INPLASY

INPLASY202450040

doi: 10.37766/inplasy2024.5.0040

Received: 09 May 2024

Published: 09 May 2024

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Insights into the Safety Profile of Upadacitinib in Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202450040

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 May 2024 and was last updated on 21 May 2024.

INTRODUCTION

Review question / Objective To assess the safety profile and the incidence of adverse events associated with the use of upadacitinib compared to placebo in adult patients with inflammatory bowel diseases (IBD), specifically Crohn's disease (CD) and ulcerative colitis (UC).

Rationale This review is in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Condition being studied Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, causes chronic inflammation of the digestive tract and significantly impacts patient's quality of life. Current treatments aim to alleviate symptoms by inducing and maintaining remission. However, many patients fail to respond to available treatments or lose response over time. Upadacitinib, a selective Janus kinase-1 (JAK-1) inhibitor has shown promising results regarding its efficacy. However, its use has raised concerns about the associated adverse events. Given that IBD requires long-term management, understanding these risks is crucial for clinical application.

METHODS

Search strategy PubMed, Embase, and Cochrane Library were searched for relevant articles. The search was restricted to studies published in English. Key search terms for the intervention included "rinvoq" and "upadacitinib," which were used interchangeably with the Boolean operator "OR" to capture all relevant literature pertaining to the drug. For the condition of interest, terms

related to inflammatory bowel disease were extensively used, including "inflammatory bowel disease" OR "IBD" OR "Crohn's disease" OR "Crohn" OR "CD" OR "Ulcerative colitis" OR "UC". These terms were combined using the Boolean operator "AND" to ensure that the retrieved studies specifically focus on the application of upadacitinib in the treatment of IBD.

Participant or population Adult patients aged ≥ 18 years with inflammatory bowel disease (Crohn's disease or ulcerative colitis).

Intervention Upadacitinib.

Comparator Placebo.

Study designs to be included Randomized controlled trials.

Eligibility criteria Studies meeting the following inclusion criteria: (1) randomized controlled trials (RCTs); (2) published in English; (3) comparing upadacitinib with placebo; (4) for induction therapy; (5) in adult patients diagnosed with inflammatory bowel disease; (6) reporting at least one of the safety outcomes of interest; (7) without overlapping patient populations.

Information sources Electronic databases: PubMed, EMBASE, Cochrane. Trial registers: ClinicalTrials.gov and European Union Clinical Trials Register (EudraCT). References of included studies, supplementary materials of included studies, and abstracts from conferences.

Main outcome(s) Incidence of serious adverse events (SAEs) in patients with inflammatory bowel disease receiving upadacitinib compared to placebo.

Additional outcome(s) Incidence of specific adverse events (AEs) of interest, including serious infections, herpes zoster, nasopharyngitis, neutropenia, anemia, hepatic disorders, creatine kinase (CK) elevation, arthralgia, venous thromboembolic events (VTE), major cardiovascular events (MACE), malignancies of any kind, and death from any cause.

Quality assessment / Risk of bias analysis Assessment using the Cochrane Collaboration's tool for the risk of bias in randomized trials.
Categories include selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.

Strategy of data synthesis Data analysis will be performed using Review Manager 5.4.1 software. Risk ratios (RRs) will be used to assess the incidence of adverse events. Pooled estimates with 95% confidence intervals (CIs) will be calculated using the weighted variance technique. Heterogeneity among studies will be assessed using the I^2 statistic. Depending on the level of heterogeneity, either random-effects or fixed-effects models will be employed.

Subgroup analysis Subgroup analyses will be performed to explore potential differences in the effects of upadacitinib on patients with ulcerative colitis (UC) and Crohn's disease (CD).

Sensitivity analysis Sensitivity analyses will be conducted by systematically removing each study one at a time, particularly when moderate or high heterogeneity is detected. This method will help determine whether any specific study disproportionately influences the overall results, ensuring the reliability of the findings.

Language restriction Studies published in English.

Country(ies) involved Brazil, United States of America

Keywords Upadacitinib, inflammatory bowel diseases, ulcerative colitis, Crohn's disease, safety, adverse events, Janus kinase inhibitors.

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