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Comparative Efficacy and Safety of JAK Inhibitors in the Management of Rheumatoid Arthritis: Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - Hematology Section, National Centre for Cancer Care and Research, Hamad Medical Corporation, Doha.

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2024100084

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 October 2024 and was last updated on 20 October 2024.

INTRODUCTION

Review question / Objective The objective of this study was to execute an NMA to evaluate the relative efficacy and safety of various JAK inhibitors and their doses in the treatment of RA. This investigation aims to synthesize existing evidence comprehensively and to facilitate clinical decision-making concerning the administration of JAK inhibitors for RA.

Condition being studied Rheumatoid Arthritis.

METHODS

Search strategy PubMed search strategy:
#1 (tofacitinib or cp 690 550 or cp 690550 or cp690 550 or cp690550 or tasocitinib or tofacitinib or xeljanz)
#2 (baricitinib or incb 28050 or ly 3009104 or ly3009104 or olumiant)
#3 (upadacitinib or ABT-494 or Rinvoq)
#4 (decernotinib or VX-509)
#5 (peficitinib or ASP015K or Smyraf)
#6 (filgotinib or GS-6034 or GLPG0634 or GLPG0634)
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 arthritis, rheumatoid[MeSH Terms]
#9 "Rheumatoid arthritis"
#10 #8 or #9
#11 #7 and #10
#12 #7 and #10 (filter applied: Clinical trials)

CENTRAL Search Query:
#1 (tofacitinib or cp 690 550 or cp 690550 or cp690 550 or cp690550 or tasocitinib or tofacitinib or xeljanz):ti,ab,kw
#2 (baricitinib or incb 028050or incb 28050 or incb028050 or incb28050 or ly 3009104 or ly3009104 or olumiant):ti,ab,kw
#3 (upadcitinib or ABT-494 or Rinvoq):ti,ab,kw
#4 (decernotinib or VX-509):ti,ab,kw
#5 (peficitinib or ASP015K or Smyraf):ti,ab,kw

#6 (filgotinib or GS-6034 or GLPG0634 or GLPG0634):ti,ab,kw
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 ("rheumatoid arthritis"):ti,ab,kw
#9 #7 and #8.

Participant or population Rheumatoid arthritis patients, without restrictions on age or sex.

Intervention Any JAK inhibitor.

Comparator Compared any JAK inhibitor against other JAK inhibitors or a placebo.

Study designs to be included Randomised controlled trials.

Eligibility criteria Our research question was structured using the PICOS format (Population, Intervention, Comparison, Outcome, Study Design) to determine study eligibility. We incorporated both published and unpublished phase II and III randomized double-blind placebo-controlled trials that assessed RA patients, without restrictions on age or sex. Studies that compared any JAK inhibitor against other JAK inhibitors or a placebo in the context of RA management were considered. Exclusions were made for open-label, single-blind, non-randomized controlled trials, quasi-experimental studies, observational studies, animal studies, case reports, reviews, editorials, abstracts, and any trials not published in English.

Information sources An exhaustive search of the literature was conducted across several databases, including PubMed, and The Cochrane Central Register of Controlled Trials (CENTRAL), for pertinent RCTs from their start dates up to December 27, 2023. Search phrases such as "Rheumatoid arthritis" alongside names of specific JAK inhibitors and "RCTs" were employed. The search strategies are detailed in Supplemental Table 5. To identify additional published and unpublished trials, we manually examined reference lists from review articles, entries from ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and relevant bibliographies. No restrictions on the date or language were imposed during the electronic searches.

Main outcome(s) The primary outcomes of interest in this analysis were the responses measured by ACR20, ACR50, and ACR70, which assess 20%, 50%, and 70% improvement in symptoms, respectively.

Additional outcome(s) The secondary outcomes included: The mean change from baseline in the HAQ-D1 score. Incidence of adverse drug reactions (ADRs), Incidence of serious ADRs. Treatment discontinuations due to ADRs.

Data management Study Selection
Two authors independently performed first-pass screening (FPS) by reviewing the titles and abstracts of all the records retrieved to identify articles that potentially met the predefined eligibility criteria. The full texts of eligible titles were downloaded and reviewed independently by the two authors in the second-pass screening (SPS) to determine relevant inclusion in the final analysis. The discrepancies between the two reviewers during the FPS and SPS were sorted by discussion with a third reviewer.

Data Extraction and Management:
Two authors independently extracted data from the included RCTs using data extraction templates. Discrepancies during the data extraction were resolved through discussion with a third reviewer. The following details were extracted: study identification, authors' details, study objectives, study design, the setting of intervention, study population (including), measures, and main findings American College of Rheumatology 20% ACR 20, ACR50, ACR70, Health Assessment Questionnaire-Disability Index (HAQ-DI), ADRs, patients with serious ADRs, and patients discontinued due to ADRs.

Quality assessment / Risk of bias analysis Two reviewers independently assessed the methodologic quality of each study using the Cochrane Collaboration tool for assessing the risk of bias [17]. The following potential domains were assessed: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. For each domain, the risk of bias was scored as low, unclear, or high.

Strategy of data synthesis All statistical analyses were performed using both STATA software, version 16 MP (StataCorp, College Station, TX), and the R programming language, version 4.2.2, to conduct a frequentist network meta-analysis (NMA). The primary outcomes of interest in this analysis were the responses measured by ACR20, ACR50, and ACR70, which assess 20%, 50%, and 70% improvement in symptoms, respectively. The secondary outcomes included the mean change in the HAQ-D1 score, which evaluates changes in disability, as well as the incidence of adverse drug

reactions (ADRs), serious ADRs, and discontinuations due to ADRs, across both treatment and comparator groups. The NMA was particularly valuable for comparing various JAKinib treatment strategies and their different doses, even when direct head-to-head comparisons were limited. Treatments were ranked based on the surface under the cumulative ranking curve (SUCRA). The relative risk (RR) was utilized to describe binary outcome variables, such as the number of patients responding to ACR20, ACR50, ACR70, and the number of patients experiencing ADRs, serious ADRs (as deemed serious by the corresponding author), and those who discontinued treatment due to ADRs. In contrast, continuous outcomes, such as the mean change in HAQ-D1 score, were reported as mean differences (MD) with 95% confidence intervals (CIs). To visually represent the mean effect size and confidence intervals for individual studies, estimates were displayed graphically in forest plots.

The magnitude of heterogeneity between the studies was assessed using the I2 statistic (% residual variation due to heterogeneity), and Tau2 (method of moments estimate of between-study variance) was used for each of the pooled estimates. I2 values range between 0 and 100%, and is considered low for I2 50% [18]. As differences between the studies were very high (95-99% inconsistency), a random effect DerSimonian-Laird model was used in all analyses [18]. The risk of publication bias was inspected using the symmetry of funnel plots, as well as Egger's and Begg's tests.

Subgroup analysis Subgroup analysis was conducted based on the varying doses of each JAK inhibitor.

Sensitivity analysis None.

Language restriction Restriction to English.

Country(ies) involved Saudi Arabia and India.

Keywords Adverse drug reactions; JAK inhibitors; Network meta-analysis; Placebo; Rheumatoid Arthritis.

Contributions of each author

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