4.0 Abstract

Title:

Drug utilisation study of upadacitinib (Rinvoq™) in Europe to evaluate the effectiveness of additional risk minimisation measures

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Rationale and Background:

Upadacitinib (Rinvoq™) is a selective and reversible inhibitor of JAK that was approved in Europe on 16 December 2019 for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). As with other JAK inhibitors already marketed in Europe, important risks have been identified with upadacitinib that require additional risk minimization measures (aRMMs) consisting of an HCP educational guide and a patient card. On 10 March 2023 the Article 20 procedure for JAK inhibitors was concluded, which prompted a label update to incorporate additional recommendations for use in the EU (Article 20 of Regulation (EC) No 726/2004). Per new recommendations in the *Warning and Precautions* section of the SmPC, upadacitinib is only recommended if no suitable treatment alternatives are available for individuals 65 years of age or older, patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers), or individuals with risk factors for malignancy (e.g., current malignancy or history of malignancy). In addition, upadacitinib should only be used with caution in individuals at risk of GI perforation and VTE. Dissemination of updated patient and HCP educational materials began in May 2023 (date varies by country). Using data derived from European RA registries, AbbVie plans to implement a drug utilisation study to characterise the use of upadacitinib (Rinvoq™) and evaluate the effectiveness of the aRMMs (HCP educational guide and patient card) in the pre-Article 20 and post-Article 20 time periods.

Research Question and Objectives:

This study aims to characterise the use of upadacitinib (Rinvoq™) in routine clinical care, including describing baseline characteristics of individuals with rheumatoid arthritis exposed to upadacitinib relative to individuals with rheumatoid arthritis exposed to other systemic treatments. This study also aims to evaluate the effectiveness of additional risk minimisation measures, including to 1) quantify the occurrence of upadacitinib use among patients who are at high risk for venous thromboembolic event (VTEs), gastrointestinal perforation, serious infections, major adverse cardiovascular events (MACE), and malignancy, 2) quantify the compliance to contraindicated use including pregnancy and patients treated for active tuberculosis, 3) describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring, and 4) describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure (i.e.: stratify outcomes of interest by the pre-Article 20 and post Article 20 time periods).

Study Design:

This will be a population-based cohort study of new users of upadacitinib (Rinvoq™) and selected bDMARDs marketed for the treatment of rheumatoid arthritis in Europe.

Population:

This study includes patients diagnosed with RA who are enrolled in one of five European RA registries ARTIS, DANBIO, BSRBR-RA, BIOBADASER, and RABBIT and initiate upadacitinib or a selected bDMARD comparator drug.

Variables:

Exposure: Each registry assigns drug exposure time to an exposure cohort based on medication classification (Table 2). Exposure is reported by the physician at enrolment into each registry; however, cohort definitions vary across the registries (Table 3). Changes to exposure are reported by the physician at follow-up visits. In ARTIS, registry

data are combined with data on prescription medication from national registries to assign exposure. The upadacitinib cohort will include patients with RA initiating treatment with upadacitinib. The comparator bDMARD cohort will include patients with RA initiating a bDMARD treatment, except for BSRBR-RA, in which the comparator cohort is more specifically an anti-TNFα cohort of patients with RA initiating anti-TNFα therapy (defined as originator etanercept, infliximab or adalimumab only and biologic naïve at registration from 2010 onwards). This is a specified cohort designed for the purpose of comparison with newer agents.

Outcomes: The European RA registries collect information related to disease duration, severity, and treatment. Variables routinely collected by each registry (or captured via linkage to national registries), including patient demographics, comorbidities, and concomitant medications, will be included in this study to characterise individuals with RA using upadacitinib in routine clinical care relative to individuals exposed to other systemic treatments (i.e., bDMARDs). Additional outcomes will be described for patients treated with upadacitinib to assess the effectiveness of additional risk minimization measures (HCP educational guide and patient card).

Data Sources:

This study will use data routinely collected by five European RA registries (ARTIS, DANBIO, BSRBR-RA, BIOBADASER, and RABBIT) or captured via linkage of RA patient data to nationwide health registers. These RA registries provide high-quality, longitudinal data capture of adult patients being treated with approved anti-rheumatic treatments.

Study Size:

The number of patients in the upadacitinib and comparator cohorts will vary between the registries. All initiators of upadacitinib or a selected bDMARD comparator treatment enrolled in one of five European RA registries during the study period will be included in the analysis. Based on available data, it is expected that the final report will include up to

1,000 upadacitinib new users each in ARTIS and DANBIO, and up to 400 upadacitinib new users in RABBIT.

Data Analysis:

All analyses will be descriptive; no statistical tests will be performed. Analyses will be performed separately for each registry and exposure group (i.e., upadacitinib cohort and selected bDMARD cohort). Baseline patient characteristics will be assessed at study drug initiation. To address important safety information communicated in the healthcare professional educational material and patient alert card, outcome indicators at the time of initiation will be evaluated in the upadacitinib cohort. Additional outcome indicators will be assessed in the upadacitinib cohort during their continuous treatment. In order to describe outcome indicators among upadacitinib users before and after the implementation of changes triggered by the JAK inhibitors Article 20 procedure, where feasible, data will be stratified by the two time periods in the final report.

Milestones:

AbbVie will initiate the study upon endorsement of the study protocol by the EMA. Study progress was reported in 2022 and will continue to be reported in 2023 (submitted), 2024 and 2025. The final study report will be submitted to the EMA in September 2026.

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