INPLASY PROTOCOL

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Conflicts of interest:
None declared.

A protocol of systematic review and meta-analysis on the efficacy, safety and bioavailability of oral methotrexate compared with parenteral methotrexate at high doses for adults patients with active rheumatoid arthritis

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Review question / Objective: **To assess the efficacy, safety and bioavailability of oral methotrexate compared with parenteral methotrexate at high doses for adults patients with active rheumatoid arthritis. The doses 15-25 mg/week will be regarded as high doses in our study.**
Condition being studied: **Rheumatoid arthritis is a chronic autoimmune inflammatory disease, with a prevalence of approximately 0.8%, but the exact pathogenesis is still unknown. Low dose methotrexate (MTX) up to 25 mg weekly is the cornerstone in the treatment of patients with rheumatoid arthritis (RA). However, the most optimal route of administration of MTX (orally or parenterally) for patients with active RA is not clear yet.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 December 2021 and was last updated on 15 December 2021 (registration number INPLASY2021120071).

INTRODUCTION

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METHODS

Participant or population: Adult patients (age>18 years) with clinical diagnosis of rheumatoid arthritis according to 1987 or 2010 classification criteria for RA will be included.

Intervention: We will include studies that compare oral MTX with parenteral MTX at high doses in adult patients with active rheumatoid arthritis.

Comparator: We will include studies that compare oral MTX with parenteral MTX at high doses in adult patients with active rheumatoid arthritis.

Study designs to be included: Randomized control trials(RCT) or randomized crossover studies(RCS).

Eligibility criteria: Randomized control trials had at least 24 weeks' duration or randomized crossover studies had a washout phase of at least 1 week, done in adults with active rheumatoid arthritis, and that compared oral MTX with parenteral MTX administration will be regarded as eligible for inclusion. Exclusion criteria: (I) observational and retrospective studies; (II) RCTs with less than 24 weeks duration of intervention; (III) studies that did not compare oral versus parenteral MTX as monotherapy.

Information sources: We did preliminary searches for randomized clinical trials(RCT & RCS) by searching PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalKey and Web of Science, from their inception to November 25, 2020. No language or date limits were used.

Main outcome(s): Main outcomes are as follows: (I) efficacy, as assessed by the percentage of patients with an ACR20, ACR50, ACR70 response, defined as at least 20%, 50%, 70% improvement respectively from baseline values in the swollen joint count and the tender joint count, as well as the other 5 disease activity measures that constitute the ACR improvement criteria; (II) incidence of any adverse events (including elevated transaminase and gastrointestinal side effects); (III) discontinuation of treatment owing to adverse event; (IV) bioavailability (AUC 0-t, Cmax, Tmax).

Additional outcome(s): None.

Quality assessment / Risk of bias analysis: The Cochrane Collaboration risk-of-bias tool will be used to assess the methodological quality of the included studies by two investigators (Jingliang Tang and Fang Wang) separately. Any conflicts will be resolved by discussion with a third author (Zhe Li). The risk of bias evalution will be assessed by the following criteria: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias. The risk-of-bias for each item will be graded as high, low or unclear risk.

Strategy of data synthesis: This meta-analysis will be performed using Review Manager Version 5.4. Odd ratio (OR) and 95% confidence intervals (CIs) will be calculated for dichotomous outcomes. Mean difference (MD) with 95% confidence intervals (CIs) will be calculated for continuous outcomes. We will use random-effects meta-analysis. Assessment of heterogeneity will be performed using the I2 statistic. I2 >50% will be taken to represent moderate heterogeneity, and I2 >75% to represent high heterogeneity. Publication bias within studies will be assessed with a funnel plot using a random effects model. All tests will be two-tailed,

and a level of $p < 0.05$ will be considered statistically significant.

Subgroup analysis: If enough studies can be done for this meta-analysis, the following subgroup analyses will be performed: (I) Rheumatoid arthritis disease duration (II) Baseline disease activity (low versus moderate high) (III) Methotrexate-naïve versus not naïve to methotrexate. We will conduct meta-regression to assess the association between trial-level variables and treatment effects. The four main outcomes will be calculated in the the subgroup analysis, when data are available.

Sensitivity analysis: We will perform a sensitivity analysis to further explore the robustness of our results. To identify any studies that might exert a disproportionate influence on the results, we will remove each individual trial from the meta-analysis, one at a time.

Country(ies) involved: China.

Keywords: Rheumatoid arthritis; Methotrexate; Oral administration; Parenteral administration.

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