INPLASY PROTOCOL

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The authors declared that they have no conflicts of interest.

Comparative efficacy and safety of Janus kinase inhibitors and biologics in rheumatoid arthritis: a systematic review and network meta-analysis

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ABSTRACT

Objective: **The aim of this network meta-analysis is to evaluate the comparative efficacy and safety of Janus kinase inhibitors and biologics in patients with active rheumatoid arthritis who inadequately respond to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or biologics. P: patients with active rheumatoid arthritis who inadequately respond to csDMARDs or biologics. I: Janus kinase inhibitors and biologics C: placebo or csDMARDs O: American College of Rheumatology20% (ACR20) response, Disease Activity Score for 28-joint counts (DAS28), Health Assessment Questionnaire-Disability Index (HAQ-DI), discontinuation due to adverse events S: randomized controlled trial (RCT).**

Search strategy: **Systematic search of PubMed, Embase, Web of Science , Cochrane Central Register of Controlled Trials and ClinicalTrials.gov are conducted from inception to April 2020. Search terms: baricitinib, tofacitinib, upadacitinib, etanercept, adalimumab, infliximab, certolizumab pegol, golimumab, tocilizumab, rituximab, abatacept, rheumatoid arthritis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 March 2020 and was last updated on 31 March 2020 (registration number INPLASY202030017.

INTRODUCTION

Objectives / Review question: **The aim of this network meta-analysis is to evaluate the comparative efficacy and safety of Janus kinase inhibitors and biologics in patients with active rheumatoid arthritis who inadequately respond to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or biologics. P: patients with active rheumatoid arthritis who inadequately respond to csDMARDs or**

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biologics. I: Janus kinase inhibitors and biologics C: placebo or csDMARDs O: American College of Rheumatology20% (ACR20) response, Disease Activity Score for 28-joint counts (DAS28), Health Assessment Questionnaire-Disability Index (HAQ-DI), discontinuation due to adverse events S: randomized controlled trial (RCT).

Condition being studied: Rheumatoid arthritis.

METHODS

Participant or population: Inclusion: Adults with active rheumatoid arthritis that inadequately responds to csDMARDs or biologics.(as diagnosed using any recognised diagnostic criteria). Exclusion: Adolescents (under 18 years of age) and elderly people (over 70).

Intervention: Baricitinib 2mg once daily, baricitinib 4mg once daily, tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, upadacitinib once 15mg daily, upadacitinib 30mg once daily, etanercept, adalimumab, infliximab, certolizumab pegol, golimumab, tocilizumab, rituximab, abatacept. Biologics were limited to currently recommended doses or dose equivalents.

Comparator: Placebo or csDMARDs.

Study designs to be included: RCT.

Eligibility criteria: Inclusion criteria: 1.only RCTs (either double-blind, single-blind or open-label) that provide the data we need and in which Janus kinase inhibitors and biologics were compared to each other or to placebo or csDMARDs in patients with active rheumatoid arthritis that inadequately responds to csDMARDs or biologics. 2.Methotrexate(MTX) or other csDMARDs were used as background drugs. Exclusion criteria: biologics were permitted as background drugs.

Information sources: Systematic search of PubMed, Embase, Web of Science , Cochrane Central Register of Controlled Trials and ClinicalTrial.gov are conducted from inception to April 2020. We also review conference abstracts for possible unpublished trials. In addition, we check the reference lists of all relevant articles and contact the drug manufacturers to identify any further studies for inclusion.

Main outcome(s): ACR20 and discontinuation due to adverse events. We extracted data on the number of people who had an outcome event at 12 weeks. If information at 12 weeks was not available, we select the data closest to 12 weeks.

Additional outcome(s): DAS28 and HAQ-DI. If a study simultaneously reported data on DAS28-CRP and DAS28-ESR, we extracted DAS28-CRP preferentially. We extracted data on the mean difference from baseline to 12 weeks. If information at 12 weeks was not available, we select the data closest to 12 weeks.

Data management: All analyses were conducted using the gemtc package in R 3.6.1 and STATA 14.0.

Quality assessment / Risk of bias analysis: Two reviewers will independently conduct the assessments of the included studies using the Cochrane risk of bias tool for randomized trials. The domains of bias include random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting risk and other bias. The risk of each bias domain will be graded as low, unclear and high. Disagreements were resolved by consulting a third reviewer or through discussion.

Strategy of data synthesis: We estimated summary odds ratios (ORs) for dichotomous outcomes (ACR20 and discontinuation due to adverse events), and weighted mean differences (WMDs) for continuous outcomes (DAS28 and HAQ-DI) using network meta-analysis. A random-effects network meta-analysis within a Bayesian framework will then be applied, and we will estimate the ranking probabilities for all treatments at each

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possible rank for each intervention using the surface under the cumulative ranking curve (SUCRA). To check the assumption of consistency in the entire analytical network, a design-by-treatment approach will be used. A loop-specific approach will be applied to evaluate the presence of inconsistency locally in each closed loop, and the node-splitting method will be used to assess the inconsistency of the model by separating evidence on particular comparisons into direct and indirect evidence. Global heterogeneity will be assessed using the I^2 statistic, and predictive interval plots which incorporate the extent of the heterogeneity will be used to evaluate the extent of the uncertainty of the estimated effect size locally. Contribution plots will be used to assess the contributions of each direct comparison to the estimation of each network meta-analytic summary effect, and additionally, a comparison-adjusted funnel plot will be used to detect potential publication bias in the results between small and large studies. All analyses were conducted using R 3.6.1 (gemtc package, network meta-analysis, assessment of global heterogeneity, and SUCRA graphs), and STATA 14.0 (estimation of inconsistency and local heterogeneity, funnel plot).

Subgroup analysis: We will conduct subgroup analysis based on subjects (i.e., csDMARDs-inadequate response (IR), biologics-IR, csDMARDs-IR or biologics-IR).

Sensibility analysis: Two sensitivity analysis will be conducted to validate the robustness of the results by the omission of small sample trials (patients < 50) and long-term follow-up trials (≥52 weeks).

Language: No.

Countries involved: China.

Keywords: rheumatoid arthritis; Janus kinase inhibitors; biologics; systematic review; network meta-analysis.

Contributions of each author:

Author 1 - Chenghua Weng conceived and designed the study, search the studies, extract data, conduct risk of bias assessment, analyze the data and write the manuscript.

Author 2 - Leixi Xue search the studies, extract data and analyze the data.

Author 3 - Qing Wang search the studies and extract data.

Author 4 - Wentian Lu search the studies and extract data.

Author 5 - Jiajun Xu conduct risk of bias assessment.

Author 6 - Zhichun Liu directed the writing and revised the manuscript.

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