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# Efficacy and safety of different doses of baricitinib for rheumatoid arthritis

## A Bayesian network meta-analysis

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**Abstract**

**Background:** To evaluate the comparative efficacy and safety of baricitinib with different dosages in patients with rheumatoid arthritis (RA).

**Methods:** PubMed, Embase, and the Cochrane Library were retrieved by computer to gather randomized controlled trials (RCTs) of baricitinib for RA from their beginning to September 2021. After 2 researchers independently screened the literature and extracted the data, the risk of bias of included RCTs was assessed, and Bayesian network meta-analysis was performed by GeMTC0.14.3 and Stata15.1 software.

**Results:** Ten publications reporting 9 RCTs were included, with 4129 patients randomized to receive 1 of the 7 interventions. Seven interventions were baricitinib 1 mg + conventional disease-modifying antirheumatic drugs (cDMARD), baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, baricitinib 4 mg, placebo + cDMARD, and cDMARD. In the efficacy outcomes at 12 weeks, nearly all doses of baricitinib with or without cDMARD were superior to placebo plus cDMARD and baricitinib 8 mg combined with cDMARD might have the best curative effect in most outcomes. In the efficacy outcomes at 24 weeks, all doses of baricitinib with or without cDMARD were superior to placebo plus cDMARD and baricitinib 4 mg monotherapy might have the best curative effect in most outcomes. The intervention with the highest incidence of adverse events (AEs) might be baricitinib 8 mg combined with cDMARD, and the intervention with the highest incidence of infections might be baricitinib 4 mg combined with cDMARD.

**Conclusions:** Baricitinib 8 mg combined with cDMARDs was suitable for short-term control of RA symptoms, and baricitinib 4 mg was more effective for treating RA over a longer period of time. But attention should be paid for the risk of baricitinib at 4 to 8 mg in clinical application due to the high incidence of AEs and infections.

**Abbreviations:** ACR = American College of Rheumatism, ACR20 = American College of Rheumatism 20%, AEs = adverse events, cDMARD = conventional disease-modifying antirheumatic drugs, CrI = credible intervals, DMARDs = disease-modifying antirheumatoid drugs, JAK = Janus kinase, OR = odds ratio, PSRF = potential scale reduced factor, RA = rheumatoid arthritis, RCT = randomized controlled trial, SDAI = simplified disease activity index, SUCRA = surface under the cumulative ranking curve.

**Key words:** baricitinib, Bayesian network meta-analysis, rheumatoid arthritis

## 1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by persistent joint damage, as well as extra-articular symptoms affecting many other organs.[1] RA affects about 0.53% to 0.55% of adults in America,[2] which leads to inability and a decreased quality of life. Cell factors are critical drivers of inflammation in RA. Janus kinases (JAKs), a family of intracellular tyrosine kinases, are mediators of the downstream signaling of multiple cell factors and growth factors that mediate several inflammatory and autoimmune diseases,[3] including RA inflammation. Drugs that inhibit JAK can modulate multiple inflammatory pathways involved in RA pathogenesis. Several small molecule JAK inhibitors have been used for treating RA,[4] including tofacitinib, baricitinib, upadacitinib, and so on.

Baricitinib is a selective JAK inhibitor with similar inhibitory for both JAK1 and JAK2 for patients with moderate to severe active RA who are intolerant to one or more disease-modifying anti rheumatoid drugs (DMARDs).[5] Baricitinib has shown positive efficacy in phase II and III clinical trials. However, due to the lack of enough multiple comparisons, the comparative efficacy and safety of baricitinib with different dosages remains unclear. The network

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**Key Points**

- To the best of our knowledge, this is the most comprehensive Bayesian network meta-analysis which includes all the available data of RCTs and evaluates the efficacy and safety of baricitinib with different dosages for RA.
- The outcomes at 24 weeks were assessed by Bayesian network meta-analysis for the first time.
- As no significant inconsistency was detected in our analysis, we did not perform subgroup analysis or sensitivity analysis.
- The results evaluation time points were limited to 12 weeks and 24 weeks. Therefore, the duration of treatment was too short to evaluate long-term efficacy and safety.

meta-analysis can evaluate the relative efficacy of drug therapy by direct or indirect comparison using cumulative probability ranking. Using a Bayesian network meta-analysis, the present study aimed to compare the efficacy and safety of once-daily administration of baricitinib 1, 2, 4, and 8 mg in patients with RA.

## 2. Methods

The protocol of this network meta-analysis was registered with PROSPERO (CRD42021268898, available from: (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021268898). The network meta-analysis was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Table S1, Supplemental Digital Content, http://links.lww.com/MD/H377).

### 2.1. Search strategy

A systematic search of PubMed, Embase, and the Cochrane Library published up to September 2021 was conducted for literature that had examined the efficacy and safety of baricitinib in patients with RA. The following subject terms were used for the search: "baricitinib" or "LY3009104" or "INCB028050," "rheumatoid arthritis," "RA," "random," etc. Additionally, relevant literature was supplemented through tracing the references of related studies. Taking PubMed for example, the specific search strategy: ([baricitinib] OR [LY3009104] OR [INCB028050]) AND ([rheumatoid arthritis] OR [RA]) AND [random]).

### 2.2. Inclusion and exclusion

Studies were included if they met all the following. Research type: randomized controlled trial (RCT), published in English or Chinese. Research object: patients diagnosed with adult-onset RA according to the American College of Rheumatism (ACR) 1987 changed/European league against rheumatism 2010 criteria, regardless of nationality, race, sex, age, onset time, course of disease, etc. Interventions: patients in the experimental group were given baricitinib (dosage: 1, 2, 4, or 8 mg, once a day) with or without conventional DMARDs (cDMARDs); patients in the control group were given cDMARDs or placebo with or without other cDMARDs. cDMARDs included synthetic DMARDs, methotrexate, other biological agents, etc. One of the outcomes was reported: efficacy outcomes at 12 and 24 weeks: ① American College of Rheumatism 20% (ACR20) response rate; ② ACR50; ③ ACR70; ④ proportion of patients achieving simplified disease activity index (SDAI) ≤ 3.3. Safety outcomes at 12 and 24 weeks; ⑤ incidence of adverse events (AEs); ⑥ incidence of infections. ACR20 and the incidence of AEs were the primary outcomes and others were the secondary outcomes.

Exclusion: the study included duplicate data; the data could not be extracted or the study did not contain enough data for inclusion; case report, review, basic pharmacological research, animal experiment, etc.

### 2.3. Study selection and data extraction

Two investigators independently screened the literature and extracted the data, and then crossed check. A third researcher resolved any difference between the investigators. During screening, the title and abstract should be read first. After excluding obviously irrelevant literature, the full text of remaining literature should be read to decide whether to include them or not. The following information was extracted from each trial: first author or title of the RCT, subject, age, gender, number, follow-up, background treatment, interventions, efficacy and safety outcomes, and time at which the outcomes were evaluated.

### 2.4. Quality assessment

Two investigators independently assessed the risk of bias of each RCT using Cochrane Collaboration's tool.[6] A third researcher resolved any difference between the investigators.

### 2.5. Statistical analysis

Stata15.1 software was used to draw an evidence network map to show the direct and indirect comparison between different interventions; GeMTC0.14.3 based on the Marko chain Monte Carlo algorithm was used for network meta-analysis. Given the methodological and clinical heterogeneity of both participants and methods among the included RCTs, the random-effects model was selected for statistical calculations. Each outcome was gained by 50,000 sample iterations with 20,000 burn-in iterations on 4 parallel chains. The potential scale reduced factor (PSRF) was used to evaluate the convergence of the model. If PSRF is between 1 and 1.05, the convergence is considered favorable. The inconsistency between direct and indirect comparisons was tested by the "node-splitting" method. If there was no significant inconsistency ($P$ value ≥ .05), the consistency model was performed. Otherwise the inconsistency model would be performed.

Mean difference with 95% credible intervals (CrI) was estimated for dichotomous outcomes and odds ratio (OR) with 95% CrI was estimated for continuous outcomes. According to the ranking probability table gained by GEMTC0.14.3, the surface under the cumulative ranking curve (SUCRA) was calculated and plotted.[7] SUCRA was used to rank the interventions for each outcome. A treatment was certain to be the best when the SUCRA was 1 and the worst when the SUCRA was 0. Evaluation of comparison-adjusted funnel plots was done using Stata15.1. $P$ value < .05 is considered statistically significant.

### 2.6. Ethical approval

The ethical approval of this study was not necessary, since the included studies are published data and the patients' privacy was not involved in the design.

## 3. Results

### 3.1. Study selection and characteristics

As shown in Figure 1, 125 studies were identified through an electronic database search. A further 4 were identified through searching for other literature.[8] After screening step-by-step, 10 publications reporting 9 RCTs were deemed eligible for inclusion, with 4129 patients (2259 cases in the experimental group

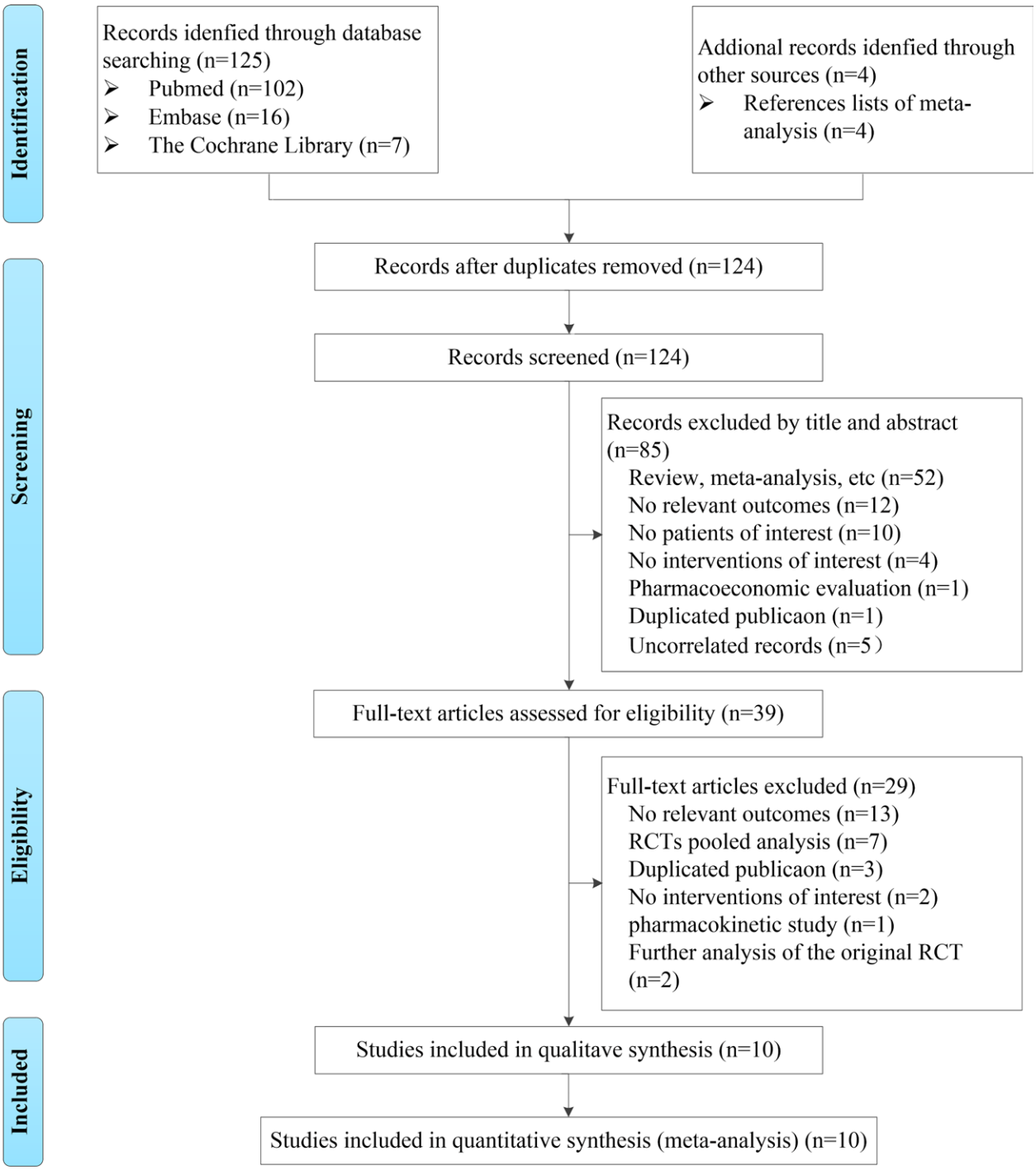


**Figure 1.** Literature search and selection. RCT = randomized control trial.

and 1870 in the control group) randomized to receive 1 of the 7 interventions.[9–18] Three RCTs were double-arm trials, and 6 were multi-arm trials. Seven interventions were baricitinib 1 mg + cDMARD, baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, baricitinib 4 mg, placebo + cDMARD, and cDMARD. Patient characteristics were broadly comparable across studies (Table 1).

### *3.2. Risk of bias*

As shown in Figure 2, overall, the risk of bias across studies was low to medium, with no studies rated with high risk of bias.

### *3.3. Network meta-analysis*

***3.3.1. Convergence assessment of the model.*** The convergence of the 12 outcomes was evaluated, and the results showed PSRF ranged from 1 to 1.05. It showed the data had good property of convergence by iterating 50,000 times.

***3.3.2. Node-splitting analysis.*** In outcomes SDAI ≤ 3.3, AEs, infections at 12 weeks, inconsistency test was not required since there are no comparisons between direct and indirect estimate to assess for inconsistency. The results of node-splitting analysis of other outcomes showed no significant inconsistency

**Table 1**

**Characteristics of included trials.**

| Author year | Subjects | Mean age (Y) | Interventions | Patient number | Gender | | Background treatment | Course of treatment | Outcomes reported |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Male | Female | | | |
| Yang 2020[9] | MTX-IR | 48.6 ± 10.9 | BARI 4 mg, qd | 116 | 12 | 104 | MTX | 52 wk | ①②③④⑤⑥ |
| | | 47.7 ± 12.5 | PBO | 115 | 29 | 86 | | | |
| Li 2020[10] | MTX-IR | 49.5 ± 10.6 | BARI 4 mg, qd | 145 | 18 | 127 | MTX | 52 wk | ①②③④⑤⑥ |
| | | 48.9 ± 12.7 | PBO | 145 | 39 | 106 | | | |
| Keystone 2018* [11] | MTX-IR | 53 ± 11 | BARI 8 mg, qd | 50 | 9 | 41 | MTX | 128 wk | ⑥ |
| | | 53 ± 10 | BARI 4 mg, qd | 52 | 15 | 37 | | | |
| | | 51 ± 13 | BARI 2 mg, qd | 52 | 8 | 44 | | | |
| Dougados 2017* [12] | csDMARDs-IR or intolerance | 52 ± 12 | BARI 4 mg, qd | 227 | 40 | 187 | csDMARDs | 24 wk | ①②③④⑤⑥ |
| | | 52 ± 12 | BARI 2 mg, qd | 229 | 45 | 184 | | | |
| | | 51 ± 13 | PBO | 228 | 39 | 189 | | | |
| Taylor 2017* [13] | MTX-IR | 54 ± 2 | BARI 4 mg, qd | 487 | 112 | 375 | MTX | 52 wk | ①②③④⑤⑥ |
| | | 53 ± 12 | adalimumab 40 mg, q2w | 330 | 79 | 251 | | | |
| | | 53 ± 2 | PBO | 488 | 106 | 382 | | | |
| Fleischmann 2017* [14] | DMARDs- intolerance | 49 ± 14 | BARI 4 mg, qd + MTX | 215 | 59 | 156 | NR | 52 wk | ①②③④⑤⑥ |
| | | 51 ± 13 | BARI 4 mg, qd | 159 | 38 | 121 | | | |
| | | 51 ± 13 | MTX, qw | 210 | 62 | 148 | | | |
| Genovese 2016* [15] | Biological agents-IR | 56 ± 11 | BARI 4 mg, qd | 177 | 28 | 149 | csDMARDs | 24 wk | ①②③④⑤⑥ |
| | | 55 ± 11 | BARI 2 mg, qd | 174 | 37 | 137 | | | |
| | | 56 ± 11 | PBO | 176 | 31 | 145 | | | |
| Tanaka 2016* [16] | MTX-IR | 53.6 ± 11.3 | BARI 8 mg, qd | 24 | 7 | 17 | MTX | 12 wk | ①②③④⑤⑥ |
| | | 57.5 ± 10.4 | BARI 4 mg, qd | 24 | 5 | 19 | | | |
| | | 56.1 ± 11.5 | BARI 2 mg, qd | 24 | 3 | 21 | | | |
| | | 52.7 ± 12.8 | BARI 1 mg, qd | 24 | 2 | 22 | | | |
| | | 51.1 ± 12.0 | PBO | 49 | 10 | 39 | | | |
| Keystone 2015* [17] | MTX-IR | 53 ± 11 | BARI 8 mg, qd | 50 | 9 | 41 | MTX | 24 wk | ①②③④⑤ |
| | | 53 ± 10 | BARI 4 mg, qd | 52 | 15 | 37 | | | |
| | | 51 ± 13 | BARI 2 mg, qd | 52 | 8 | 44 | | | |
| | | 53 ± 11 | BARI 1 mg, qd | 49 | 7 | 42 | | | |
| | | 49 ± 12 | PBO | 98 | 13 | 85 | | | |
| Greenwald2010[18] | DMARDs-IR | 54-58 | BARI 4 mg, qd | 31 | | NR | MTX | 24 wk | ①②③④⑤ |
| | | | PBO | 31 | | | | | |

Outcomes reported: ① American College of Rheumatism 20% (ACR20) response rate, ② ACR50, ③ ACR70, ④ simplified disease activity index ≤ 3.3, ⑤ adverse events, ⑥ infections.
BARI = baricitinib, csDMARDs = conventional synthetic disease-modifying antirheumatoid drugs, DMARDs = disease-modifying antirheumatoid drugs, IR = inadequate response, MTX = methotrexate, NR = not reported, PBO = placebo, wk = weeks.
*Multi-arm trial.

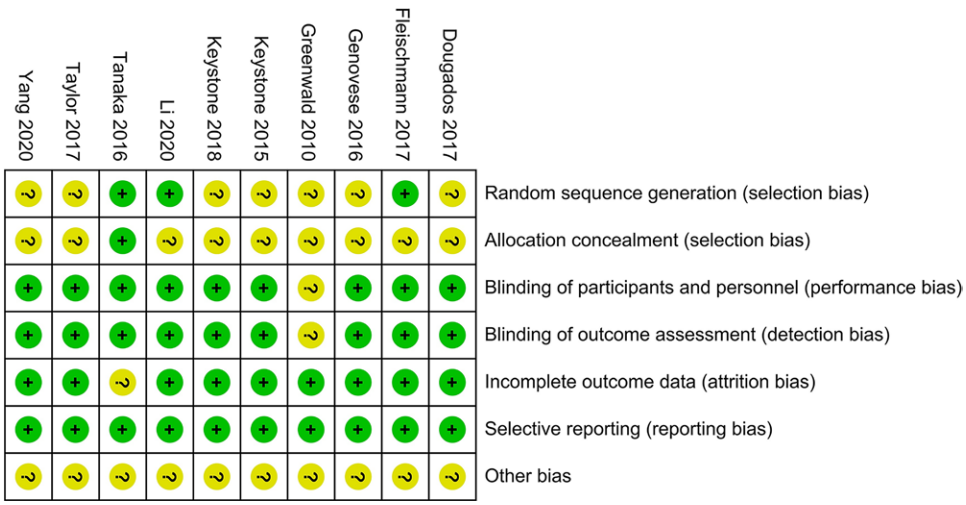


**Figure 2.** Risk of bias summary.

was detected between direct and indirect estimate for each comparison (*P* value > .05, as shown in Table 2).

#### *3.3.3. Network meta-analysis of efficacy outcomes at 12 weeks.*

*3.3.3.1. ACR20/50/70.* Nine studies[9,10,12–18] reported ACR20/50/70 response rate, involving seven interventions, such as baricitinib 1 mg + cDMARD, baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, baricitinib 4 mg, placebo + cDMARD, cDMARD. Evidence network map is shown in Figure 3A. Results of the network meta-analysis are presented in Tables 3A–C.

At ACR20 (Table 3A), 12 direct or indirect comparisons showed statistically significant differences. Baricitinib 1 mg + cDMARD, baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD were less effective than baricitinib 8 mg + cDMARD (OR = 0.34, 95%CrI 0.14–0.75; OR = 0.42, 95%CrI 0.20–0.86; OR = 0.47, 95%CrI 0.23–0.94). Baricitinib 1 mg + cDMARD, baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, and baricitinib 4 mg were more effective than placebo + cDMARD (OR = 2.43, 95%CrI 1.32–4.52; OR = 3.02, 95%CrI 2.09–4.34; OR = 3.42, 95%CrI 2.66–4.48; OR = 7.24, 95%CrI 3.71–14.68; OR = 4.52, 95%CrI 2.25–9.18). Baricitinib 4 + cDMARD, baricitinib 8 mg + cDMARD, and baricitinib 4 mg were more effective than cDMARD (OR = 1.71, 95%CrI 1.14–2.66; OR = 3.61, 95%CrI 1.68–8.21; OR = 2.24, 95%CrI 1.18–4.50). Placebo + cDMARD was less effective than cDMARD (OR = 0.50, 95%CrI 0.32–0.79). The ranking probability based on the SUCRA showed baricitinib 8 mg + cDMARD was likely to achieve the best ACR20 response rate (SUCRA = 96.83%), followed by baricitinib 4 mg (79.50%), baricitinib 4 mg + cDMARD (64.50%), baricitinib 2 mg + cDMARD (50.17%), baricitinib 1 mg + cDMARD (36.17%), cDMARD (22.83%), placebo + cDMARD (0.17%, Fig. 4A).

At ACR50 (Table 3B), 9 direct or indirect comparisons showed statistically significant differences. Baricitinib 1 mg + cDMARD, baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, and baricitinib 4 mg were more effective than placebo + cDMARD (OR = 3.75, 95%CrI 1.82–7.90; OR = 3.46, 95%CrI 2.22–5.33; OR = 4.85, 95%CrI 3.56–7.00; OR = 6.79, 95%CrI 3.42–14.13; OR = 4.74, 95%CrI 2.29–10.39). Baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, and baricitinib 4 mg were more effective than cDMARD (OR = 2.10, 95%CrI 1.35–3.46; OR = 2.94, 95%CrI 1.30–6.80; OR = 2.04, 95%CrI 1.03–4.17). Placebo + cDMARD was less effective than cDMARD (OR = 0.43, 95%CrI 0.25–-0.72). The ranking probability based on the SUCRA showed baricitinib 8 mg + cDMARD was likely to achieve the best ACR50 response rate (SUCRA = 91.67%), followed by baricitinib 4 mg + cDMARD (73.67%), baricitinib 4 mg (69.00%), baricitinib 1 mg + cDMARD (51.67%), baricitinib 2 mg + cDMARD (43.17%), cDMARD (20.83%), placebo + cDMARD (0%, Fig. 4B).

At ACR70 (Table 3C), 7 direct or indirect comparisons showed statistically significant differences. Baricitinib 1 mg + cDMARD, baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, and baricitinib 4 mg were more effective than placebo + cDMARD (OR = 4.09, 95%CrI 1.26–11.75; OR = 6.39, 95%CrI 3.75–12.69; OR = 7.08, 95%CrI 4.67–13.27; OR = 7.66, 95%CrI 3.33–19.98; OR = 6.79, 95%CrI 3.09–19.13). Baricitinib 4 mg + cDMARD was more effective than cDMARD (OR = 2.12, 95%CrI 1.27–4.12). Placebo + cDMARD was less effective than cDMARD (OR = 0.30, 95%CrI 0.14–0.57). The ranking probability based on the SUCRA showed baricitinib 8 mg + cDMARD was likely to achieve the best ACR70 response rate (SUCRA = 79.00%), followed by baricitinib 4 mg + cDMARD (74.83%), baricitinib 4 mg (70.83%), baricitinib 2 mg + cDMARD (64.00%), baricitinib 1 mg + cDMARD (36.50%), cDMARD (23.83%), placebo + cDMARD (0.17%, Fig. 4C).

*3.3.1.2. SDAI ≤ 3.3.* Seven studies[9,10,12,13,15–18] reported the proportion of patients achieving SDAI ≤ 3.3, involving 6 interventions, such as baricitinib 1 mg + cDMARD, baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, placebo + cDMARD, cDMARD. Evidence

**Table 2**

**Node-splitting analysis results.**

| Interventions | Direct effect | Indirect effect | Overall | *P* value |
|---|---|---|---|---|
| ACR20 at 12 weeks | | | | |
| PBO + cDMARD, cDMARD | 0.84 (0.34, 1.40) | 0.37 (−0.27, 1.02) | 0.70 (0.23, 1.13) | .18 |
| ACR50 at 12 weeks | | | | |
| PBO + cDMARD, cDMARD | 1.02 (0.44, 1.58) | 0.44 (−0.22, 1.16) | 0.84 (0.33, 1.37) | .15 |
| ACR70 at 12 weeks | | | | |
| PBO + cDMARD, cDMARD | 1.25 (0.15, 2.12) | 0.96 (−0.03, 2.25) | 1.19 (0.56, 1.97) | .62 |
| ACR20 at 24 weeks | | | | |
| BARI 2 mg + cDMARD, PBO + cDMARD | −0.81 (−1.26, −0.36) | −1.42 (−1.88, −0.78) | −0.97 (−1.52, −0.40) | .09 |
| PBO + cDMARD, cDMARD | 1.18 (0.41, 2.07) | 0.44 (−0.56, 1.42) | 0.84 (0.19, 1.47) | .18 |
| ACR50 at 24 weeks | | | | |
| BARI 2 mg + cDMARD, PBO + cDMARD | −0.81 (−1.53, −0.14) | −1.23 (−2.00, −0.34) | −0.92 (−1.46, −0.24) | .35 |
| PBO + cDMARD, cDMARD | 1.25 (0.33, 2.16) | 0.60 (−0.40, 1.68) | 1.01 (0.29, 1.70) | .23 |
| ACR70 at 24 weeks | | | | |
| BARI 2 mg + cDMARD, PBO + cDMARD | −1.38 (−2.21, −0.60) | −1.51 (−2.43, −0.59) | −1.43 (−2.01, −0.76) | .8 |
| PBO + cDMARD, cDMARD | 1.18 (0.20, 2.12) | 0.80 (−0.20, 2.05) | 1.06 (0.47, 1.75) | .47 |
| SDAI ≤ 3.3 at 24 weeks | | | | |
| BARI 2 mg + cDMARD, PBO + cDMARD | −1.33 (−2.62, −0.01) | −1.54 (−3.11, 0.06) | −1.36 (−2.28, −0.30) | .8 |
| PBO + cDMARD, cDMARD | 1.59 (0.28, 3.08) | 0.77 (−0.75, 2.53) | 1.32 (0.29, 2.49) | .28 |
| AEs at 24 weeks | | | | |
| BARI 2 mg + cDMARD, PBO + cDMARD | −0.08 (−0.48, 0.33) | −0.31 (−0.82, 0.17) | −0.16 (−0.55, 0.19) | .36 |
| PBO + cDMARD, cDMARD | 0.31 (−0.23, 0.89) | 0.31 (−0.42, 1.02) | 0.32 (−0.08, 0.72) | .95 |
| Infections at 24 weeks | | | | |
| BARI 2 mg + cDMARD, PBO + cDMARD | −0.18 (−0.61, 0.29) | −0.35 (−0.93, 0.17) | −0.23 (−0.64, 0.14) | .52 |
| PBO + cDMARD, cDMARD | 0.28 (−0.34, 0.90) | 0.10 (−0.65, 0.84) | 0.23 (−0.20, 0.64) | .68 |

ACR = American College of Rheumatism, AEs = adverse events, BARI = baricitinib, cDMARDs = conventional disease-modifying antirheumatoid drugs, PBO = placebo, SDAI = simplified disease activity index.

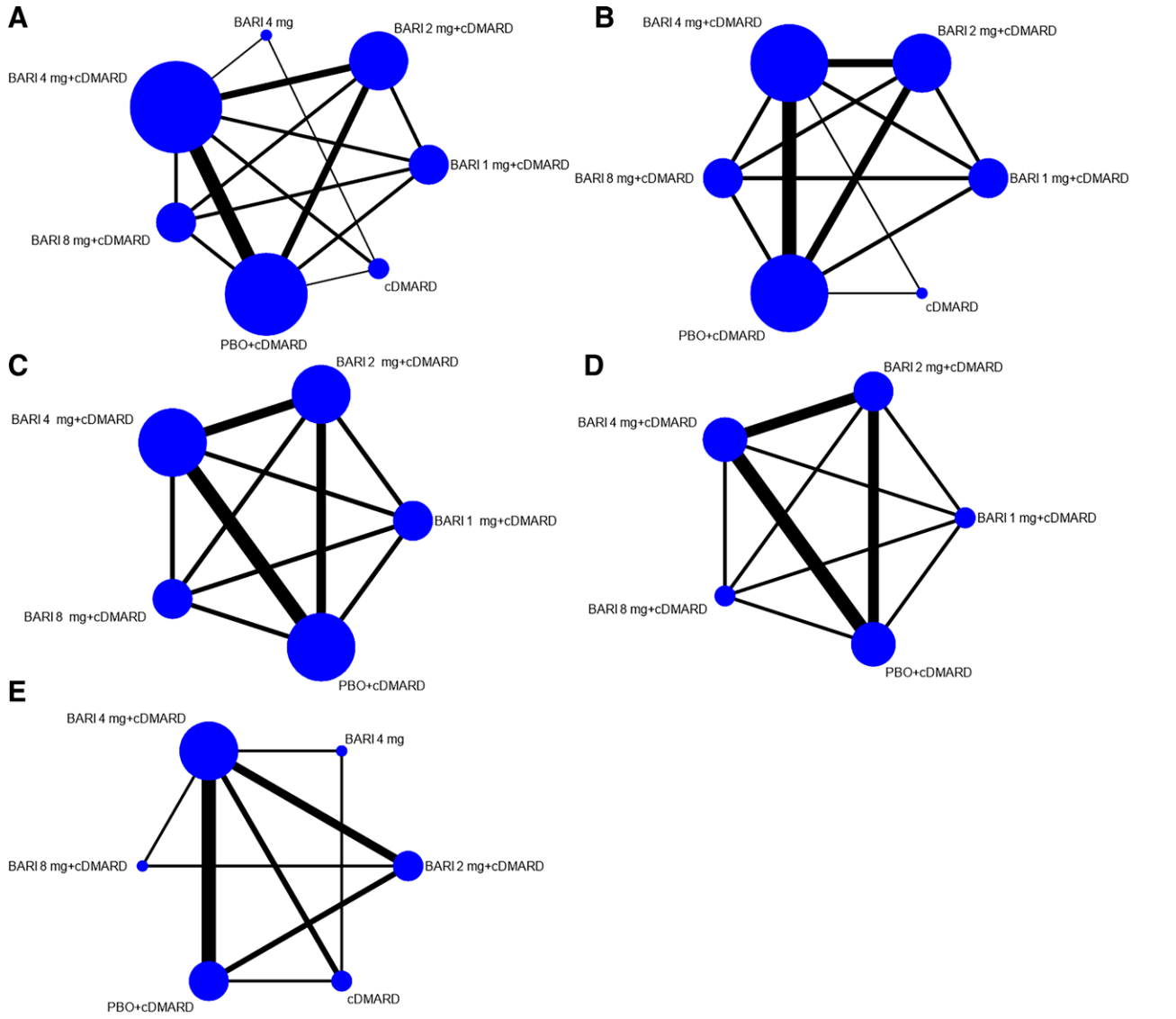


**Figure 3.** Evidence network map for the network meta-analysis. (A) ACR20/50/70 at 12 weeks; (B) SDAI ≤ 3.3 at 12 weeks; (C) AEs at 12 weeks; (D) infections at 12 weeks; (E) ACR20/50/70, SDAI ≤ 3.3, AEs and infections at 24 weeks. ACR = American College of Rheumatism, AEs = adverse events, BARI = baricitinib, cDMARDs = conventional disease-modifying anti rheumatoid drugs, PBO = placebo, SDAI = simplified disease activity index. (The nodes represent the interventions and the lines show there is direct comparative evidence between the two interventions. The size of the nodes is proportional to the number of patients randomized to receive the intervention. The width of the lines is proportional to the number of trials comparing the connected treatments.)

network map is shown in Figure 3B. Results of the network meta-analysis are presented in Table 3D. Three direct or indirect comparisons showed statistically significant differences. Baricitinib 1 mg + cDMARD was worse than BARI 4 mg + cDMARD (OR = 0.18, 95%CrI 0.03–0.79). Baricitinib 2 mg + cDMARD and baricitinib 4 mg + cDMARD were better than PBO + cDMARD (OR = 4.12, 95%CrI 1.56–11.60; OR = 5.71, 95%CrI 2.58–15.16). The ranking probability based on the SUCRA showed baricitinib 4 mg + cDMARD was likely to be the best intervention to increase the proportion of patients achieving SDAI ≤ 3.3 (SUCRA = 86.80%), followed by cDMARD (68.40%), baricitinib 2 mg + cDMARD (66.60%), baricitinib 8 mg + cDMARD (51.40%), baricitinib 1 mg + cDMARD (15.40%), placebo + cDMARD (11.20%, Fig. 4D).

### *3.3.4. Network meta-analysis of safety outcomes at 12 weeks.*

*3.3.4.1. AEs.* Six studies[10,12,15–18] reported the incidence of AEs, involving 5 interventions, such as baricitinib 1 mg + cDMARD, baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, placebo + cDMARD. Evidence network map is shown in Figure 3C. Results of the network meta-analysis are presented in Table 3E. No direct or indirect comparison showed statistically significant differences. The ranking probability based on the SUCRA showed baricitinib 1 mg + cDMARD was likely to be the safest intervention (SUCRA = 78.75%), followed by baricitinib 2 mg + cDMARD (69.00%), placebo + cDMARD (61.50%), baricitinib 4 mg + cDMARD (36.00%), baricitinib 8 mg + cDMARD (5.50%, Fig. 4E).

*3.3.4.2. Infections* Four studies[10,12,15,16] reported the incidence of infections, involving 5 interventions, such as baricitinib 1 mg + cDMARD, baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, placebo + cDMARD. Evidence network map is shown in Figure 3D. Results of the network meta-analysis are presented in Table 3F. No direct or indirect comparison showed

**Table 3**

**Results of network meta-analysis at 12 weeks.**

| | | | | | | |
|---|---|---|---|---|---|---|
| **A. OR with 95%CrI for ACR20 at 12 weeks** | | | | | | |
| BARI 1 mg + cDMARD | | | | | | |
| 0.81 (0.41, 1.55) | BARI 2 mg + cDMARD | | | | | |
| 0.54 (0.22, 1.37) | 0.67 (0.32, 1.42) | BARI 4 mg | | | | |
| 0.71 (0.38, 1.31) | 0.88 (0.61, 1.25) | 1.31 (0.68, 2.61) | BARI 4 mg + cDMARD | | | |
| ***0.34 (0.14, 0.75)*** | ***0.42 (0.20, 0.86)*** | 0.62 (0.23, 1.58) | ***0.47 (0.23, 0.94)*** | BARI 8 mg + cDMARD | | |
| ***2.43 (1.32, 4.52)*** | ***3.02 (2.09, 4.34)*** | ***4.52 (2.25, 9.18)*** | ***3.42 (2.66, 4.48)*** | ***7.24 (3.71, 14.68)*** | PBO + cDMARD | |
| 1.22 (0.59, 2.54) | 1.51 (0.90, 2.59) | ***2.24 (1.18, 4.50)*** | ***1.71 (1.14, 2.66)*** | ***3.61 (1.68, 8.21)*** | ***0.50 (0.32, 0.79)*** | cDMARD |
| **B. OR with 95%CrI for ACR50 at 12 weeks** | | | | | | |
| BARI 1 mg + cDMARD | | | | | | |
| 1.09 (0.50, 2.29) | BARI 2 mg + cDMARD | | | | | |
| 0.80 (0.28, 2.12) | 0.73 (0.32, 1.60) | BARI 4 mg | | | | |
| 0.77 (0.36, 1.61) | 0.71 (0.45, 1.07) | 0.98 (0.48, 1.95) | BARI 4 mg + cDMARD | | | |
| 0.55 (0.23, 1.27) | 0.51 (0.24, 1.04) | 0.70 (0.26, 1.86) | 0.71 (0.36, 1.42) | BARI 8 mg + cDMARD | | |
| ***3.75 (1.82, 7.90)*** | ***3.46 (2.22, 5.33)*** | ***4.74 (2.29, 10.39)*** | ***4.85 (3.56, 7.00)*** | ***6.79 (3.42, 14.13)*** | PBO + cDMARD | |
| 1.62 (0.69, 3.81) | 1.49 (0.81, 2.72) | ***2.04 (1.03, 4.17)*** | ***2.10 (1.35, 3.46)*** | ***2.94 (1.30, 6.80)*** | ***0.43 (0.25, 0.72)*** | cDMARD |
| **C. OR with 95%CrI for ACR70 at 12 weeks** | | | | | | |
| BARI 1 mg + cDMARD | | | | | | |
| 0.64 (0.21, 1.66) | BARI 2 mg + cDMARD | | | | | |
| 0.59 (0.17, 1.99) | 0.94 (0.36, 2.38) | BARI 4 mg | | | | |
| 0.56 (0.20, 1.46) | 0.90 (0.52, 1.47) | 0.95 (0.42, 2.08) | BARI 4 mg + cDMARD | | | |
| 0.53 (0.16, 1.49) | 0.83 (0.35, 2.00) | 0.89 (0.29, 2.91) | 0.92 (0.41, 2.18) | BARI 8 mg + cDMARD | | |
| ***4.09 (1.26, 11.75)*** | ***6.39 (3.75, 12.69)*** | ***6.79 (3.09, 19.13)*** | ***7.08 (4.67, 13.27)*** | ***7.66 (3.33, 19.98)*** | PBO + cDMARD | |
| 1.22 (0.40, 3.69) | 1.93 (0.94, 4.13) | 2.05 (0.95, 4.87) | ***2.12 (1.27, 4.12)*** | 2.34 (0.85, 6.46) | ***0.30 (0.14, 0.57)*** | cDMARD |
| **D. OR with 95%CrI for SDAI ≤ 3.3 at 12 weeks** | | | | | | |
| BARI 1 mg + cDMARD | | | | | | |
| 0.26 (0.04, 1.25) | BARI 2 mg + cDMARD | | | | | |
| ***0.18 (0.03, 0.79)*** | 0.74 (0.26, 1.71) | BARI 4 mg + cDMARD | | | | |
| 0.36 (0.05, 2.11) | 1.39 (0.35, 5.81) | 1.93 (0.52, 8.43) | BARI 8 mg + cDMARD | | | |
| 1.03 (0.18, 5.31) | ***4.12 (1.56, 11.60)*** | ***5.71 (2.58, 15.16)*** | 2.92 (0.73, 12.90) | PBO + cDMARD | | |
| 0.24 (0.03, 2.06) | 0.95 (0.17, 5.42) | 1.30 (0.31, 6.61) | 0.68 (0.09, 4.93) | 0.23 (0.05, 1.06) | cDMARD | |
| **E. OR with 95%CrI for AEs at 12 weeks** | | | | | | |
| BARI 1 mg + cDMARD | | | | | | |
| 0.92 (0.47, 1.70) | BARI 2 mg + cDMARD | | | | | |
| 0.77 (0.42, 1.42) | 0.85 (0.61, 1.25) | BARI 4 mg + cDMARD | | | | |
| 0.50 (0.23, 1.04) | 0.56 (0.29, 1.06) | 0.67 (0.34, 1.18) | BARI 8 mg + cDMARD | | | |
| 0.86 (0.47, 1.56) | 0.96 (0.69, 1.36) | 1.12 (0.82, 1.51) | 1.72 (0.94, 3.25) | PBO + cDMARD | | |
| **F. OR with 95%CrI for infections at 12 weeks** | | | | | | |
| BARI 1 mg + cDMARD | | | | | | |
| 1.11 (0.26, 4.18) | BARI 2 mg + cDMARD | | | | | |
| 0.94 (0.22, 3.42) | 0.86 (0.44, 1.56) | BARI 4 mg + cDMARD | | | | |
| 1.28 (0.24, 7.08) | 1.17 (0.31, 5.25) | 1.38 (0.37, 6.04) | BARI 8 mg + cDMARD | | | |
| 1.32 (0.31, 4.69) | 1.20 (0.63, 2.16) | 1.39 (0.82, 2.46) | 1.01 (0.24, 3.71) | PBO + cDMARD | | |

ACR = American College of Rheumatism, AEs = adverse events, BARI = baricitinib, cDMARDs = conventional disease-modifying antirheumatoid drugs, CrI = credible intervals, OR = odds ratio, PBO = placebo, SDAI = simplified disease activity index.

statistically significant differences. The ranking probability based on the SUCRA showed placebo + cDMARD was likely to be the intervention with the lowest incidence of infections (SUCRA = 70.00%), followed by baricitinib 8 mg + cDMARD (59.00%), baricitinib 2 mg + cDMARD (47.75%), baricitinib 1 mg + cDMARD (43.00%), baricitinib 4 mg + cDMARD (29.00%, Fig. 4F).

### *3.3.5. Network meta-analysis of outcomes at 24 weeks.*

*3.3.5.1. ACR20/50/70, SDAI ≤ 3.3, AEs, and infections.* Seven studies[9,10,12–15,17] reported ACR20/50/70 response rate, proportion of patients achieving SDAI ≤ 3.3, the incidence of AEs and infections, involving 6 interventions, such as baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, baricitinib 4 mg, placebo + cDMARD, cDMARD. Evidence network map is shown in Figure 3E. Results of the network meta-analysis are presented in Tables 3G–L.

At ACR20 (Table 4G), 5 direct or indirect comparisons showed statistically significant differences. Baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, and baricitinib 4 mg were more effective than placebo + cDMARD (OR = 2.64, 95%CrI 1.49–4.56; OR = 3.51, 95%CrI 2.38–5.24; OR = 3.70, 95%CrI 1.24–10.81; OR = 4.00, 95%CrI 1.56–9.96). Placebo + cDMARD was less effective than cDMARD (OR = 0.43, 95%CrI 0.23–0.83). The ranking probability based on the SUCRA showed baricitinib 4 mg was likely to achieve the best ACR20 response rate (SUCRA = 77.40%), followed by baricitinib 4 mg + cDMARD (74.00%), baricitinib 8 mg + cDMARD (69.80%), baricitinib 2 mg + cDMARD (43.20%), cDMARD (33.80%), placebo + cDMARD (0.40%, Fig. 4G).

At ACR50 (Table 4H), 7 direct or indirect comparisons showed statistically significant differences. Baricitinib 2 mg + cDMARD was less effective than baricitinib 4 mg + cDMARD and baricitinib 8 mg + cDMARD (OR = 0.59, 95%CrI 0.31–0.98; OR = 0.31, 95%CrI 0.10–0.83). Baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, and baricitinib 4 mg were more effective than placebo + cDMARD (OR = 2.51, 95%CrI 1.27–4.32; OR = 4.25, 95%CrI 2.78–6.77; OR = 8.10, 95%CrI 2.67–25.68; OR = 4.37, 95%CrI 1.68–11.61). Placebo + cDMARD was less effective than cDMARD (OR = 0.36, 95%CrI 0.18–0.75). The ranking probability based on the SUCRA showed baricitinib 8 mg + cDMARD was likely to achieve the best ACR50 response rate (SUCRA = 93.80%), followed by baricitinib 4 mg + cDMARD (69.60%), baricitinib 4 mg (69.40%),

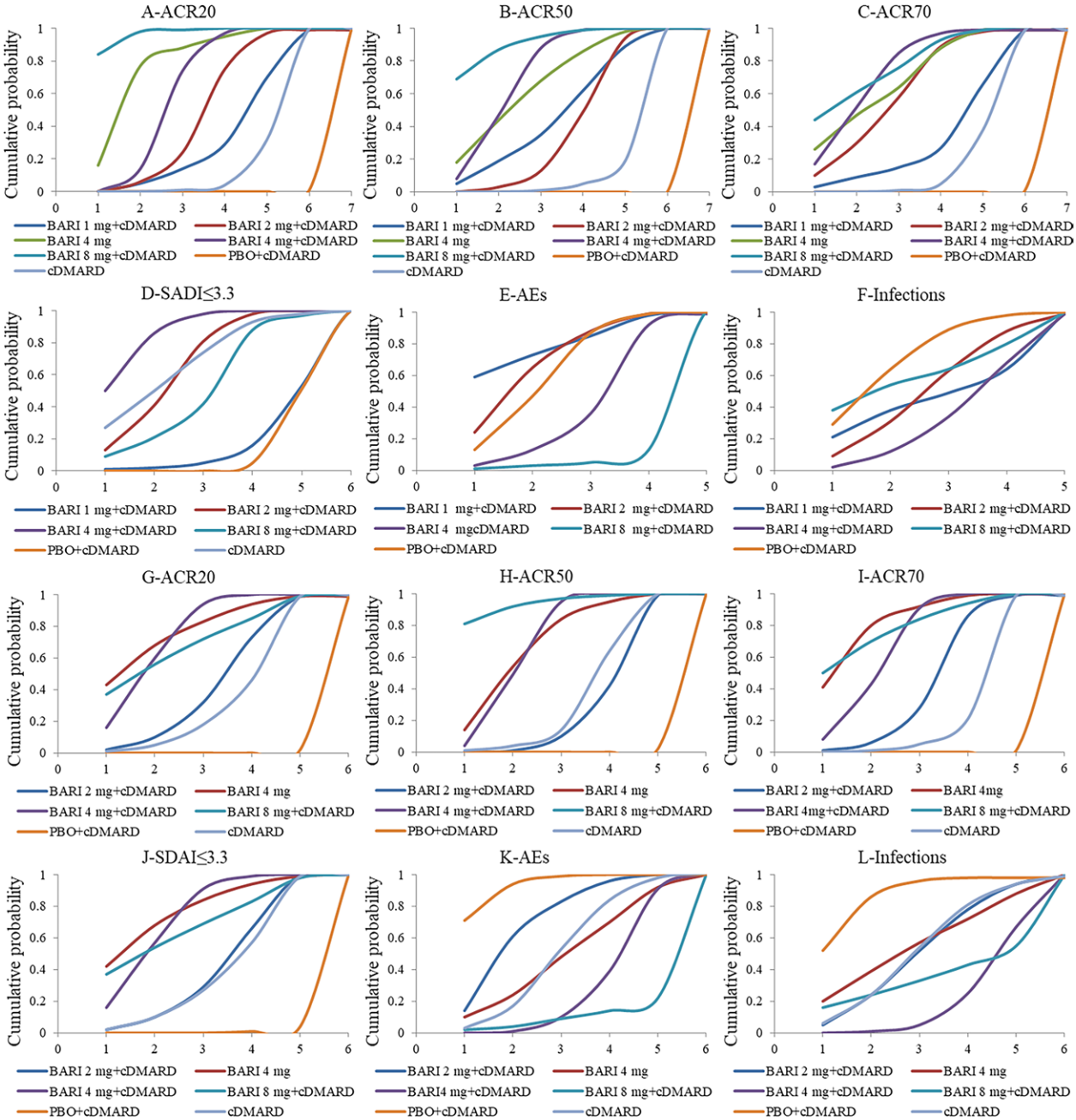


**Figure 4.** SUCRA curve of each outcome. (A–F) outcomes at 12 weeks; (H–L) outcomes at 24 weeks. ACR = American College of Rheumatism, AEs = adverse events, BARI = baricitinib, cDMARDs = conventional disease-modifying anti rheumatoid drugs, PBO = placebo, SDAI = simplified disease activity index.

cDMARD (36.60%), baricitinib 2 mg + cDMARD (30.40%), placebo + cDMARD (0.40%, Fig. 4H).

At ACR70 (Table 4I), 7 direct or indirect comparisons showed statistically significant differences. Baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, and baricitinib 4 mg were more effective than placebo + cDMARD (OR = 4.20, 95%CrI 2.15–7.45; OR = 5.45, 95%CrI 3.72–9.39; OR = 7.13, 95%CrI 2.16–23.26; OR = 6.83, 95%CrI 2.92–17.98). Baricitinib 4 mg + cDMARD and baricitinib 4 mg were more effective than cDMARD (OR = 2.34, 95%CrI 1.02–5.43; OR = 1.86, 95%CrI 1.12–3.42). Placebo + cDMARD was less effective than cDMARD (OR = 0.34, 95%CrI 0.17–0.63). The ranking probability based on the SUCRA showed baricitinib 4 mg was likely to achieve the best ACR70 response rate (SUCRA = 82.40%), followed by baricitinib 8 mg + cDMARD (79.60%), baricitinib 4 mg + cDMARD (68.40%), baricitinib 2 mg + cDMARD (44.00%), cDMARD (25.20%), placebo + cDMARD (0.20%, Fig. 4I).

At SDAI ≤ 3.3 (Table 4J), 5 direct or indirect comparisons showed statistically significant differences. Baricitinib 2 mg + cDMARD, baricitinib 4 mg + cDMARD, baricitinib 8 mg + cDMARD, and baricitinib 4 mg were more effective than placebo + cDMARD (OR = 3.90, 95%CrI 1.34–9.81; OR = 6.02, 95%CrI 2.92–13.92; OR = 6.27, 95%CrI 1.20–34.50; OR = 7.08, 95%CrI 1.68–33.23). Placebo + cDMARD was less effective than cDMARD (OR = 0.27, 95%CrI 0.08–0.75). The ranking probability based on the SUCRA showed baricitinib 4 mg was likely to be the best intervention to increase the proportion of patients achieving SDAI ≤ 3.3 (SUCRA = 77.40%), followed by baricitinib 4 mg + cDMARD (72.60%), baricitinib 8 mg + cDMARD (68.20%), baricitinib 2 mg + cDMARD (41.40%), cDMARD (39.00%), placebo + cDMARD (1.00%, Fig. 4J).

**Table 4**

**Results of network meta-analysis at 24 weeks.**

| | | | | | |
|---|---|---|---|---|---|
| **G. OR with 95%CrI for ACR20 at 24 weeks** | | | | | |
| BARI 2 mg + cDMARD | | | | | |
| 0.66 (0.24, 1.81) | BARI 4 mg | | | | |
| 0.75 (0.43, 1.23) | 1.13 (0.46, 2.66) | BARI 4 mg + cDMARD | | | |
| 0.71 (0.25, 1.97) | 1.09 (0.27, 4.16) | 0.96 (0.33, 2.78) | BARI 8 mg + cDMARD | | |
| ***2.64 (1.49, 4.56)*** | ***4.00 (1.56, 9.96)*** | ***3.51 (2.38, 5.24)*** | ***3.70 (1.24, 10.81)*** | PBO + cDMARD | |
| 1.13 (0.53, 2.42) | 1.72 (0.73, 4.13) | 1.52 (0.85, 2.82) | 1.59 (0.49, 5.18) | ***0.43 (0.23, 0.83)*** | cDMARD |
| **H. OR with 95%CrI for ACR50 at 24 weeks** | | | | | |
| BARI 2 mg + cDMARD | | | | | |
| 0.57 (0.18, 1.55) | BARI 4 mg | | | | |
| ***0.59 (0.31, 0.98)*** | 1.03 (0.41, 2.52) | BARI 4 mg + cDMARD | | | |
| ***0.31 (0.10, 0.83)*** | 0.54 (0.13, 2.12) | 0.53 (0.18, 1.50) | BARI 8 mg + cDMARD | | |
| ***2.51 (1.27, 4.32)*** | ***4.37 (1.68, 11.61)*** | ***4.25 (2.78, 6.77)*** | ***8.10 (2.67, 25.68)*** | PBO + cDMARD | |
| 0.91 (0.38, 2.02) | 1.60 (0.65, 4.12) | 1.55 (0.84, 3.08) | 2.95 (0.89, 10.57) | ***0.36 (0.18, 0.75)*** | cDMARD |
| I. **OR with 95%CrI for ACR70 at 24 weeks** | | | | | |
| BARI 2 mg + cDMARD | | | | | |
| 0.61 (0.21, 1.49) | BARI 4 mg | | | | |
| 0.75 (0.39, 1.21) | 1.25 (0.54, 2.76) | BARI 4 mg + cDMARD | | | |
| 0.59 (0.19, 1.76) | 0.95 (0.27, 3.99) | 0.78 (0.28, 2.45) | BARI 8 mg + cDMARD | | |
| ***4.20 (2.15, 7.45)*** | ***6.83 (2.92, 17.98)*** | ***5.45 (3.72, 9.39)*** | ***7.13 (2.16, 23.26)*** | PBO + cDMARD | |
| 1.43 (0.61, 2.82) | ***2.34 (1.02, 5.43)*** | ***1.86 (1.12, 3.42)*** | 2.42 (0.69, 7.78) | ***0.34 (0.17, 0.63)*** | cDMARD |
| **J. OR with 95%CrI for SDAI ≤ 3.3 at 24 weeks** | | | | | |
| BARI 2 mg + cDMARD | | | | | |
| 0.56 (0.10, 2.29) | BARI 4 mg | | | | |
| 0.65 (0.24, 1.40) | 1.17 (0.31, 4.37) | BARI 4 mg + cDMARD | | | |
| 0.62 (0.12, 2.88) | 1.12 (0.16, 8.48) | 0.97 (0.21, 4.77) | BARI 8 mg + cDMARD | | |
| ***3.90 (1.34, 9.81)*** | ***7.08 (1.68, 33.23)*** | ***6.02 (2.92, 13.92)*** | ***6.27 (1.20, 34.50)*** | PBO + cDMARD | |
| 1.04 (0.26, 3.25) | 1.87 (0.51, 7.19) | 1.60 (0.58, 4.22) | 1.68 (0.26, 9.58) | ***0.27 (0.08, 0.75)*** | cDMARD |
| **K. OR with 95%CrI for AEs at 24 weeks** | | | | | |
| BARI 2 mg + cDMARD | | | | | |
| 0.85 (0.46, 1.61) | BARI 4 mg | | | | |
| 0.75 (0.53, 1.08) | 0.88 (0.50, 1.52) | BARI 4 mg + cDMARD | | | |
| 0.49 (0.21, 1.16) | 0.59 (0.22, 1.55) | 0.66 (0.28, 1.53) | BARI 8 mg + cDMARD | | |
| 1.17 (0.82, 1.73) | 1.39 (0.78, 2.51) | ***1.58 (1.23, 2.04)*** | ***2.36 (1.02, 5.68)*** | PBO + cDMARD | |
| 0.86 (0.53, 1.40) | 1.01 (0.58, 1.81) | 1.15 (0.80, 1.64) | 1.74 (0.71, 4.24) | 0.73 (0.49, 1.08) | cDMARD |
| **L. OR with 95%CrI for infections at 24 weeks** | | | | | |
| BARI 2 mg + cDMARD | | | | | |
| 1.03 (0.52, 2.09) | BARI 4 mg | | | | |
| 0.82 (0.57, 1.22) | 0.80 (0.44, 1.47) | BARI 4 mg + cDMARD | | | |
| 0.82 (0.34, 1.93) | 0.78 (0.27, 2.22) | 1.00 (0.41, 2.32) | BARI 8 mg + cDMARD | | |
| 1.26 (0.87, 1.90) | 1.23 (0.66, 2.38) | ***1.53 (1.18, 2.04)*** | 1.55 (0.65, 3.80) | PBO + cDMARD | |
| 1.00 (0.61, 1.74) | 0.98 (0.52, 1.82) | 1.22 (0.83, 1.83) | 1.23 (0.49, 3.26) | 0.79 (0.53, 1.22) | cDMARD |

ACR = American College of Rheumatism, AEs = adverse events, BARI = baricitinib, cDMARDs = conventional disease-modifying antirheumatoid drugs, CrI = credible intervals, OR = odds ratio, PBO = placebo, SDAI = simplified disease activity index.

At AEs (Table 4K), 2 direct or indirect comparisons showed statistically significant differences. Baricitinib 4 mg + cDMARD and baricitinib 8 mg + cDMARD had a higher incidence of AEs than placebo + cDMARD (OR = 1.58, 95%CrI 1.23–2.04; OR = 2.36, 95%CrI 1.02–5.68). The ranking probability based on the SUCRA showed placebo + cDMARD was likely to be the safest intervention (SUCRA = 92.80%), followed by baricitinib 2 mg + cDMARD (70.80%), cDMARD (51.00%), baricitinib 4 mg (48.80%), baricitinib 4 mg + cDMARD (28.20%), baricitinib 8 mg + cDMARD (10.20%, Fig. 4K).

At infections (Table 4L), 1 direct or indirect comparisons showed statistically significant differences. Baricitinib 4 mg + cDMARD had a higher incidence of infections than placebo + cDMARD (OR = 1.53, 95%CrI 1.18–2.04). The ranking probability based on the SUCRA showed placebo + cDMARD was likely to be the intervention with the lowest incidence of infections (SUCRA = 86.00%), followed by baricitinib 4 mg (55.20%), cDMARD (51.80%), baricitinib 2 mg + cDMARD (50.60%), baricitinib 8 mg + cDMARD (34.20%), baricitinib 4 mg + cDMARD (19.60%, Fig. 4L).

### 3.4. Publication bias

Comparison-adjustment funnel plots were drawn for each outcome at 12 weeks and 24 weeks respectively, as shown in Figures 5 and 6. The results showed the comparison-adjustment funnel plots had poor symmetry, suggesting there might be a certain publication bias.

## 4. Discussion

In recent years, the researchers realized that JAKs play an important role in physiological signaling pathways of various growth factors, cell factors, and hormones, as well as their pathogenic role in RA. The first JAK inhibitor, tofacitinib, was approved by the US Food and Drug Administration in 2012. Baricitinib was the first JAK inhibitor to be approved for treating RA in the European Union and was launched in February 2017.[19] The European Federation of Rheumatism societies recommended adding biological agents or JAK inhibitors as supplements in cases of poor response or intolerance to the two traditional DMARDs.[20] However, due to the lack of clinical studies with direct comparisons, the ideal dosage of barrictinib needs to be weighed.

This network meta-analysis assessed the available evidence on the efficacy and safety of different doses of baricitinib for treating rheumatoid arthritis. ① Efficacy. In the efficacy outcomes at 12 weeks, nearly all doses of baricitinib with or without cDMARD were superior to placebo plus cDMARD,

and baricitinib 8 mg combined with cDMARD might have the best curative effect in most of efficacy (ACR20, ACR50, ACR70). In the efficacy outcomes at 24 weeks, all doses of baricitinib with or without cDMARD were superior to placebo plus cDMARD, and baricitinib 4 mg monotherapy might have the best curative effect in most outcomes of efficacy (ACR20, ACR70, SDAI ≤ 3.3). ② Safety. The incidence of AEs and infections was lower with placebo and low-dose baricitinib at both 12 and 24 weeks of treatment. The intervention with the highest incidence of AEs might be baricitinib 8 mg combined with cDMARD, and the intervention with the highest incidence of infections might be baricitinib 4 mg combined with cDMARD.

Further, a dose response to short-term use of baricitinib (12 weeks) was observed, with increased efficacy with a higher dose. The treatment benefit was larger for the 8 mg dose than for the lower dose. Therefore, high doses of baricatinib can be used to control the symptoms of RA in the short term. But if the course of treatment was extended (24 weeks), baricitinib 4 mg showed better efficacy and a lower incidence of AEs. This may be one reason the recommended dose of baricitinib is 4 mg.[21] The incidence of infections was higher with baricitinib 4 mg, consistent with baricitinib's immune adjustment action.[22] Patients with long-term baricitinib use at recommended doses should be carefully noted for infection risk, and dosage should be reduced in proper patients (e.g., patients with chronic or recurrent infections).

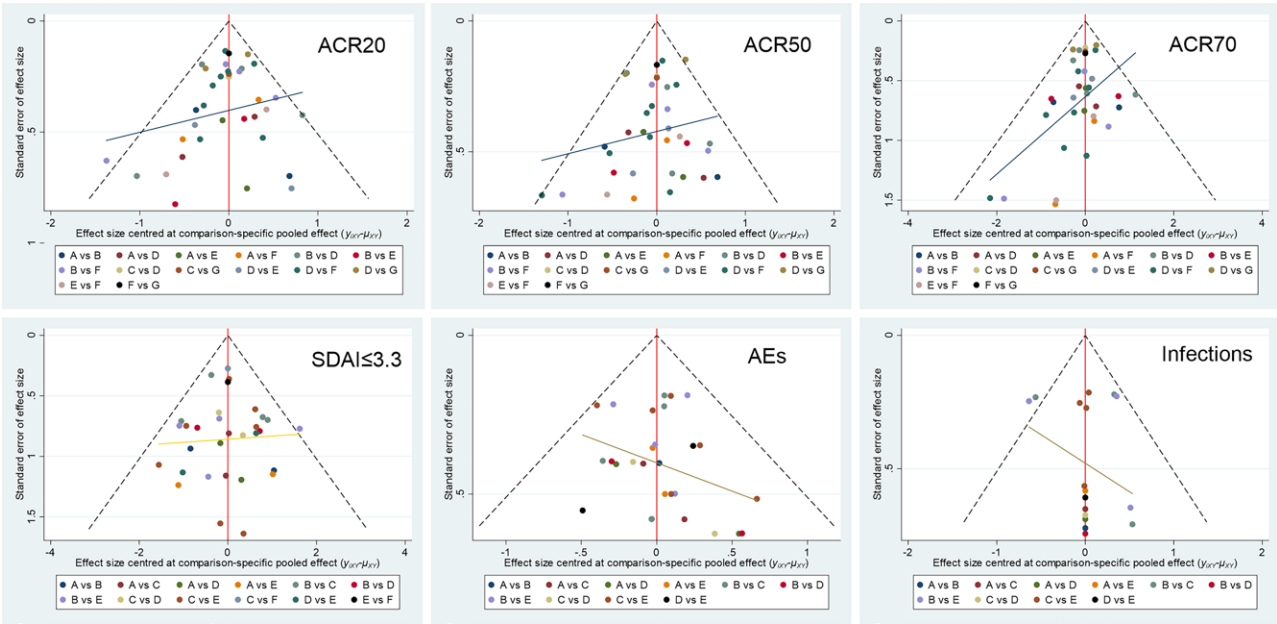


**Figure 5.** Comparison-adjustment funnel plot of outcomes at 12 weeks. ACR = American College of Rheumatism, AEs = adverse events, SDAI = simplified disease activity index.

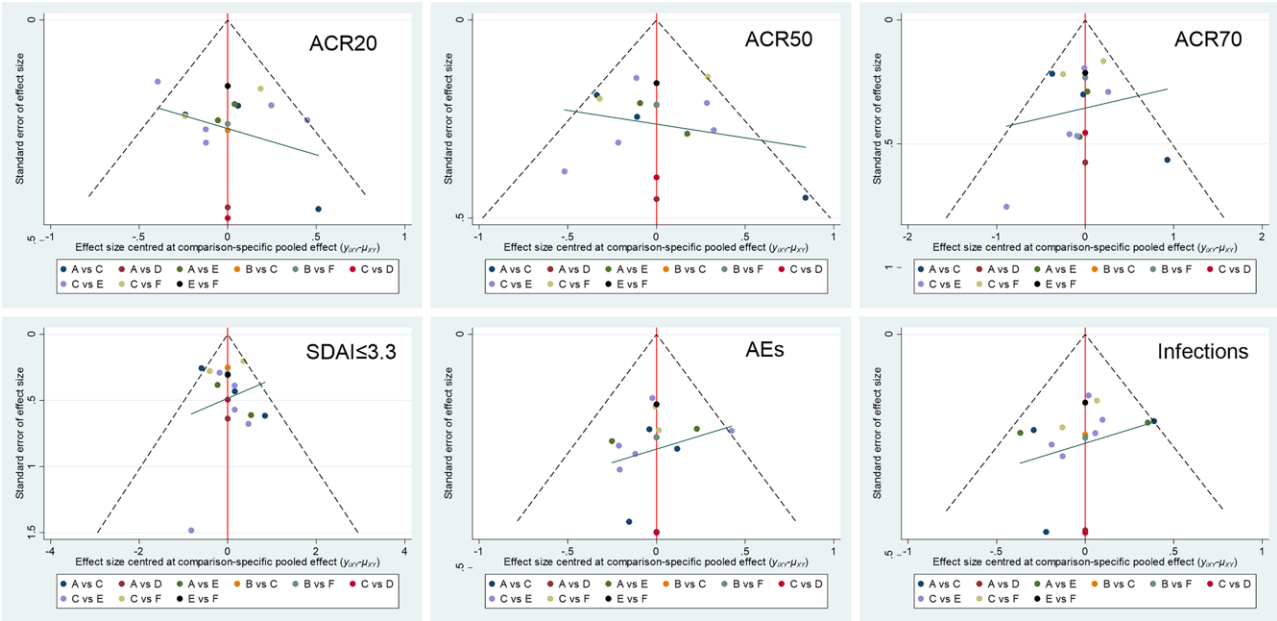


**Figure 6.** Comparison-adjustment funnel plot of outcomes at 24 weeks. ACR = American College of Rheumatism, AEs = adverse events, SDAI = simplified disease activity index.

The results should be interpreted with caution, as there are inevitably some limits in this study. First, the outcomes evaluation time points were limited to 12 weeks and 24 weeks. Therefore, the duration of treatment was too short to evaluate long-term efficacy and safety. Second, cDMARDs included multiple drugs. Differences between cDMARDs might affect the results of analysis, leading to the risk of bias. Third, some literature included a small number of patients, which might reduce the reliability of the experimental results. Four, we did not include other safety outcomes, such as the incidence of serious AEs, herpes zoster, and serious infections, due to the limit of article length.

## 5. Conclusion

In summary, baricitinib 8 mg combined with cDMARDs was suitable for short-term control of RA symptoms, and baricitinib 4 mg was more effective for treating RA over a longer period of time. But, baricitinib 8 mg had a high incidence of AEs and baricitinib 4 mg had a high incidence of infection. So, attention should be paid for the risk of baricitinib at 4~8 mg in clinical application. Due to some limits of this study, more long-term, high-quality studies are needed to further verify conclusions.

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**Writing – review & editing:** Wang Haikun, Wu Na, Su Dan.

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