INPLASY

Comparative Efficacy of Different Biologic Agents on Radiographic Progression in Patients with Rheumatoid Arthritis: A Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 May 2026 and was last updated on 6 May 2026.

INTRODUCTION

Review question / Objective Objective: To systematically compare the efficacy and safety of different classes of biologic disease-modifying antirheumatic drugs (bDMARDs) in suppressing radiographic progression in patients with rheumatoid arthritis (RA), using a Bayesian network meta-analysis, and to generate a relative efficacy ranking to inform clinical decision-making.
The review question is framed using the PICOS structure:
P (Population): Adult patients (≥18 years) diagnosed with rheumatoid arthritis according to the ACR 1987, ACR/EULAR 2010, or EULAR/ACR 2022 classification criteria, regardless of sex, race, disease duration, or disease activity.
I (Intervention): Six classes of approved bDMARDs — TNF-α inhibitors (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab); IL-6 receptor antagonists (tocilizumab, sarilumab); T-cell co-stimulation modulators (abatacept); B-cell depleting agents (rituximab, ocrelizumab); IL-17 inhibitors (secukinumab, ixekizumab); and IL-23 inhibitors (guselkumab).
C (Comparator): Placebo, conventional synthetic DMARDs (e.g., methotrexate, leflunomide), or another bDMARD.
O (Outcomes): Primary — change from baseline in modified Total Sharp Score (mTSS) at 12 months. Secondary — change in bone erosion score, ACR20 response rate, and incidence of serious adverse events.
S (Study design): Published randomized controlled trials (RCTs).

Condition being studied Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent symmetric synovitis as its core pathological feature. The global prevalence of RA is approximately 0.42%, with a peak age of onset between 35 and 50 years; incidence in women is 2–3 times higher than in men. Without standard treatment, 50–75% of patients develop radiographically detectable joint erosion within two years of symptom onset, and the 5-year disability rate reaches up to 43%. The risk of extra-articular

complications such as cardiovascular disease and interstitial lung disease is 2–3 times higher than in the general population, imposing a substantial burden on patients, families, and society.

The principal long-term harm of RA arises from the destruction of articular cartilage and bone structures driven by sustained inflammation, ultimately leading to joint deformity, loss of function, and disability. Radiographic progression therefore represents irreversible structural joint damage and serves as a key objective indicator for evaluating long-term disease outcomes.

The treatment paradigm for RA has shifted from simple symptom control to a treat-to-target strategy. The 2025 EULAR recommendations explicitly define the absence of radiographic progression as one of the three core criteria for achieving treat-to-target goals, of equal importance to clinical remission and functional preservation. The introduction of biologic DMARDs (bDMARDs) has been a milestone in RA management, and multiple RCTs have demonstrated their superiority over conventional synthetic DMARDs in delaying structural damage. However, substantial uncertainty remains regarding whether bDMARDs with different mechanisms of action differ in their ability to inhibit radiographic progression, which directly affects individualized drug selection in clinical practice and constitutes the clinical gap that this review aims to address.

METHODS

Participant or population Adult patients (≥18 years) with a confirmed diagnosis of rheumatoid arthritis (RA) according to any of the following internationally recognized classification criteria: the American College of Rheumatology (ACR) 1987 RA Classification Criteria, the ACR/European League Against Rheumatism (EULAR) 2010 RA Classification Criteria, or the EULAR/ACR 2022 Early RA Classification Criteria. There is no restriction on sex, race, ethnicity, disease duration, or disease activity at baseline. Both biologic-naïve patients and those with prior inadequate response or intolerance to conventional synthetic DMARDs or bDMARDs will be included. Studies conducted exclusively in special subpopulations — such as patients with coexisting active hepatitis B infection or pregnant women — will be excluded.

Intervention The interventions of interest are six classes of approved biologic disease-modifying antirheumatic drugs (bDMARDs), used either as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs:

TNF-α inhibitors (TNF-i): adalimumab, etanercept, infliximab, certolizumab pegol, golimumab

IL-6 receptor antagonists (IL-6Ri): tocilizumab, sarilumab

T-cell co-stimulation modulators: abatacept

B-cell depleting agents: rituximab, ocrelizumab

IL-17 inhibitors: secukinumab, ixekizumab

IL-23 inhibitors: guselkumab

All drugs, doses, and routes of administration consistent with regulatory approval or late-phase clinical trial protocols will be eligible. Head-to-head comparisons between any two bDMARD classes, as well as comparisons against placebo or conventional synthetic DMARDs, will be incorporated into the network for Bayesian network meta-analysis.

Comparator Eligible comparators include: (1) placebo, with or without background conventional synthetic DMARDs; (2) conventional synthetic DMARDs (csDMARDs), such as methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine, used as active controls; and (3) another bDMARD from a different mechanistic class, in head-to-head randomized controlled trials. All comparators will be connected within a single evidence network to allow both direct and indirect comparisons. Studies comparing only different doses or formulations of the same drug without an eligible comparator arm will not be included in the network meta-analysis.

Study designs to be included Randomized controlled trials (RCTs).

Eligibility criteria Additional inclusion criteria:

(1) Intervention duration of at least 6 months, ensuring adequate time for radiographic outcomes to be meaningfully assessed;

(2) Reporting of at least one radiographic outcome measure (e.g., modified Total Sharp Score, bone erosion score, joint space narrowing score);

(3) Availability of extractable quantitative outcome data (means and standard deviations, event rates, or data that can be converted using Cochrane-recommended formulas).

Additional exclusion criteria:

(1) Duplicate publications arising from the same trial — only the report with the largest sample size and longest follow-up will be retained;

(2) Studies from which valid outcome data cannot be extracted and whose corresponding authors do not respond within two weeks of an emailed data request;

(3) Studies with an intervention duration of less than 6 months;

(4) Studies restricted to specific subpopulations (e.g., patients with coexisting hepatitis B, pregnant women) whose results are not generalizable;

(5) Studies not reporting any radiographic outcome measure;
(6) Non-English publications;
(7) Studies for which the full text cannot be obtained despite attempts through institutional access, interlibrary loan, and author contact.

Information sources Electronic databases: Four major international databases will be systematically searched from database inception to 31 December 2025:
PubMed / MEDLINE
Embase
Web of Science
Cochrane Central Register of Controlled Trials (CENTRAL)
Search strategy: A combination of Medical Subject Headings (MeSH) and free-text terms will be used, including "arthritis, rheumatoid", "biological agents", "tumor necrosis factor inhibitors", "abatacept", "rituximab", "tocilizumab", "sarilumab", "secukinumab", "ixekizumab", "guselkumab", "randomized controlled trial", "radiographic progression", and "Sharp score". Boolean operators (AND, OR) will be applied, and the strategy will be adapted to each database's syntax.
Supplementary sources:
(1) Manual screening of reference lists of all included studies and relevant systematic reviews and meta-analyses;
(2) Conference abstracts from the 2023–2025 annual meetings of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR);
(3) Trial registries including ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) to identify ongoing or unpublished trials;
(4) Contact with corresponding authors via email to request missing or unclear data, with a two-week response window.
Language: English only.

Main outcome(s) Change from baseline in the modified Total Sharp Score (mTSS) at 12 months of treatment. The mTSS is a validated composite radiographic measure for RA, comprising two components: a bone erosion score (range 0–128) and a joint space narrowing score (range 0–64), with a total score ranging from 0 to 192. Higher scores indicate more severe structural joint damage. Because mTSS is a continuous outcome, effect sizes will be expressed as the mean difference (MD) with 95% confidence intervals (for pairwise meta-analysis) and 95% credible intervals (for Bayesian network meta-analysis). For studies reporting only median and interquartile range, values will be converted to mean ± standard deviation using formulas recommended by the Cochrane Handbook. When data are available only in graphical form, numerical values will be extracted using GetData Graph Digitizer 2.26. Treatment ranking will be performed using the Surface Under the Cumulative Ranking curve (SUCRA) and the probability of being best (ProbBest).

Quality assessment / Risk of bias analysis The methodological quality of all included randomized controlled trials will be assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool, recommended by the Cochrane Collaboration for randomized trials. Each study will be evaluated across five pre-specified domains:
(1) Bias arising from the randomization process, including sequence generation and allocation concealment;
(2) Bias due to deviations from the intended interventions, assessing the effect of assignment to the intervention;
(3) Bias due to missing outcome data, evaluating the completeness of outcome data and reasons for attrition;
(4) Bias in measurement of the outcome, with particular attention to blinding of outcome assessors — especially important for radiographic outcomes such as mTSS, where central, blinded reading is considered the methodological standard;
(5) Bias in the selection of the reported result, assessed by comparing the published report with the pre-specified protocol or trial registry record whenever available.
For each domain, the risk of bias will be rated as "low risk", "some concerns", or "high risk". An overall risk-of-bias judgment will then be derived for each study according to the RoB 2.0 algorithm.
Two reviewers will independently conduct the assessments. Any disagreements will be resolved through discussion, and, if necessary, adjudication by a third senior reviewer. Inter-rater agreement will be documented. The results will be presented using traffic-light plots and summary risk-of-bias figures.

Strategy of data synthesis Traditional pairwise meta-analysis. For each pairwise comparison with at least three direct trials, a conventional pairwise meta-analysis will be conducted. For continuous outcomes (mTSS, bone erosion score), effect sizes will be expressed as mean difference (MD) with 95% confidence intervals. For binary outcomes (ACR20 response, serious adverse events), odds ratios (OR) with 95% confidence intervals will be used. Statistical heterogeneity will be evaluated

using the I^2 statistic and Cochran's Q test: a fixed-effects model will be applied when I^2 0.1; otherwise a random-effects model will be used. Pairwise meta-analyses will be performed in RevMan 5.4.
Bayesian network meta-analysis. A Bayesian framework will be employed using the Markov Chain Monte Carlo (MCMC) algorithm with a consistency model. Four independent Markov chains will be run with 20,000 burn-in iterations followed by 100,000 iterations for parameter estimation. Model convergence will be assessed using the Gelman-Rubin-Brooks statistic, with values below 1.05 indicating adequate convergence. A normal-likelihood model will be fitted for continuous outcomes, and a binomial-likelihood model with a logit link for binary outcomes. A random-effects term will be incorporated to account for between-study heterogeneity, and non-informative priors will be applied to all parameters.
Assessment of consistency. Global consistency will be evaluated by comparing fit and deviance information criteria (DIC) between consistency and inconsistency models. Local consistency will be examined using the node-splitting method: $P > 0.05$ indicates agreement between direct and indirect evidence, and a consistency model will be applied; $P \leq 0.05$ indicates inconsistency, prompting exploration of its sources and the use of an inconsistency model.
Publication bias. Comparison-adjusted funnel plots and Egger's test will be used to assess small-study effects and publication bias for each outcome.
Treatment ranking. The Surface Under the Cumulative Ranking curve (SUCRA) will be calculated to rank the relative efficacy and safety of all interventions, with values closer to 1 indicating greater likelihood of being the most effective. The probability of being best (ProbBest) will also be reported for each intervention.
Software. Bayesian NMA will be conducted in R (gemtc package) and/or WinBUGS; frequentist NMA, network geometry plots, and funnel plots will be generated using the "network" package in Stata 17.0. The significance level will be set at $\alpha = 0.05$.

Subgroup analysis Pre-specified subgroup analyses will be conducted to explore potential sources of clinical and methodological heterogeneity and to examine whether treatment effects vary across patient and study characteristics. Subgroups will be defined along the following dimensions:
(1) Disease duration at baseline: early RA (≤2 years since symptom onset) versus established RA (>2 years), given that earlier intervention may yield greater structural benefit;
(2) Prior treatment history: biologic-naïve patients versus those with inadequate response or intolerance to prior csDMARDs or bDMARDs, as prior exposure may influence responsiveness;
(3) Concomitant methotrexate use: bDMARD monotherapy versus bDMARD plus methotrexate combination therapy, since co-administration is known to enhance efficacy for some agents;
(4) Baseline disease activity: moderate (DAS28 3.2–5.1) versus high disease activity (DAS28 >5.1);
(5) Risk-of-bias level: studies judged as low overall risk of bias versus those with some concerns or high risk, to evaluate whether effect estimates are robust to study quality;
(6) Publication period: studies published before versus after 2015, to account for temporal changes in standards of care, outcome assessment, and concomitant therapy.
Subgroup analyses will be performed for the primary outcome (mTSS at 12 months) whenever sufficient data are available (≥3 studies per subgroup). Between-subgroup differences will be tested formally, and results will be interpreted cautiously given the observational nature of subgroup comparisons within a meta-analysis.

Sensitivity analysis Sensitivity analyses will be performed to evaluate the robustness of the primary findings and to assess the influence of specific methodological and analytical decisions. The following sensitivity analyses are pre-planned:
(1) Exclusion of studies at high risk of bias: the primary analysis will be repeated after excluding studies judged to be at high overall risk of bias according to the Cochrane RoB 2.0 tool, to examine whether the direction and magnitude of effect estimates remain consistent;
(2) Exclusion of studies with imputed or converted data: analyses will be re-run excluding studies in which means and standard deviations were derived from medians and interquartile ranges using Cochrane-recommended formulas, or in which continuous data were extracted from graphs using GetData Graph Digitizer, to assess the impact of data-extraction uncertainty;
(3) Alternative statistical models: the robustness of pooled estimates will be tested by switching between fixed-effects and random-effects models, and by re-running Bayesian analyses with alternative prior distributions (e.g., weakly informative priors) to evaluate prior sensitivity;
(4) Leave-one-out analysis: studies will be removed one at a time to identify any single study that disproportionately influences the pooled effect estimate;
(5) Exclusion of studies with short follow-up: studies with an intervention duration close to the 6-month minimum threshold will be excluded, and

the analysis restricted to trials reporting 12-month outcomes, to assess whether results are driven by follow-up heterogeneity;
(6) Exclusion of open-label studies: analyses will be restricted to double-blind RCTs to evaluate the influence of blinding on effect estimates.
Consistency between the primary and sensitivity analyses will be considered evidence of the robustness of the conclusions.

Country(ies) involved China.

Keywords rheumatoid arthritis; Biologics; advances in radiology; network meta-analysis; B cell scavengers; IL-23 inhibitors; Improved Sharp overall score.

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