Cardiovascular risk and JAK inhibitor for the treatment of spondyloarthritis: A systematic review protocol

Risque cardiovasculaire associé à l'utilisation des anti-JAK au cours des spondylarthrites: Revue systématique

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Abstract

Introduction: JAK inhibitors, a newer class of medications, work by blocking specific enzymes (Janus kinases) that play a key role in inflammation. By inhibiting these enzymes, JAK inhibitors help alleviate inflammation and symptoms, providing an alternative treatment option to conventional therapies like NSAIDs and biologics. Considering the lack of updated findings on cardiovascular effects in SpA patients treated with JAK inhibitors, we will perform a systematic review of the literature to investigate the safety of JAK inhibitors in SpA patients. The aim of this review is to evaluate cardiovascular safety of JAK inhibitors.
Methods: We will search multiple databases, including PubMed, Embase, and the Cochrane Library, using specific keywords such as "Janus kinase inhibitors," "JAK inhibitors," "spondyloarthritis," and "cardiac risk." Our inclusion criteria will focus on randomized controlled trials, that reports Major Adverse Cardiovascular Events (MACE), in patients treated with JAK inhibitors for spondyloarthritis. We will exclude cohort studies, and those without relevant cardiac data, as well as animal studies or those outside the scope of JAK inhibitor treatment. After screening titles and abstracts, we performed a full-text review of the selected articles to ensure the inclusion of studies with high methodological quality and relevant data on cardiac risk factors. The various stages of this literature search will be summarized using the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) flow chart format to visualize the processes and findings of the review.
Results: The preliminary results demonstrated that the existing data indicated no significant change in cardiovascular risk for JAK inhibitors-treated patients with SpA. Data analyze find no notable difference in the occurrence of MACE between the interventions and the placebo groups. These finding are to interpret with caution, given the limitations of the study numbers and duration. However, these findings provide a foundation for further investigation in this area.
Conclusions: This systemic review highlights the safety of JAK inhibitors according to MACE occurrence in patients with SpA when compared to placebo. These results needs to be interpreted with caution regarding the limited long-term data and small sample sizes in clinical trials. Long-term studies are needed to clarify these risks.
Key words: Heart Disease Risk Factors, Cardiovascular Risk, spondyloarthritis, spondylarthritides, Janus Kinase Inhibitors, janus Kinase Inhibitors, tofacitinib, upadacitinib, baricitinib

Résumé

Introduction: Les spondylarthrites font partie des rhumatismes inflammatoires chroniques dont les manifestations cliniques sont variées.
Les anti-JAK, sont une nouvelle classe de médicaments, agissent en bloquant des enzymes spécifiques (Janus kinases) qui jouent un rôle clé dans l'inflammation. En inhibant ces enzymes, les anti-JAK contribuent à contrôler l'inflammation et les symptômes, offrant ainsi une alternative aux traitements conventionnels tels que les anti-inflammatoires non stéroïdiens (AINS) et les biologiques.
Compte tenu de l'absence de résultats actualisés sur les effets cardiovasculaires des anti-JAK dans l'SpA, nous allons réaliser une revue systématique de la littérature pour étudier la sécurité cardiovasculaire des anti-JAK chez les patients atteints de SpA.
L'objectif de cette revue sera d'évaluer le risque cardiovascualire associé aux anti-JAK.
Méthodes: Nous allons consulter les bases de données : PubMed, Embase et Cochrane Library, en utilisant des mots-clés spécifiques tels que « Janus kinase inhibitors », « JAK inhibitors », « spondyloarthritis » et « cardiac risk ». Nos critères d'inclusion seront les essais contrôlés randomisés, qui ont rapporté des résultats cardiovasculaires, tels que l'hypertension, l'infarctus du myocarde ou l'accident vasculaire cérébral, chez des patients traités par les anti- JAK pour SpA. Nous avons exclu les études de cohorte et celles qui ne contenaient pas de données suffisantes, ainsi que les études animales ou celles qui n'étaient pas liées au traitement par anti-JAK.
Après avoir examiné les titres et les résumés, nous allons procéder à une analyse du texte intégral des articles sélectionnés. Les différentes étapes de cette recherche documentaire seront résumées à l'aide de l'organigramme PRISMA (Preferred Reporting of Systematic Reviews and Meta-Analysis).
Résultats: Les résultats préliminaires révèlent que les données disponibles ne montrent pas une augmentation significative du risque cardiovasculaire chez les patients atteints de SpA traités par inhibiteurs de JAK. L'analyse des données n'a pas mis en évidence un différence dans l'incidence des événements cardiovasculaires majeurs entre les groupes sous traitement et les groupes placebo. Ces conclusions doivent toutefois être interprétées avec prudence, étant donné les limites de l'étude, notamment en termes d'effectif et de durée.
Conclusion: Cette revue systématique souligne la sécurité des inhibiteurs de JAK concernant la survenue d'événements cardiovasculaires majeurs chez les patients suivis pour SpA. Cependant, ces résultats doivent être analysés avec prudence, étant donné les données limitées sur le long terme et les échantillons de petite taille dans les essais cliniques disponibles
Mots-clés : Risque cardiovasculaire, spondylarthrite, inhibiteurs de la Janus Kinase, tofacitinib, upadacitinib, baricitinib

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Introduction

Spondyloarthritis (SpA) is a group of inflammatory disorders that mainly affect the spine and joints, leading to symptoms like pain, stiffness, and swelling [1]. Conditions such as ankylosing spondylitis and psoriatic arthritis fall under this category. Janus kinase (JAK) inhibitors, a newer class of medications, acts through blocking specific enzymes that play a key role in inflammation symptoms, providing an alternative treatment option to conventional therapies like non-steroidal anti-inflammatory drugs. By inhibiting these enzymes, JAK inhibitors help alleviate inflammation and (NSAIDs) and biologics [2].
In rheumatoid arthritis patients, cardiovascular safety of JAK inhibitors was well studied [3]
However, there is a lack of updated findings on cardiovascular effects in SpA patients treated with JAK inhibitors. Hence, an updated systematic review is highly required
Herein, we will perform a systematic review of the literature to investigate the cardiovascular safety of JAK inhibitors in SpA patients.

Methods

All data analyzed will be extracted from published studies. A narrative synthesis will be used to integrate the findings due to anticipated heterogeneity among the included studies, particularly in terms of study designs, interventions, and outcome measures. For the present paper, no ethical approval or written informed consent was required. The search strategy, literature selection, and data extraction were conducted by two investigators independently, then discussed, and any disagreement was resolved by a third investigator.
This systematic review was registered in prospero: [CRD42024600570].

Eligibility criteria

Participants: Our review will include studies involving individuals with SpA aged 18 years and over with no pre-existing confirmed or suspected cardiovascular diseases.
Intervention: The interventions will be the treatment with JAK inhibitors that have been approved for SpA, including tofacitinib, upadacitinib, baricitinib, used either as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or steroids.
Comparator: Placebo or no comparator.
Outcomes: Occurrence of MACE (composite of total death, myocardial infarction, coronary revascularization, stroke, and hospitalization because of heart failure). Secondary outcome is occurrence of hypertension.

Information sources

A comprehensive search will be conducted from inception until September 7th of 2024. Only full papers available and written in English were considered. We selected in this systematic review randomized controlled trials (RCTs). Studies will be included if they reported MACE or hypertension in patients treated with JAK inhibitors for SpA.
Papers will be excluded if:
- They are cohort studies, systematic reviews and meta-analysis, and those without relevant cardiac data, as well as animal studies or those outside the scope of JAK inhibitor treatment.
- They were written in another language than English.
- Publications not representing original research (i.e.; reviews, editorials, qualitative papers, case reports, and letters to editors) will be excluded.

Search strategy

This systematic review followed the preferred reporting items for systematic reviews guidelines (PRISMA)[4]. Eligible articles were searched in PubMed, Embase, and Cochrane Library. For PubMed, the search was carried out using a strategy employing the combination of the MeSH (Medical Subject Headings) terms associating the combination of synonyms of "Janus kinase inhibitors," "spondyloarthritis," and "cardiac risk" (table 1).
For Scopus and Cochrane Library, the previous terms were searched in the article title, abstract, or keywords. In addition, the reference lists of the included articles were checked. The authors of this systematic review agreed on the articles to be included in this paper. All the aspects of systematic review methods will be specified before starting the review.

Data extraction and quality assessment

Extracted data from each study will be evaluated independently by two investigators. A third party will resolve any disagreement. The extracted data will include the main methodological characteristics of the articles: study data (year of publication, country, study design, number and mean age of included subjects, inclusion and exclusion criteria, and duration of the follow-up), population characteristics (Age, gender, disease duration and co morbidities) as well as intervention details (details of the JAK inhibitors used (type, dosage, duration of treatment).
Furthermore, we will identify potential biases using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [4,5]. Only studies that met high quality belonged to our final selection.

Statistical analysis

A random-effects model will be used to evaluate heterogeneity within and across subgroups. Interaction tests will assess differences between JAK inhibitor and placebo groups.
For continuous outcomes, results will show mean differences (95% CI). For dichotomous outcomes, relative risk (RR) or odds ratios (OR) will be used.
Subgroup analyses will include interaction p-values to evaluate subgroup differences.

Software and tools:
Covidence for title and abstracts screening and full text review.
SCISPACE for data extraction
ZOTERO for references management

Results

The preliminary findings suggest that JAK inhibitors do not significantly increase cardiovascular risk in patients with SpA. Analyses revealed no notable difference in the incidence of MACE between JAKi-treated groups and placebo controls. Different JAKi used in SpA patients , including tofacitinib, baricitinib, filgotinib and upadacitinib were comparable regarding to cardiovascular risk. However, the interpretation of these results is limited by the short duration of many trials and the need for long-term studies to fully assess cardiovascular safety.

Table 1. Applied terms in the present systematic review

Synonyms of spondyloarthritis	Synonyms of Heart Disease Risk Factors	Synonyms of Janus Kinase Inhibitors
«Spondylarthritis»[MeSH Terms] OR «spondyloarthritis» OR «Spondylarthritides» OR «Arthritis, Spinal» OR «Spinal Arthritis» OR «Spinal Arthritides» OR «spondylitis, ankylosing»[MeSH Terms] OR «spondylitis, ankylosing» OR «Bechterew's Disease» OR «Bechterews Disease» OR «Marie-Struempell Disease» OR «Marie Struempell Disease» OR «Spondylarthritis Ankylopoietica» OR «Rheumatoid Spondylitis» OR «Spondylitis, Rheumatoid» OR «Ankylosing Spondylitis» OR «Ankylosing Spondylarthritis» OR «Ankylosing Spondylarthritides» OR «Spondylarthritides, Ankylosing» OR «Spondylarthritis, Ankylosing» OR «Ankylosing Spondyloarthritis» OR «Ankylosing Spondyloarthritides» OR «Spondyloarthritides, Ankylosing» OR «Spondyloarthritis, Ankylosing» OR «Spondylitis Ankylopoietica» OR «Bechterew Disease» OR «Spondyloarthritis Ankylopoietica»	«Heart Disease Risk Factors»[MeSH Terms] OR «Heart Disease Risk Factors « OR «Risk Factors for Cardiovascular Disease» OR «Cardiovascular Risk Factors» OR «Cardiovascular Risk Factor» OR «Factor, Cardiovascular Risk» OR «Risk Factor, Cardiovascular» OR «Risk Factors for Heart Disease» OR «Cardiovascular Risk» OR «Cardiovascular Risks» OR «Risk, Cardiovascular» OR «Residual Cardiovascular Risk» OR «Cardiovascular Risk, Residual» OR «Residual Cardiovascular Risks» OR «Risk, Residual Cardiovascular» OR «Cardiovascular Risk Score» OR «Cardiovascular Risk Scores» OR «Risk Score, Cardiovascular» OR «Score, Cardiovascular Risk» OR «Cardiovascular Diseases»[Mesh] OR «Cardiovascular Diseases « OR «Cardiovascular Disease» OR «Disease, Cardiovascular» OR «Cardiac Events» OR «Cardiac Event» OR «Event, Cardiac» OR «Adverse Cardiac Event» OR «Adverse Cardiac Events» OR «Cardiac Event, Adverse» OR «Cardiac Events, Adverse» OR «Major Adverse Cardiac Events» OR «Arrhythmias, Cardiac» OR «Heart Arrest» OR «Heart Failure» OR «Myocardial Ischemia» OR «Stroke»[Mesh] OR «Stroke» OR «Strokes» OR «Cerebrovascular Accident» OR «myocardial infarction» OR «heart attack» OR «cardiovascular death» OR «instable angina»	«Janus Kinase Inhibitors»[MeSH Terms] OR «Janus Kinase Inhibitors»[Pharmacological Action] OR «Janus Kinase Inhibitors « OR «tofacitinib» OR «upadacitinib» OR «Rinvoq» OR «Xeljanz» OR «ABT-494» OR «tasocitinib» OR «tofacitinib citrate» OR «CP 690,550» OR «CP 690550» OR «CP-690,550» OR «CP-690550» OR «CP690550»)

Conclusions

This systematic review explores the cardiovascular risk associated with JAK inhibitors patients with SpA. JAK inhibitors showed no increased risk of cardiovascular disease compared to placebo. The findings suggest that JAK inhbitors, including tofacitinib, baricitinib, filgotinib, and upadacitinib, do not significantly increase the risk of major adverse cardiovascular events.
However, the safety of JAK inhibitors according to MACE remains unclear due to limited long-term data and small sample sizes in clinical trials.

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