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Comparison of the Efficacy and Safety of Disease-Modifying Antirheumatic Drugs Combination Therapies: A Systematic Review and Network Meta-Analysis

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ABSTRACT

There are several disease-modifying antirheumatic drugs currently available to treat rheumatoid arthritis (RA). However, the optimal combination therapy with methotrexate for treating RA remains unclear. We aimed to identify combination therapies with high-efficacy and safety by employing the Bayesian method in a network meta-analysis. We systematically searched PubMed, Embase, CENTRAL, Ichushi web, and PMDA review reports and application materials through October 2020, and found 86 randomized controlled trials. The primary efficacy outcome was the 50% improvement rate according to the American College of Rheumatology criteria (ACR50), and the primary safety outcome was the incidence of serious adverse events. We calculated odds ratios (ORs) and its 95% credible intervals (CrIs) between each treatment, and the surface under the cumulative ranking curve (SUCRA) score for each treatment to rank disease-modifying antirheumatic drug combinations. Individually, most disease-modifying antirheumatic drugs combined with methotrexate are more likely to achieve ACR50 than methotrexate monotherapy, with significant differences ($p < 0.05$), whereas the incidence of serious adverse events was not significantly different compared with methotrexate monotherapy ($p > 0.05$). Infliximab combined with methotrexate had the highest efficacy ranking (OR = 10.53, 95% CrI: [3.20, 42.87], SUCRA score: 0.884), and etanercept combined with methotrexate had the highest safety ranking (OR = 0.29, 95% CrI: [0.03, 2.04], SUCRA score: 0.893). Comprehensive cluster analysis revealed that the combination of etanercept, an Fc-fusion protein targeting tumor necrosis factor α, with methotrexate demonstrated higher efficacy and safety. These findings could support the selection of combination therapies for the treatment of RA.

1 | Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by joint pain, swelling, stiffness, and loss of function, arises from the immune system attacking healthy joint tissues. Additionally, RA leads to complications in organs beyond the joints [1]. Among the treatments for RA, disease-modifying antirheumatic drugs (DMARDs) are the primary treatment choice, among which methotrexate is one of the most widely used and effective treatments for RA, with low toxicity and good tolerability [2, 3]. The American College of Rheumatology (ACR), Japan College of Rheumatology (JCR), and European League Against Rheumatism (EULAR) guidelines recommend methotrexate as the first-line treatment for RA, unless contraindicated or not tolerated by the patient [4–6]. However, as methotrexate alone may not adequately control

Summary

- What is the current knowledge on the topic?
  - Combination therapy of disease-modifying antirheumatic drugs (DMARDs) with methotrexate is recommended by multiple guidelines for the treatment of rheumatoid arthritis (RA) in patients intolerant to methotrexate. However, despite the availability of several types of DMARDs, it is unclear which DMARD combination therapy has the highest efficacy and safety.
- What question did this study address?
  - This network meta-analysis was performed to rank the efficacy and safety of DMARD combination therapies and explore the possible factors for high efficacy and safety.
- What does this study add to our knowledge?
  - The combination therapy of etanercept with methotrexate has the highest efficacy and safety among those of the combination therapies using different DMARDs for the treatment of patients with RA.
- How might this change clinical pharmacology or translational science?
  - The characteristic of the high efficacy and safety DMARD etanercept, the Fc-fusion protein targeting TNF-α, may be shared by high efficacy and safe drugs for RA treatment. This may serve as an exploratory for identifying RA treatments with high efficacy and safety.

RA disease activity, ACR guidelines also include the recommendation for combination therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) [4]. Abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, and tocilizumab are the bDMARDs used for RA treatment, whereas baricitinib, peficitinib, tofacitinib, and upadacitinib are the tsDMARDs used for RA treatment. These medications target various molecules such as cluster of differentiation 20/80/86 (CD20/80/86), tumor necrosis factor (TNF)-α, interleukin 1 (IL-1), interleukin 6 (IL-6), and Janus kinase (JAK). Owing to the crucial roles of these targets in RA disease activity, inhibiting their expression may effectively control the disease progression [7–9].

Systematic review/meta-analysis (MA) is a method use to synthesize data from published research in a specific field, allowing for refined conclusions. Although traditional MA can only be used to compare the effects of two interventions, but cannot compare three or more, so it may not fully meet the needs of clinical decision-making. Conversely, network meta-analysis (NMA) enables the simultaneous comparison of three or more interventions by integrating direct and indirect evidence from a network of studies based on an anchor drug that is used as the control group [10]. As most clinical studies on DMARDs combination therapy compare the efficacy and safety of those to these of methotrexate monotherapy, using methotrexate as the anchor drug may be useful for analyzing the efficacy and safety of DMARDs.

Numerous studies have been conducted to test the efficacy and safety of methotrexate combination therapy with bDMARDs or tsDMARDs in RA treatment. However, in many studies, combination therapies are compared only against methotrexate monotherapy, and direct comparisons among different DMARDs combination therapies are lacking. Moreover, existing MA studies on the combination therapies of DMARDs with methotrexate have limitations. These studies typically included only a small number of DMARDs treatments, focused solely on efficacy or safety, or included treatments that were not combined with methotrexate.

For example, Donahue et al. only compared the efficacy of certain bDMARDs (6 types) combined with methotrexate versus methotrexate monotherapy using NMA [11]. Baradat et al. solely focused on safety comparisons of some bDMARDs (7 types) combined with methotrexate versus methotrexate monotherapy through MA [12]. Weng et al. compared both bDMARDs (8 types) and tsDMARDs (3 types), but not all combination therapies were evaluated with methotrexate through NMA [13].

In this study, we aimed to compare and rank the combinations of 10 types of bDMARDs and 4 types of tsDMARDs with methotrexate based on their efficacy and safety for RA treatment using NMA.

2 | Methods

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [14]. Three researchers (L.L., M.O., and Y.Y.) independently performed literature screening, data extraction, and evidence assessment. In case of discrepancies, K.A. acted as a third party and resolved any disagreements between the authors.

2.1 | Data Sources

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (https://www.cochranelibrary.com/central) for records published up to October 2020. CENTRAL included records from PubMed, Embase, International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, and CINAHL. In addition, records from the Ichushi Web database (https://login.jamas.or.jp/) and the review reports and application materials from the Pharmaceuticals and Medical Devices Agency (PMDA) (https://www.pmda.go.jp/PmdaSearch/iyakuSearch/) prior to October 2020 were included. Based on the treatment drugs of interest, we set the following search terms: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab, baricitinib, peficitinib, tofacitinib, upadacitinib, and methotrexate. The search strategies used are shown in Table S1.

2.2 | Study Selection

Abstracts and full texts of the retrieved literature were reviewed based on the inclusion and exclusion criteria. The inclusion

criteria for the studies were (i) randomized controlled trial (RCT) study design; (ii) patients with RA; (iii) comparison of combination therapies of two different DMARDs with methotrexate, or comparison of combination therapy of DMARDs with methotrexate versus methotrexate monotherapy; and (iv) written in English or Japanese. The exclusion criteria for the studies were (i) non-RCT study design (post hoc analysis, subgroup analysis, pooled analysis, secondary analysis, exposure-response analysis, systematic review or meta-analysis, cohort analysis, or experience of patients); (ii) healthy volunteers or patients with diseases other than RA; (iii) comparison of combination therapies of non-DMARDs with methotrexate, or comparison of bDMARDs/tsDMARDs monotherapy versus placebo therapy; and (iv) written in languages other than English or Japanese. Although duplicate studies were excluded, the corresponding clinical trials were recorded and used as additional data when necessary.

2.3 | Data Extraction

Patient backgrounds data and baseline characteristics were extracted from the studies that met the inclusion criteria. Patient backgrounds data included mean age, body weight, sex, disease duration, methotrexate use status, and race/ethnicity. The baseline characteristics included tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, disease activity score-28 using ESR (DAS28-ESR), and disease activity score-28 using CRP (DAS28-CRP). According to the preset unit standard, all data were converted to the same unit before recording. For missing or imprecise data, data of the same clinical trial but from different databases were used; the databases were prioritized in the following order: (i) PubMed, (ii) PMDA, (iii) Embase, and (iv) ICTRP/ClinicalTrials.gov. When only the measurement accuracy differed, the most accurate data were selected regardless of priority. For groups within the same clinical trial with different dosages of the same treatment, the group with the U.S. Food and Drug Administration (FDA) recommended dosage or the closest dosage was chosen as the intervention group. The FDA public prescription information for the 14 DMARDs treatments is shown in Table S2.

The extracted outcome data included efficacy and safety. The primary efficacy outcome was ACR50, a set of comprehensive evaluation indices recommended by the ACR. This comprehensive evaluation indices refers to a 50% improvement in both TJC and SJC, and a 50% improvement in three of the following five items: patient pain assessment, patient physical function assessment, patient global disease activity assessment, physician global disease activity assessment, and acute-phase reactant (ESR or CPR) [15]. For the "ACR" indices, the number following it represents the degree of improvement. The primary safety outcome was serious adverse events (SAEs) using with disease terms from MedDRA (https://www.meddra.org/). Secondary outcomes were used to assist with the primary outcomes. The secondary efficacy outcome was ACR20, and the secondary safety outcome was adverse events (AEs). Outcome data have included data from all available periods whenever possible. For efficacy outcomes, data from 12 ± 4 weeks were used, and for safety outcomes, the final data obtained were used. Data beyond the clinical trial period were recorded but not analyzed.

2.4 | Quality Assessment

The risk of bias was evaluated by two authors (L.L. and M.O.) using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) [16]. Five domains of risk bias were reviewed and rated as high risk, some concern, or low risk. The overall risk of bias was determined based on the evaluation results.

2.5 | Statistical Analysis

An NMA was conducted using the Bayesian method based on the Markov chain Monte Carlo (MCMC) simulation of the posterior distribution. NMA using the Bayesian methods was performed using the "gemtc" package v1.0–1 in R v4.2.1 software and the Just Another Gibbs Sampler v4.3.1 program [17–19]. Efficacy and safety outcomes of combination therapies of DMARDs with methotrexate versus methotrexate monotherapy are presented as binary outcomes, with odds ratios (ORs), that is, the ratio of the odds of the event of incidence to nonincidence in the experimental group to the odds of the event of incidence to nonincidence in the control group, as effect size indicators. We used a random effects model with binomial likelihood accounting for study bias, summarized OR estimates and between-trial variance from the posterior distributions, and obtained 95% credible intervals (95% CrI) and corresponding medians. A fixed effects model was used when the random effects model failed to converge. To facilitate a clearer interpretation of the rankings and reduce the uncertainty from the Bayesian method, we calculated the surface under the cumulative ranking curves (SUCRA) score using cumulative ranking probabilities [20]. To enhance the credibility of the analysis, we also validated the efficacy and safety results using the frequentist method, an alternative method to NMA. In the frequentist method, the p score similar to the SUCRA score was used for ranking.

The relationship between the targets and structural types of DMARDs with their efficacy and safety was also discussed to analyze whether there are treatments with advantages in efficacy and safety.

As NMA combines direct and indirect evidence, the heterogeneity, consistency, and transitivity of the network need to be assessed to evaluate the validity of NMA. The heterogeneity assumption judges the internal disagreement of direct evidence, the consistency assumption judges the consistency of the results of direct evidence and indirect evidence, and the transitivity assumption judges whether indirect evidence could be used [21]. Heterogeneity was evaluated using the I^2 statistic to determine the degree of variation in expression. Based on a rough interpretation of the Cochrane guidelines, the thresholds for the degree of heterogeneity were set at $I^2 \leq 35\%$ for low heterogeneity, $35 < I^2 \leq 70\%$ for moderate to significant heterogeneity, and $I^2 > 70\%$ for high heterogeneity [10]. For outcomes with high heterogeneity, we explored the sources of heterogeneity between studies and the factors that may have caused high heterogeneity based on the study characteristics. Consistency of the network was evaluated using node-splitting and based on the deviance information criterion (DIC) value. The consistency was considered good when the absolute difference between the DIC values of the

consistent model (or NMA model) and the inconsistent model (or UME model) was less than five [22]. Transitivity was assessed by evaluating demographic characteristics, disease characteristics, and methodological differences between the intervention and control groups at baseline.

The impact of unpublished studies, that is, publication bias, was evaluated using the quantitative Egger's test and the qualitative funnel plot [23]. Egger's test was performed using the "metafor" package v3.8–1 in R v4.2.1 software [17, 24]. The funnel plot plots log odds ratios (logORs) against its standard error, and if there is no publication bias, the funnel plot takes the shape of a symmetrical inverted funnel.

The statistical significance level was set at $\alpha = 0.05$ for all analyses.

3 | Results

3.1 | Study Collection and Study Characteristics

We identified 1730 manuscripts from the databases (PubMed: 708; Embase: 438; CENTRAL: 556; Ichushi Web: 28). After applying the inclusion and exclusion criteria, we excluded 1567 articles based on abstract and full-text reviews to include 163 articles. Additionally, 408 studies were identified from the PMDA review reports, of which 37 met the inclusion criteria. After combining studies from both sources, removing duplicates and studies without efficacy or safety results, we conducted an NMA of 86 studies. (Figure 1).

Among the included 86 studies, 50 studies included ACR50 (12 ± 4 weeks) data, 50 studies included ACR20 (12 ± 4 weeks) data, 55 studies included SAE (final) data, and 54 studies included AE (final) data. The network diagrams of the primary efficacy and safety outcomes are shown in Figures 2 and 3. Ten studies (four on adalimumab; two on anakinra; one on etanercept; one on infliximab; and two on rituximab) did not include primary or secondary efficacy and safety outcomes for the specified period. The sources of the 86 studies are listed in Table S3. Owing to the lack of efficacy data for the specified period, rituximab was not included in the NMA. The demographic characteristics and baseline disease characteristics of patients in the combination therapy and methotrexate monotherapy groups were confirmed and are shown in Tables S4 and S5. There were no statistically significant differences between the two groups (Table S6).

3.2 | Risk of Bias and Publication Bias

We assessed the risk of bias in the 86 studies using RoB 2 (Table S7 and Figure S1). Fifteen studies (4 of 23 with adalimumab; 4 of 5 with etanercept; 3 of 4 with anakinra; 3 of 11 with infliximab; 1 of 3 with rituximab) identified to be at high overall

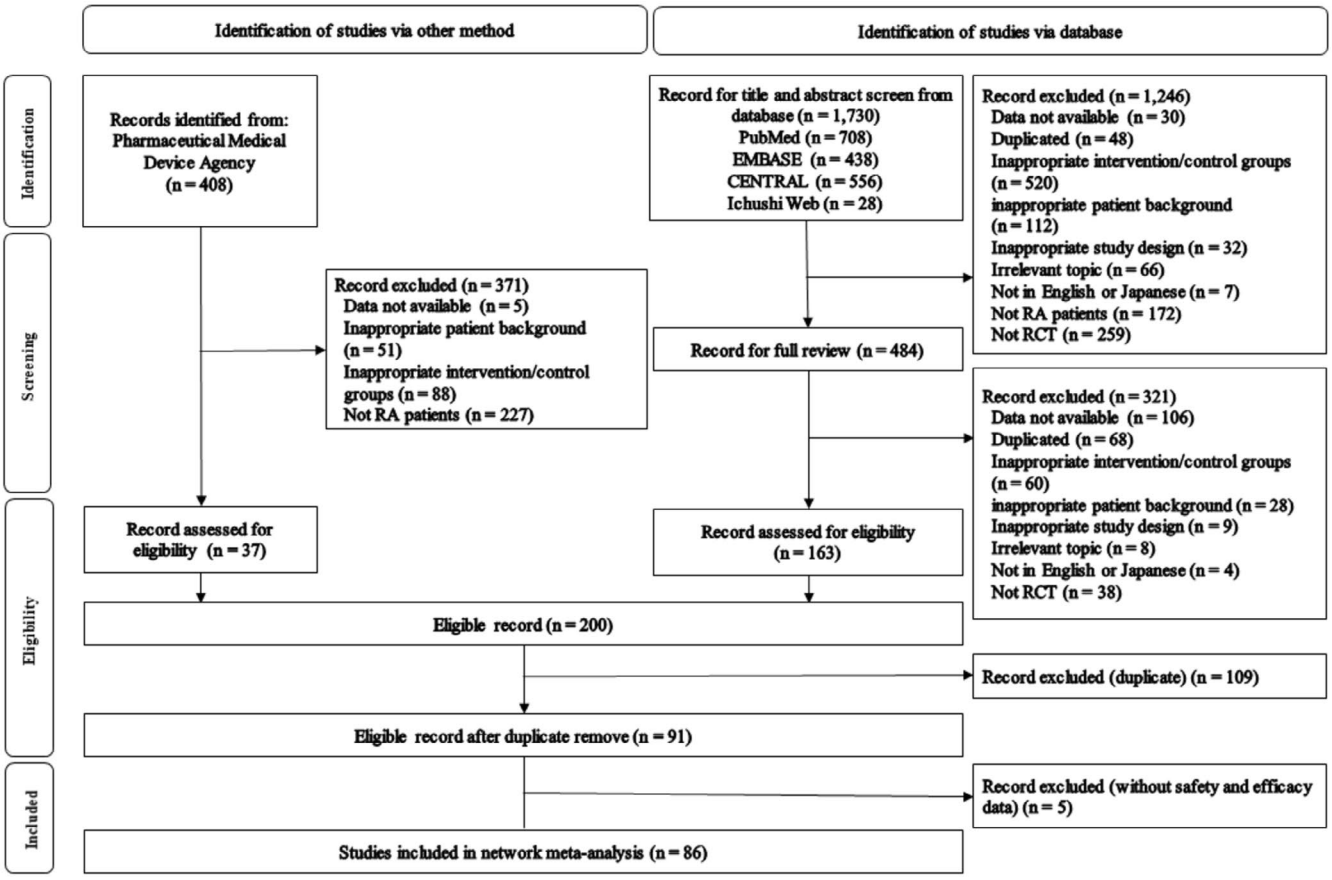

FIGURE 1 | Flow chart of the study selection process. Three researchers independently performed the literature screening, data extraction, and evidence assessment according to the inclusion and exclusion criteria. RA, Rheumatoid arthritis; RCT, Randomized controlled trials.

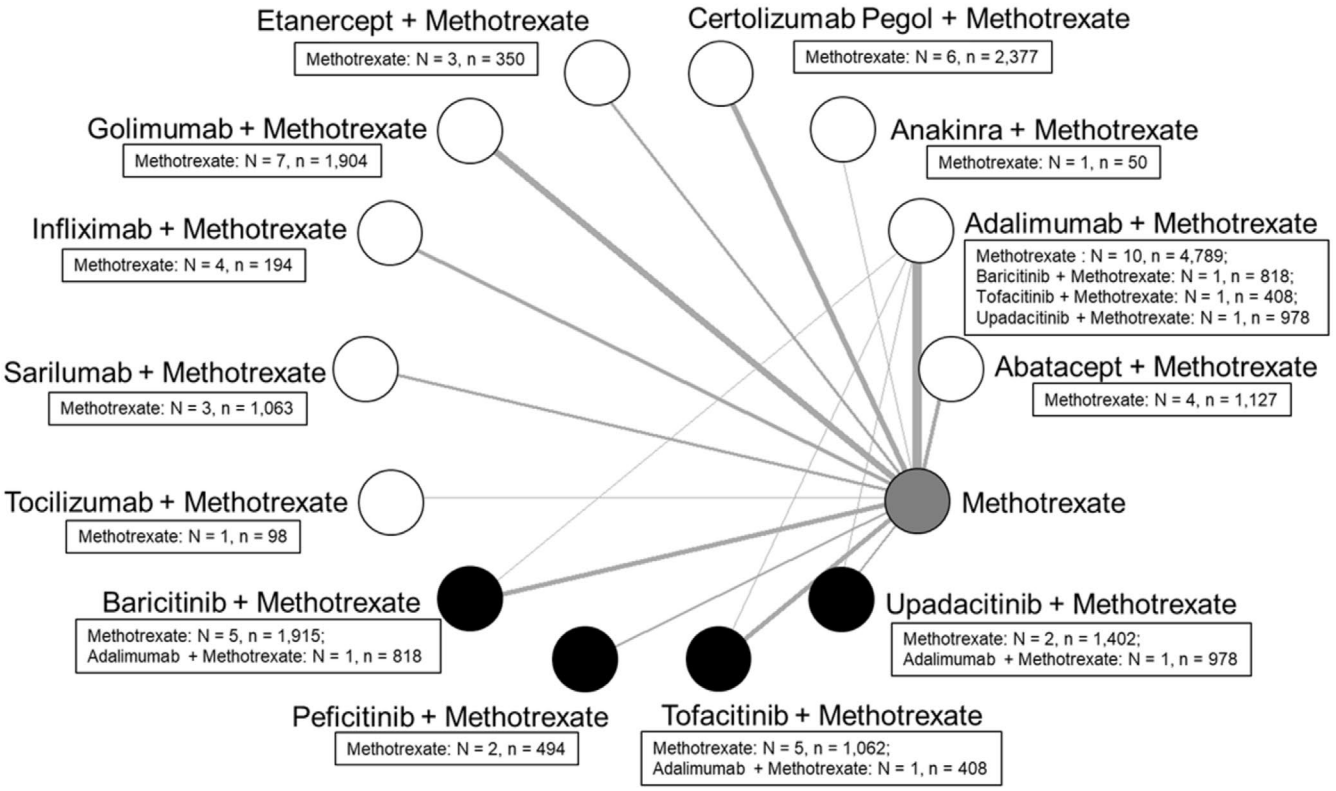

FIGURE 2 | Network of primary efficacy outcomes. White, black, and gray circles represent bDMARDs combination therapy, tsDMARDs combination therapy, and methotrexate monotherapy. The line between two treatments indicates the existence of comparative studies, and the line width represents the number of studies. N: Number of studies; n: Number of patients.

risk of bias. Among them, six (two each with adalimumab and etanercept, one each with anakinra and infliximab) studies included ACR50 (12 ± 4 weeks) data, four (one each with adalimumab, anakinra, infliximab, and rituximab) studies included SAE (final) data, six (two each with adalimumab, and etanercept, one each with anakinra, and infliximab) studies included ACR20 (12 ± 4 weeks) data, and seven (two each with adalimumab and infliximab, one each with etanercept, anakinra, and rituximab) studies included AE (final) data.

For publication bias, Egger's test showed significant asymmetry for efficacy ($p = 0.02$; ACR50 and 0.03; ACR20) but not in safety ($p = 0.78$; SAE and 0.56; AE). The funnel plot represented this result. Thus, the efficacy outcomes were subject to publication bias that may have affected the NMA results, whereas the safety outcomes showed no publication bias (Figure S2).

3.3 | ORs, SUCRA Score and Cluster Analysis of Efficacy and Safety of Combination Therapies of DMARDs With Methotrexate and Methotrexate Monotherapy

We conducted an NMA combining the efficacy and safety outcome data of 83 studies (rituximab excluded). As the safety outcome data could not achieve convergence using the random effects model, a fixed effects model was used for the analysis. We calculated the ORs and 95% CrIs of DMARD plus methotrexate combination therapies compared to methotrexate monotherapy using Bayesian method and used these values to calculate their SUCRA scores and rankings.

For the primary efficacy outcome ACR50 (12 ± 4 weeks) (Table 1), the ORs for combination therapy groups were above 1.00 compared with the monotherapy group; however, some combination therapy groups did not show significant differences (anakinra, OR = 2.51, 95% CrIs: 0.34–25.77; tocilizumab, OR = 1.47, 95% CrIs: 0.35–6.08). Infliximab combined with methotrexate showed the highest OR point estimate (OR = 10.53, 95% CrIs: 3.20–42.87). The combination treatment groups did not differ significantly, except for tocilizumab with infliximab (OR = 7.24, 95% CrIs: 1.12–53.66). According to SUCRA scores, which were the ranking indicators for the Bayesian method, infliximab combined with methotrexate had the highest ACR50 (12 ± 4 weeks) ranking (SUCRA: 0.884) (Table 2).

For the primary safety result SAE (final) (Table 1), the ORs for some combination therapy groups were above 1.00 compared with the monotherapy group, whereas other groups were below 1.00. However, most combination therapy groups did not show significant differences, and only a few showed significant differences compared to methotrexate monotherapy (adalimumab, OR = 1.21, 95% CrIs: 1.00–1.47; tofacitinib, OR = 1.65, 95% CrIs: 1.04–2.63). Etanercept combined with methotrexate showed the lowest OR point estimate (OR = 0.29, 95% CrIs: 0.03–2.04). No significant differences were observed among the combined

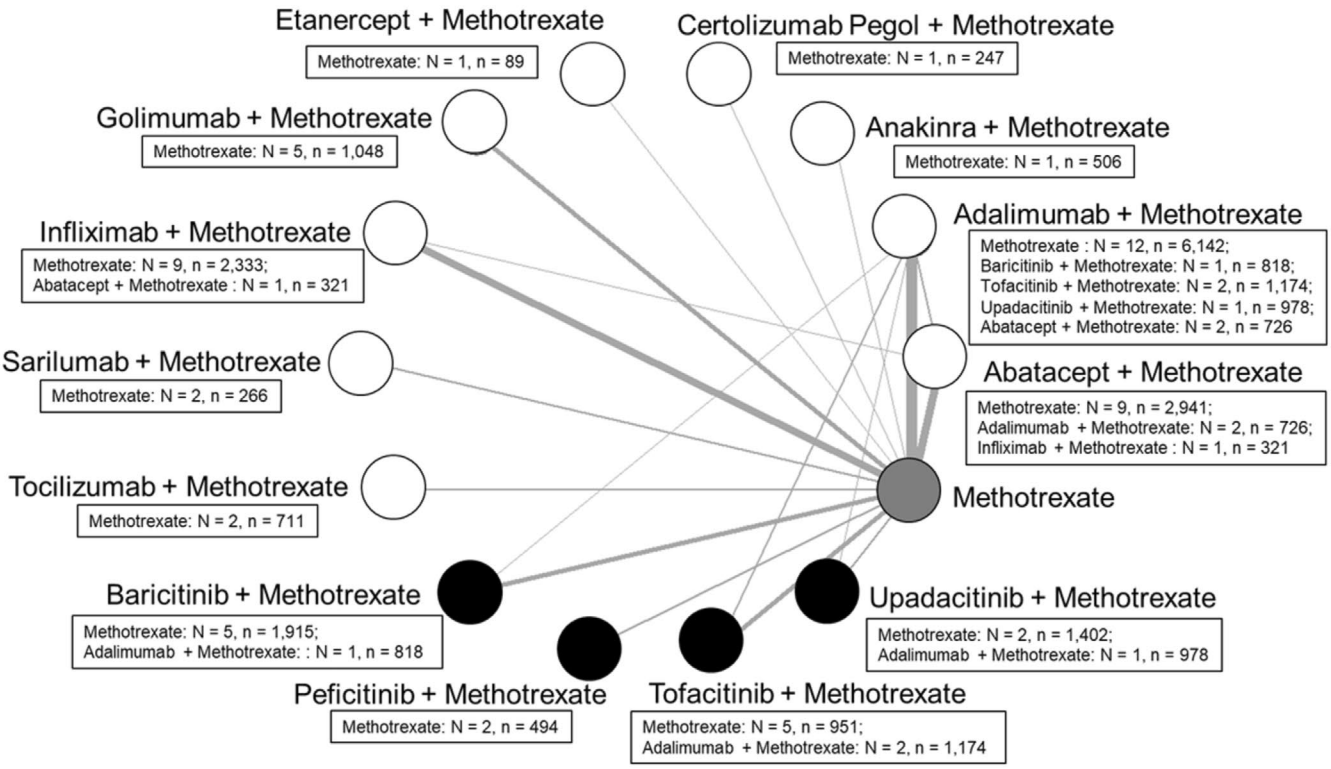

FIGURE 3 | Network of primary safety outcomes. White, black, and gray circles represent bDMARDs combination therapy, tsDMARDs combination therapy, and methotrexate monotherapy. The line between two treatments indicates the existence of comparative studies, and the line width represents the number of studies. N: Number of studies; n: Number of patients.

treatment groups. According to the SUCRA scores, etanercept combined with methotrexate had the highest SAE (final) ranking (SUCRA: 0.893). (Table 2).

Cluster analysis of the SUCRA scores for ACR50 (12 ± 4 weeks) and SAE (final) data revealed that etanercept combined with methotrexate had the highest overall efficacy and safety, followed by sarilumab/infliximab combined with methotrexate (Figure 4).

For the secondary efficacy outcome ACR20 (12 ± 4 weeks), tofacitinib plus methotrexate showed the highest OR point estimate with statistical significance (OR = 4.56, 95% CrIs: 2.61–8.29) (Table S8). Tofacitinib combined with methotrexate also ranked the highest for ACR20 (12 ± 4 weeks) data, based on the SUCRA scores (SUCRA: 0.735) (Table S9). For the secondary efficacy outcome AE (final), although etanercept plus methotrexate showed the lowest OR point estimate the difference was not significant (OR = 0.99, 95% CrIs: 0.62–1.58) (Table S8). Etanercept combined with methotrexate had the highest AE (final) ranking based on the SUCRA score (SUCRA: 0.844) (Table S9). Cluster analysis for ACR20 (12 ± 4 weeks) and AE (final) showed that etanercept/tofacitinib combined with methotrexate had the highest overall efficacy and safety (Figure S3).

The *p* scores and rankings of DMARD plus methotrexate combination therapies based on the efficacy and safety outcome data were also calculated using the frequentist method (Tables S10 and S11). With respect to the primary outcome, etanercept combined with methotrexate had the highest ACR50 (12 ± 4 weeks; *p* score: 0.778) ranking and SAE (final; *p* score: 0.891) ranking based on *p* scores. Based on the secondary outcome data, certolizumab pegol combined with methotrexate had the highest ACR20 (12 ± 4 weeks; *p* score: 0.715) ranking, whereas etanercept combined with methotrexate had the highest AE (final; *p* scores: 0.844) ranking. By incorporating the *p* scores into a cluster plot, etanercept combined with methotrexate was shown to possess the highest overall efficacy and safety across both primary and secondary outcomes (Figure S4). A comparison of the cluster plots of *p* scores and SUCRA scores revealed that the distribution of the various combination therapies did not change significantly. Thus, the results of the frequentist cluster analysis were consistent with those obtained using the Bayesian approach.

3.4 | Evaluation of the Validity of NMA

We assessed the validity of the NMA based on its heterogeneity, transitivity, and consistency (Table 3). The I^2 values for pairwise and network comparisons between the combination therapies of DMARDs with methotrexate and methotrexate monotherapy are presented in Table 3. For the primary efficacy and safety outcome data, considerable heterogeneity was observed with respect to ACR50 (12 ± 4 weeks) during pairwise ($I^2 = 76.7\%$) and network ($I^2 = 75.4\%$) comparisons, whereas SAE (final) exhibited low heterogeneity during pairwise ($I^2 = 8.3\%$) and network ($I^2 = 9.9\%$) comparisons. For the secondary efficacy and safety outcomes, considerable heterogeneity was observed for ACR50 (12 ± 4 weeks) data during pairwise ($I^2 = 77.8\%$) and network ($I^2 = 76.9\%$) comparisons, whereas AE (final) exhibited low heterogeneity during pairwise ($I^2 = 5.4\%$) and network ($I^2 = 14.6\%$)

TABLE 1 | Results of the primary efficacy and safety outcomes.

SAE ACR50	Abatacept + MTX	Adalimumab + MTX	Anakinra + MTX	Certolizumab pegol + MTX	Etanercept + MTX	Golimumab + MTX	Infliximab + MTX	Sarilumab + MTX	Tocilizumab + MTX	Baricitinib + MTX	Peficitinib + MTX	Tofacitinib + MTX	Upadacitinib + MTX	MTX
Abatacept + MTX		0.81 (0.62,1.05)	0.76 (0.28,2.04)	0.73 (0.31,1.68)	3.33 (0.47,28.94)	0.67 (0.34,1.30)	0.96 (0.68,1.36)	2.10 (0.6,8.53)	0.80 (0.44,1.46)	0.73 (0.45,1.21)	0.99 (0.22,4.48)	0.59 (0.36,0.97)	0.65 (0.34,1.26)	0.98 (0.77,1.23)
Adalimumab + MTX	1.14 (0.51,2.57)		0.94 (0.35,2.51)	0.91 (0.40,2.07)	4.12 (0.59,36.2)	0.83 (0.43,1.60)	1.19 (0.85,1.67)	2.60 (0.75,10.65)	1.00 (0.56,1.78)	0.91 (0.57,1.46)	1.24 (0.28,5.58)	0.73 (0.47,1.14)	0.81 (0.43,1.51)	**1.21 (1.00,1.47)**
Anakinra + MTX	1.45 (0.13,12.05)	1.28 (0.12,9.72)		0.97 (0.27,3.44)	4.40 (0.5,46.67)	0.88 (0.28,2.82)	1.26 (0.47,3.51)	2.78 (0.58,14.70)	1.06 (0.35,3.25)	0.97 (0.33,2.84)	1.31 (0.22,7.92)	0.77 (0.27,2.3)	0.85 (0.27,2.72)	1.28 (0.49,3.43)
Certolizumab pegol + MTX	0.70 (0.27,1.72)	0.61 (0.29,1.22)	0.47 (0.06,5.21)		4.54 (0.55,45.24)	0.91 (0.33,2.55)	1.31 (0.56,3.09)	2.88 (0.65,14.10)	1.09 (0.41,2.92)	1.00 (0.40,2.55)	1.36 (0.25,7.36)	0.80 (0.32,2.05)	0.88 (0.32,2.46)	1.33 (0.60,3.00)
Etanercept + MTX	0.45 (0.14,1.42)	0.40 (0.14,1.04)	0.31 (0.03,3.59)	0.66 (0.22,1.91)		0.20 (0.02,1.54)	0.29 (0.03,2.04)	0.63 (0.05,6.73)	0.24 (0.03,1.81)	0.22 (0.02,1.60)	0.30 (0.02,3.40)	0.18 (0.02,1.29)	0.20 (0.02,1.49)	0.29 (0.03,2.04)
Golimumab + MTX	0.95 (0.39,2.28)	0.84 (0.43,1.60)	0.66 (0.08,7.07)	1.37 (0.63,3.13)	2.10 (0.76,6.13)		1.43 (0.73,2.85)	3.13 (0.78,14.27)	1.20 (0.53,2.76)	1.10 (0.51,2.38)	1.48 (0.29,7.60)	0.88 (0.41,1.93)	0.96 (0.4,2.36)	1.45 (0.78,2.74)
Infliximab + MTX	0.35 (0.07,1.39)	0.30 (0.07,1.07)	0.24 (0.02,3.17)	0.50 (0.11,1.93)	0.76 (0.15,3.49)	0.37 (0.08,1.33)		2.18 (0.62,8.98)	0.84 (0.45,1.55)	0.76 (0.45,1.30)	1.03 (0.23,4.72)	0.61 (0.36,1.05)	0.67 (0.34,1.33)	1.02 (0.77,1.34)
Sarilumab + MTX	0.78 (0.27,2.25)	0.69 (0.28,1.65)	0.54 (0.06,6.14)	1.13 (0.43,3.11)	1.72 (0.53,5.84)	0.82 (0.32,2.11)	2.25 (0.54,11.09)		0.38 (0.09,1.47)	0.35 (0.08,1.30)	0.47 (0.06,3.27)	0.28 (0.07,1.05)	0.31 (0.07,1.22)	0.47 (0.12,1.59)
Tocilizumab + MTX	2.49 (0.51,12.4)	2.19 (0.50,9.68)	1.76 (0.14,25.11)	3.60 (0.78,17.52)	5.50 (1.05,30.82)	2.61 (0.58,12.07)	**7.24 (1.12,53.66)**	3.20 (0.63,16.49)		0.91 (0.45,1.87)	1.24 (0.25,6.10)	0.74 (0.36,1.49)	0.81 (0.36,1.84)	1.22 (0.70,2.11)
Baricitinib + MTX	0.86 (0.34,2.13)	0.75 (0.39,1.46)	0.59 (0.07,6.46)	1.23 (0.55,2.94)	1.88 (0.67,5.69)	0.90 (0.42,1.97)	2.48 (0.66,11.12)	1.10 (0.42,2.93)	0.34 (0.07,1.59)		1.35 (0.29,6.35)	0.80 (0.43,1.51)	0.88 (0.41,1.89)	1.33 (0.85,2.07)
Peficitinib + MTX	0.85 (0.27,2.70)	0.74 (0.27,2.01)	0.58 (0.06,7.01)	1.22 (0.42,3.77)	1.86 (0.53,7.02)	0.88 (0.31,2.57)	2.44 (0.54,12.90)	1.08 (0.33,3.65)	0.34 (0.06,1.85)	0.99 (0.34,2.90)		0.59 (0.12,2.82)	0.65 (0.13,3.29)	0.98 (0.22,4.37)
Tofacitinib + MTX	0.67 (0.26,1.73)	0.59 (0.30,1.17)	0.46 (0.06,5.07)	0.97 (0.42,2.34)	1.49 (0.52,4.56)	0.71 (0.32,1.58)	1.95 (0.51,8.85)	0.86 (0.32,2.34)	0.27 (0.06,1.27)	0.79 (0.34,1.80)	0.80 (0.27,2.39)		1.10 (0.51,2.36)	**1.65 (1.04,2.63)**
Upadacitinib + MTX	0.76 (0.26,2.31)	0.67 (0.28,1.61)	0.52 (0.06,6.23)	1.10 (0.41,3.22)	1.67 (0.51,6.01)	0.80 (0.30,2.18)	2.21 (0.52,11.26)	0.98 (0.31,3.14)	0.30 (0.06,1.61)	0.89 (0.33,2.46)	0.90 (0.26,3.14)	1.13 (0.41,3.20)		1.51 (0.81,2.79)
MTX	**3.66 (1.81,7.49)**	**3.21 (2.17,4.79)**	2.51 (0.34,25.77)	**5.26 (2.97,10.06)**	**8.04 (3.38,20.80)**	**3.83 (2.31,6.53)**	**10.53 (3.20,42.87)**	**4.67 (2.16,10.41)**	1.47 (0.35,6.08)	**4.26 (2.42,7.62)**	**4.32 (1.74,10.81)**	**5.42 (2.98,10.05)**	**4.80 (2.06,10.99)**	

Note: Lower left, ACR50 (12 ± 4 weeks); upper right, SAE (final). The results are presented as OR (95% CrI), with values in bold indicating significant differences. For efficacy outcomes, an OR greater than one indicates that treatment on the upper side was better than that on the left side. Forsafety outcomes, an OR greater than one indicates that the treatment on the left side was worse than that on the upper side. If the 95% CrI range includes one, the result is not statistically significant; if it does not include one, the result is statistically significant. ACR50: Comprehensive evaluation indexes put forward by the American College of Rheumatology, indicating that the patient has improved by at least 50% in specified indicators.

Abbreviations: CrI: Credible interval; MTX: Methotrexate; OR, Odds ratio; SAE, Serious adverse events.

comparisons. Efficacy outcomes generally exhibited high heterogeneity, whereas safety outcomes showed low heterogeneity.

We compared the demographic and baseline disease characteristics of the DMARD plus methotrexate combination therapies groups with those of methotrexate monotherapy groups and found no significant differences, suggesting good transitivity (Table S6). Methodologically, the study designs met the inclusion and exclusion criteria, and most the studies were rated as low risk or some concern according to the RoB2 (Tables S4 and S5). On testing the consistency of the data of primary efficacy outcome ACR50 (12 ± 4 weeks), no significant difference was observed between the results of direct and indirect evidence, and the difference in DIC values was within a reasonable range ($|DIC_{CON}\text{-}DIC_{INC}| = 1.50$). Similarly, for the data of primary efficacy outcome SAE (final), there was no significant difference between the results of direct and indirect evidence, except for the following combination therapies, namely, upadacitinib and adalimumab, baricitinib and adalimumab, and abatacept and infliximab, which showed significant differences ($p = 0.01$, 0.04, and 0.03, respectively) (Table S12). Nevertheless, the differences in DIC values were within a reasonable range ($|DIC_{CON}\text{-}DIC_{INC}| = 2.37$). Thus, some discrepancies were observed in the consistency of the primary safety outcomes.

4 | Discussion

Due to differences in the patient's demographic background and disease activity, etc. among clinical studies, it is difficult to show objective effects directly in general when comparing multiple studies. However, NMA evaluates the treatment effect of each study by using the difference in effect between the experimental group and the control group of the same study (i.e., effect size, OR was used in this study). Comparison of the ORs across studies using NMA can reduce the impact of background differences between studies and more objectively show the effect of treatment. Background differences between studies can also be shown in NMA through the quantitative uncertainty of the effect size. This advantage of NMA makes it possible to integrate studies with different backgrounds [10].

The current NMA-based study and the associated cluster analysis plots revealed important insights into the applicability of combination therapies according to the SUCRA scores and rankings for efficacy and safety outcomes. Based on the primary efficacy and safety outcomes, etanercept combination therapy demonstrated excellent overall efficacy and safety according to the cluster plot analysis, whereas the other combination therapies, such as those of infliximab and sarilumab, showed relatively good efficacy and safety. The negative results of some combination therapies may be attributed to the low outcome-based ranking obtained in our study. For instance, certolizumab pegol, upadacitinib, and tofacitinib combination therapies exhibited high efficacy but low safety. In contrast, abatacept combination therapy had a higher safety ranking but lower efficacy. For infliximab and salirumab combination therapies, which showed relatively good comprehensive efficacy and safety with respect to primary outcomes, the secondary efficacy and safety outcomes were reduced owing to the low ranking of the secondary safety outcome data AE (final).

TABLE 2 | SUCRA scores and ranking based ACR50 (12 ± 4 weeks) and SAE (final).

	ACR50		SAE	
Treatment	**SUCRA**	**Rank**	**SUCRA**	**Rank**
Abatacept + Methotrexate	0.426	10	0.673	3
Adalimumab + Methotrexate	0.319	12	0.418	7
Anakinra + Methotrexate	0.359	11	0.410	8
Baricitinib + Methotrexate	0.519	8	0.350	10
Certolizumab pegol + Methotrexate	0.657	4	0.378	9
Etanercept + Methotrexate	0.837	2	0.893	1
Golimumab + Methotrexate	0.446	9	0.296	11
Infliximab + Methotrexate	0.884	1	0.621	4
Peficitinib + Methotrexate	0.529	7	0.553	5
Sarilumab + Methotrexate	0.576	6	0.866	2
Tocilizumab + Methotrexate	0.145	13	0.437	6
Tofacitinib + Methotrexate	0.674	3	0.181	13
Upadacitinib + Methotrexate	0.591	5	0.270	12
Methotrexate	0.037	—	0.656	—

Note: The SUCRA score ranges from zero to one, with one corresponding to the highest ranking. ACR50: Comprehensive evaluation indexes put forward by the American College of Rheumatology, indicating that the patient has improved by at least 50% in specified indicators.
Abbreviations: SAE, Serious adverse event; SUCRA, Surface under the cumulative ranking curves.

Tofacitinib combination therapy, which showed excellent overall efficacy and safety for secondary outcomes, ranked low for the primary safety outcome data SAE (final) (Tables 2 and S9). Thus, safety concerns may affect the high evaluations of combination therapies and be a factor challenges their applicability despite their relatively high overall efficacy and safety. The minor differences between the Bayesian SUCRA scores (Tables 2 and S9) and frequentist *p* score (Tables S10 and S11) were considered acceptable because they were derived using different models [25].

We also analyzed the relationship between treatment targets and structural types with their efficacy and safety. The list of targets and structures of the 15 DMARDs treatments used in the study are shown in Table S13. In terms of efficacy

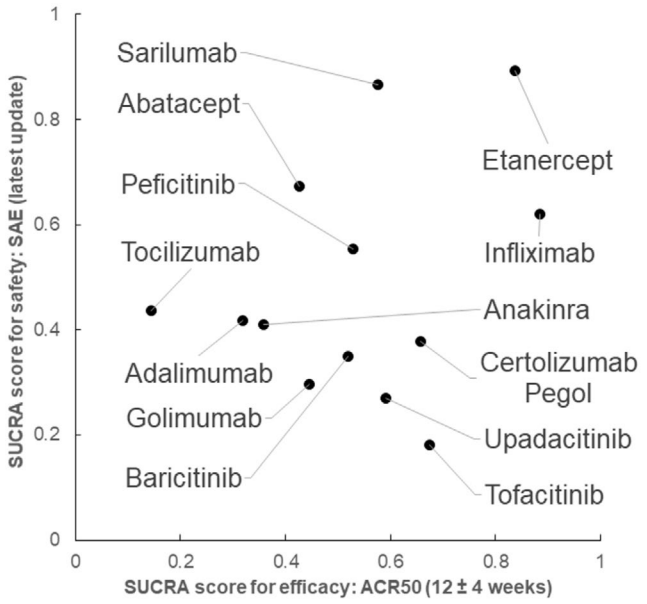

FIGURE 4 | Cluster plot of ACR50 (12 ± 4 weeks) with SAE (final). The *x*-axis represents the SUCRA score for ACR50 (12 ± 4 weeks), the *y*-axis represents the SUCRA score for SAE (final), and solid circles represent each combination therapy. Therapies represented in the upper right corner had a high overall ranking for both ACR50 (12 ± 4 weeks) and SAE (final). Therapies represented in the lower left corner had low combined rankings for ACR50 (12 ± 4 weeks) and SAE (final). Therapies represented in the lower right corner had high ACR50 (12 ± 4 weeks) ranking but low SAE (final) ranking, whereas therapies represented in the upper left corner had low ACR50 (12 ± 4 weeks) ranking but high SAE (final) ranking. ACR50: Comprehensive evaluation indexes put forward by the American College of Rheumatology, indicating that the patient has improved by at least 50% in specified indicators; SAE, Serious adverse event; SUCRA, Surface under the cumulative ranking curves. All treatments except methotrexate monotherapy, were administered in combination with methotrexate.

outcomes, no distinct advantages were identified based on the structure; however, analysis based on targets revealed that tofacitinib, the only drug targeting the three JAKs, ranked high for efficacy. When targets and structures were considered together in the efficacy results cluster diagram, treatments targeting TNF-α combined with methotrexate tended to have high efficacy rankings, except for adalimumab and golimumab, which belong to human monoclonal antibodies. Although Donahue et al. [11] also rated etanercept and infliximab combination therapies to be high efficacy, certolizumab pegol combination therapy was not indicated. Weng et al. [13] reported high efficacy for etanercept and certolizumab pegol combination therapies, but low efficacy for infliximab combination therapy. Hazlewood et al. [26] found that combination therapy with etanercept and tofacitinib had high efficacy, whereas combination therapy with certolizumab pegol and infliximab had modest efficacy. The differences between their findings and those of our study may be attributed to the amount of evidence or the study background. Although the efficacy of combination therapies requires more evidence, etanercept combination therapy has consistently shown high efficacy in our study, as well as in studies by Donahue et al. [11], Weng et al. [13] and Hazlewood et al. [26]. Although sarilumab was also ranked high, it lacks distinctive features, challenging the analysis of the factors contributing to its high efficacy under the current circumstances.

In terms of safety outcomes, no advantageous features emerged when only the target was considered. However, examination of the structures revealed that the Fc-fusion proteins (abatacept and etanercept) ranked high for both safety outcomes, also validated using cluster analysis. Despite being a part of a study evaluating the reasons for discontinuation owing AEs, the high safety profiles of therapies using these two drugs were reflected in the NMA by Weng et al. as well [13] This suggests that Fc-fusion proteins may be a feature of highly safe treatments. Compared to drugs used in other TNF-α therapies, these are recombinant proteins rather than monoclonal antibodies. Recombinant proteins are fusion proteins that bind to the human IgG-Fc domain [27]. Tofacitinib combination therapy showed high efficacy and AE (final) rankings (Table S9), consistent with the results of Qu et al. [28], although the SAE (final) ranking was very low (Table 2).

Based on the above two characteristics, Fc-fusion proteins targeting TNF-α could be the choice of interest, and etanercept is a DMARD for the treatment of RA with this characteristic. This finding is consistent with the results of our study. However, as only one drug exists with this characteristic, conclusively proving that this feature alone leads to high efficacy and safety is challenging.

Some evidence included in our review was considered high risk because of inappropriate data handling methods, inadequate blinding, or unpublished information. The risks posed by excessive missing data that are not properly handled or by the use of open-label studies are likely to interfere with the data included in this study. However, the impacts of other risk factors can be mitigated by obtaining supplementary information. Hence, we analyzed the high-risk evidence for infliximab and adalimumab combination therapies and confirmed that these high-risk studies did not significantly affect our results (Figure S5). Similarly, for etanercept and anakinra combination therapies, we cannot exclude high-risk studies owing to the lack of low-risk evidence. Although the risks posed by the high-risk evidence cannot be completely ruled out, they represent the highest level of evidence currently available. Therefore, additional information on completed studies is needed to increase credibility, and more high-quality literature is required for more reliable results.

The high heterogeneity in efficacy outcomes may stem from the variations between the different combination therapies. Combination therapies that exhibited high heterogeneity with respect to the ACR50 (12 ± 4 weeks) outcome, when compared with methotrexate monotherapies, included adalimumab, certolizumab pegol, and peficitinib combination therapies. After excluding the study by Kavanaugh et al. (No. 14, Table S3), heterogeneity from adalimumab combination therapy was eliminated, and the exclusion of Emery et al. (No. 34, Table S3) eliminated the heterogeneity from certolizumab pegol combination therapy. However, the heterogeneity from peficitinib combination therapy could not be reduced by excluding studies, as only two studies (Kivitz et al. and Takeuchi et al.; No. 61 and No. 62, Table S3) were available. After removing the studies by

TABLE 3 | Heterogeneity and consistency in efficacy and safety outcomes.

	ACR20	ACR50	AE	SAE
Consistency				
DIC (Consistency)	198.33	193.65	187.79	191.83
DIC (Inconsistency)	198.97	195.15	191.65	194.20
DIC (Con)–DIC (Inc)	0.64	1.50	3.86	2.37
Heterogeneity				
I^2 (Consistency)	76.94	75.44	5.40	9.91
I^2 (Inconsistency)	77.83	76.65	14.59	8.26

Note: Cosistency is consider good when the difference between the DIC values of the consistent and the nonconsistent does not exceed five. A high I^2 value indicates high heterogeneity. ACR20: Comprehensive evaluation indexes put forward by the American College of Rheumatology, indicating that the patient has improved by at least 20% in specified indicators; ACR50: Comprehensive evaluation indexes put forward by the American College of Rheumatology, indicating that the patient has improved by at least 50% in specified indicators. Abbreviations: AE, Adverse event; DIC, deviance information criterion; SAE, Serious adverse event.

Kavanaugh et al. (No. 14, Table S3) and Emery et al. (No. 34, Table S3) that may have caused heterogeneity, we found that the efficacy outcome ranking of certolizumab pegol combination therapy improved significantly; however, the cluster plot of efficacy and safety outcomes still indicated had the highest comprehensive efficacy and safety ranking for etanercept combination therapy (Figure S6). This implies that the heterogeneity arising from these studies did not affect the results. We also conducted a brief analysis of the study backgrounds to understand the potential reasons for the heterogeneity (Tables S4 and S5). Study No. 14 was the only Phase 4 trial in the adalimumab combination study, and study No. 34 was the only non-RAPID study with certolizumab pegol as the DMARD for combination study. Study No. 34 was also the only study in which patients had not previously received methotrexate therapy. The two studies on peficitinib combination therapy differed in clinical trial stages and participant ethnicity and race. These findings suggest that ethnic background and prior use of methotrexate may be sources of heterogeneity in combination therapy studies. Finally, the inconsistency in the SAE (final) outcomes may arise from differences between direct and indirect evidence. Although we did not analyze the reasons for these differences, the low proportion of indirect evidence suggests minimal impact on the overall consistency.

4.1 | Limitations

This study had several limitations. Although the ACR updated its latest guidelines in 2021, which are different from the guidelines that were used as theoretical references for our study, these two versions of the guidelines did not change the recommendations on the combination of bDMARDs/tsDMARDs with methotrexate [4, 29]. Therefore, we believe that for our study, referring to the older version of the guidelines is still useful and feasible even today.

While we aimed to rank all combination treatments of bDMARDs/tsDMARDs with methotrexate for RA treatment in terms of their efficacy and safety, the following drugs were excluded from our study. Filgotinib was a small molecule that inhibits JAK, which was approved by Japan in September 2020. Since the period of our study design was until October 2020, there were few studies related to filgotinib and it was excluded from our study. Additionally, ozoralizumab was a humanized monoclonal antibody that inhibits TNF-α, which approved in Japan only in September 2022, after we began this study; hence, it was not included in our study. Furthermore, rituximab despite its inclusion during the research search, was eventually excluded from our analysis because of insufficient efficacy data for the specified period.

For data analysis, we compiled documents from multiple databases for the same research. Although this approach aims to enhance the data sufficiency, it also introduces potential errors. For example, patient background data might be from PubMed, whereas result data might be from CENTRAL, leading to possible discrepancies between different versions.

In addition, the efficacy outcomes in this study focused on a 12 ± 4 week period owing to the abundance of data within this timeframe. There was a lack of data beyond 52 weeks, precluding long-term efficacy analysis. Hence, our findings reflect only the short-term efficacy. Furthermore, safety outcomes were assessed at the end of the trials, as most studies collect safety data at this point. However, the varying study periods, led to differences in the time point of safety data collection, introducing possible differences between the safety outcomes, and our findings do not explain the possible impact of these differences.

For the NMA, different effect models were used for efficacy and safety outcomes because safety outcomes could not be fitted with a random effects model. This introduced certain limitations to the generalizability of the conclusions. Additionally, the risk of bias and publication bias could not be eliminated. Although consistency and heterogeneity concerns were analyzed, the reasons for their existence remain unclear. Therefore, the results of this NMA should be interpreted with caution.

5 | Conclusion

Most bDMARDs/tsDMARDs combined with methotrexate demonstrated significantly better efficacy than methotrexate monotherapy, with no significant differences in safety. The NMA results indicated that etanercept, an Fc-fusion protein targeting TNF-α, had the highest efficacy and safety among the bDMARDs/tsDMARDs combination therapies tested for combination therapies with methotrexate.

Author Contributions

L.L., K.A., and M.T. wrote the manuscript; L.L., M.O., Y.Y., K.A., T.M., and M.T. designed the research; L.L., M.O., and Y.Y. performed the research and analyzed the data.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.