16] conducted a systematic review and meta-analysis and found that rituximab was more strongly associated with an infusion reaction compared with other biological response modifiers. Certolizumab was more likely to cause serious infections (RR: 2.95, NNH: 37.31). Infusion reactions develop more commonly with rituximab (RR: 1.52, NNH: 8.47). Henry et al[17] revealed that the use of reduced doses of rituximab can reduce the rate of serious infections. In the current meta-analysis, the low dose of rituximab had a lower incidence of infection than the high dose of rituximab. This outcome was in line with the finding in a previous study and showed that a low dose of rituximab was safer than a high dose of rituximab.

Our meta-analysis has several potential limitations:

(1) (1) Only five RCTs were included, and their sample sizes were relatively small, which may result in a certain level of bias in the conclusions.
(2) For the safety assessment of rituximab in RA patients, relative short-term follow-ups can underestimate the number of real complications.
(3) The doses of rituximab and MTX were different in the included studies.
(4) There was a large heterogeneity between the outcomes, which can thus affect the precision of the final results.

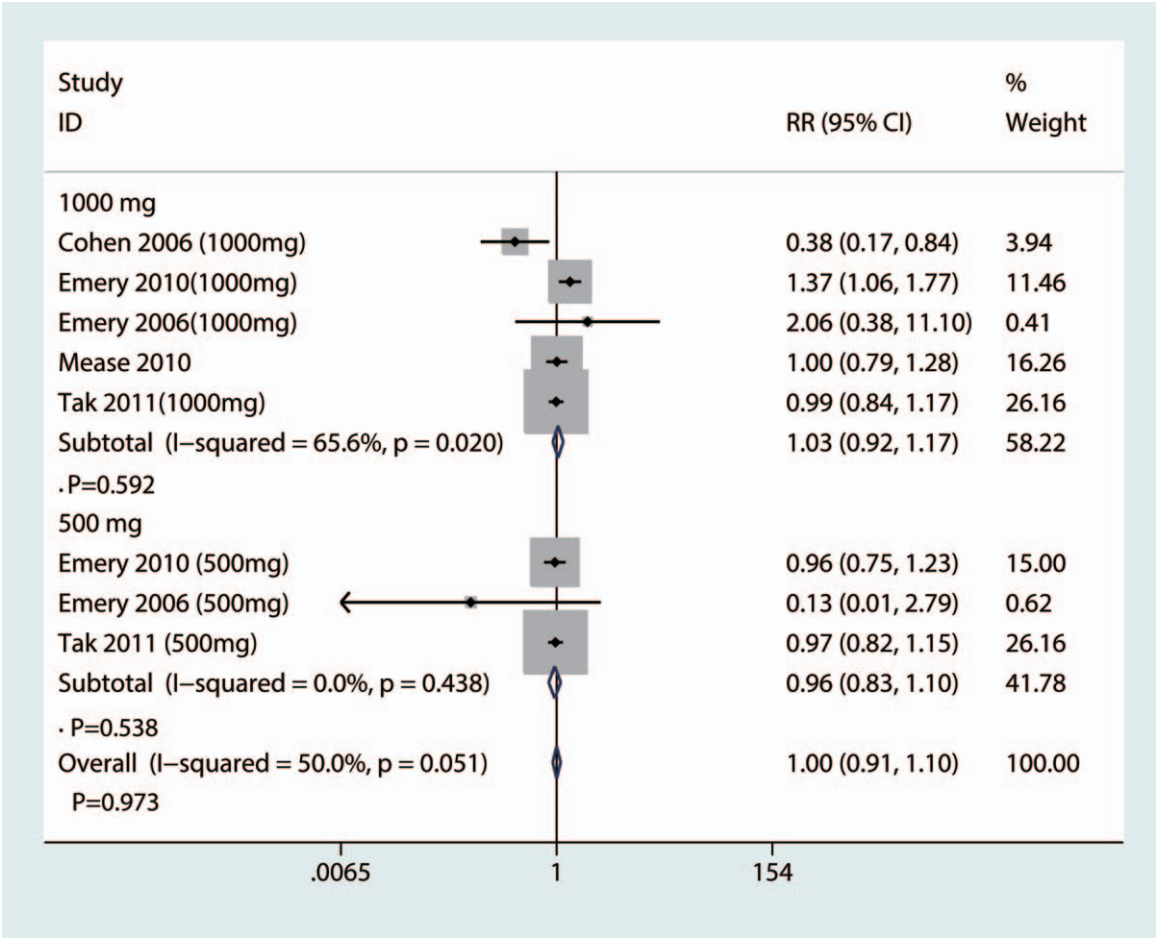

Figure 7. Forest plot comparing the occurrence of infections between the rituximab combined with methotrexate and methotrexate only groups.

(5) Only English articles were included, and studies published in other language were omitted, so important studies may have been overlooked.

6. Conclusion

Based on the current evidence, the present meta-analysis showed that rituximab combined with MTX increased ACR20, ACR50, and ACR70 in RA patients without increasing the occurrence of complications. Additional high-quality RCTs should be designed to examine the best therapeutic dose of rituximab for RA patients.

Author contributions

Visualization: Zhao Wang, Hong-wei Bao, Yong Ji.
Writing – original draft: Hong-wei Bao, Yong Ji.
Writing – review & editing: Zhao Wang.

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