LA TUNISIE MEDICALE

Special issue: Septembre 2025

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

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

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Abstract

Objective: The aim of this review is to evaluate cardiovascular safety of Janus Kinas (JAK) inhibitors in patients with spondyloarthritis (SpA).
Methods: Applying the PRISMA methodology, we searched PubMed, Embase, and the Cochrane Library databases using the following search terms: Janus kinase inhibitors, spondyloarthritis, cardiac risk and major adverse cardiovascular event. Randomized controlled trials that reported Major Adverse Cardiovascular Events (MACE) in patients treated with JAK inhibitors for SpA were included.
Results: Ten radomized controlled trials conducted between 2017 and 2024 were analyzed, encompassing 2671 patients with an active SpA and treated with JAK inhibitors (tofacitinib, upadacitinib and filgotinib). The follow-up duration ranged from 12 to 104 weeks. Only three MACE were reported with upadacitinib (15 mg/day) : one non-fatal haemorrhagic stroke after 52 weeks of treatment in a patient with a history of smoking and a myocardial infarction and a cerebral hemorrhage after 104 weeks in the same population, corresponding to an incidence rate of 0.3 per 100 patient-years (95% CI: 0.0–1.1).
Conclusions: This systemic review highlights the safety of JAK inhibitors according to MACE occurrence in patients with SpA when compared to placebo. These results need 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: Major adverse cardiovascular event, Cardiovascular risk, Spondyloarthritis, Janus Kinase Inhibitors, systematic review

Résumé

Objectif: L'objectif de cette revue est d'évaluer la sécurité cardiovasculaire des inhibiteurs du Janus Kinas (JAK) chez les patients atteints de spondyloarthrite (SpA).
Méthodes: En appliquant la méthodologie PRISMA, nous avons effectué une recherche dans les bases de données PubMed, Embase et la Cochrane Library en utilisant les termes de recherche suivants : Inhibitors du Janus kinase, spondyloarthrite, risque cardiaque et événements cardiovasculaires indésirables majeurs. Les essais contrôlés randomisés ayant rapporté des événements cardiovasculaires indésirables majeurs (MACE) chez des patients traités par des inhibiteurs du JAK pour la spondyloarthrite ont été inclus.
Résultats: Dix essais contrôlés randomisés menés entre 2017 et 2024 ont été analysés, englobant 2671 patients atteints d'une SpA active et traités par des inhibiteurs de JAK (tofacitinib, upadacitinib et filgotinib). La durée du suivi allait de 12 à 104 semaines. Seuls trois MACE ont été rapportés avec l'upadacitinib (15 mg/jour): un accident vasculaire cérébral hémorragique non fatal après 52 semaines de traitement chez un patient ayant des antécédents de tabagisme et un infarctus du myocarde et une hémorrhagie cérébrale après 104 semaines dans la même population, ce qui correspond à un taux d'incidence de 0,3 pour 100 années-patients (IC à 95 % : 0,0-1,1).
Conclusion: Cette revue systémique met en évidence la sécurité des inhibiteurs de JAK en fonction de la survenue de MACE chez les patients atteints de SpA par rapport au placebo. Ces résultats doivent être interprétés avec prudence compte tenu du peu de données à long terme et de la petite taille des échantillons dans les essais cliniques. Des études à long terme sont nécessaires pour clarifier ces risques.

Mots-clés : Événement cardiovasculaire indésirable majeur, Risque cardiovasculaire, Spondyloarthrite, Inhibiteur du Janus Kinase, Revue systématique

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LA TUNISIE MEDICALE-2025; Vol 103 (09): 1202-1209 DOI: 10.62438/tunismed.v103i9.6218

Introduction

Spondyloarthritis (SpA) represents a heterogeneous group of chronic inflammatory rheumatic diseases, including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), which predominantly affect the axial skeleton, peripheral joints, and entheses (1) . These conditions are characterized by hallmark clinical features such as chronic inflammatory back pain, peripheral arthritis, enthesitis, and extra-articular manifestations, including uveitis, psoriasis, and inflammatory bowel disease. The progressive nature of SpA can lead to structural damage, impaired physical function, and diminished quality of life (2) .

In recent years, Janus kinase (JAK) inhibitors, an emerging class of targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), have been introduced as a promising therapeutic option for patients with SpA, particularly those with an inadequate response or intolerance to conventional treatments such as non-steroidal anti-inflammatory drugs (NSAIDs), tumor necrosis factor (TNF) inhibitors, and interleukin (IL)-17 inhibitors (3–5). JAK inhibitors exert their effect by selectively blocking intracellular signaling pathways involved in the immune response, thereby reducing inflammation and disease activity (3).

While the cardiovascular safety profile of biologic DMARDs (6) and JAK inhibitors has been the focus of several large-scale clinical trials and real-world studies in rheumatoid arthritis (RA) (7), concerns have been raised regarding their potential association with adverse cardiovascular outcomes, including major adverse cardiovascular events (MACE) (8,9), thromboembolic complications (10), and lipid profile alterations (11). However, data regarding the cardiovascular risks and benefits of JAK inhibitors in the specific context of SpA remain limited and inconclusive (12). Given the distinct pathophysiological mechanisms and demographic characteristics of SpA compared to RA, as well as the inherent cardiovascular risk associated with chronic inflammation in SpA, there is a critical need for robust, disease-specific evidence to guide clinicians in the safe and effective use of JAK inhibitors in this population. In this perspective, we conducted this study with the aim to systematically review papers dealing with this topic.

Methods

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13). Predefined protocol was registered with PROSPERO (Registration No.CRD42024600570). and in La Tunisie Medicale journal (14).

Search strategy

Electronic databases including PubMed, Embase and Cochrane Library were searched and screened independently by two authors (DR. and LBA). In case of discordance, a discussion was made with BS. The final systematic search was conducted on December 12, 2024. Medical Subject Headings terms (MeSH) and free-text terms were used as the search strategy for PubMed associating the combination of synonyms of "(supplementary materials). For Embase and Cochrane Library, the previous terms were searched in the article title, abstract, or keywords. All references cited in the selected literature were also scanned to identify other pertinent publications. Duplicate studies were removed and managed by Covidence.

Study selection

The eligible criteria for inclusion in the current systematic review were: i) randomized controlled trials, ii) patients above 18 years-old, diagnosed with ankylosing spondylitis (AS) according to the modified New York criteria for AS (1), or the 2009 ASAS classification criteria (15) and treated with Janus Kinase Inhibitors, iii) studies who reported cardiovascular events, such as Major Adverse Cardiovascular Event (MACE) and hypertension, and iiii) articles in English.

We excluded: 1) cohort studies, systematic review and meta-analysis, 2) animal studies, 3) publications not representing original research (i.e.; reviews, editorials, qualitative papers, case reports, and letters to editors) , 4) Papers written in another language than English, 5) Studies without relevant cardiac data and outside the scope of JAK inhibitor treatment and 6) patients below 18 years-old or with pre-existing cardiovascular disease.

Data extraction

Two investigating authors (LBA. and DR) evaluated the quality and extracted the data of each article based on the CONsolidated Standarts Of Reporting Trials (CONSORT) scale specialized for assessing the quality of RCTs (16). The CONSORT scores of below 15, 15-20, and above 20 indicated low, medium and high-quality of studies, respectively. In case of uncertainty, a third investigator (BS) was consulted (supplementary materials).

The following information of each selected study were extracted: 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).

Our main judgement criteria was the occurrence of MACE (composite of total death, myocardial infarction, coronary revascularization, stroke, and hospitalization because of heart failure). We also checked the occurrence of hypertension.

Risk of bias assessment

Two investigators (LBA. and DR) independently evaluated the risk of bias for each eligible RCT using the revised Cochrane 'Risk of bias' tool for randomised trials (RoB 2.0) (17). We categorized each eligible RCT into three categories: low, some concerns, or high risk of bias (supplementary materials).

Results

The search results, presented in Figure 1, included 134 publications extracted from all databases. After excluding duplicates, 87 records were screened. Finally ten RCTs were included in the review (18-27). All the included studies are listed in table 1.

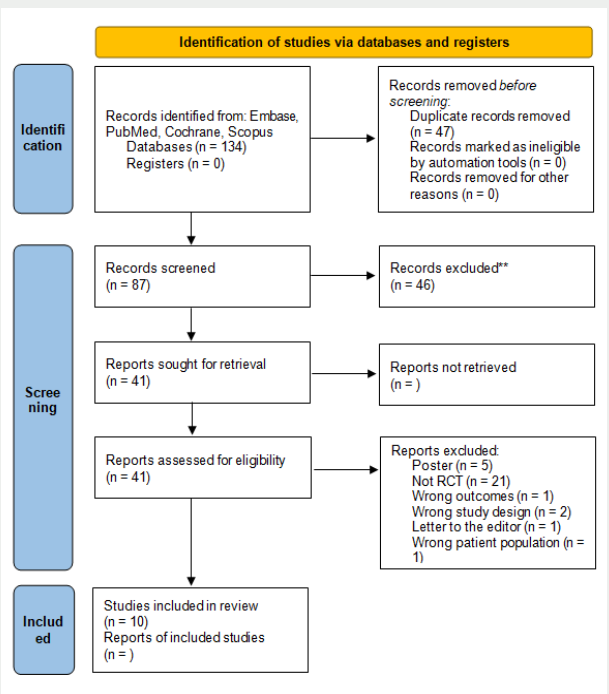

Figure 1. PRISMA flow chart of studies selection

Ten RCTs evaluated the cardiovascular safety of Janus kinase (JAK) inhibitors in patients with axial spondyloarthritis (axSpA). They were conducted between 2017 (22) and 2024 (19) and included a total of 2,671 patients, with sample sizes ranging from 116 (24) to 409 (18,19) per study. Participants were consistently aged ≥18 years on average, although precise mean age values were not uniformly reported. All patients included had active radiographic ankylosing spondylitis (AS) or non-radiographic (nr-axSpA) with high BASDAI (≥4) and low back pain (≥4) scores, as well as an inadequate response to or intolerance of at least two NSAIDs. Most trials excluded prior exposure to JAKIs (18,19,21,22,27) , and several excluded the use of biological disease-modifying antirheumatic drugs (bDMARDs) or total spinal ankylosis (21-23,26).

Study characteristics

All studies used standardised criteria (modified New York or ASAS 2009) to define axSpA (1,15). In the nr-axSpA trial, objective signs of inflammation (MRI and/or elevated C-reactive protein (CRP)) were required for inclusion.

The follow-up duration ranged from 12 (24) to 104 weeks (19). While some studies focused on short-term outcomes (12–16 weeks) (22,24), others provided extensive safety data over one to two years (18,19,22,26).

Major Adverse Cardiovascular Events

In the ten RCTs, only three major adverse cardiovascular events (MACE) were reported, resumed in Figure 2.

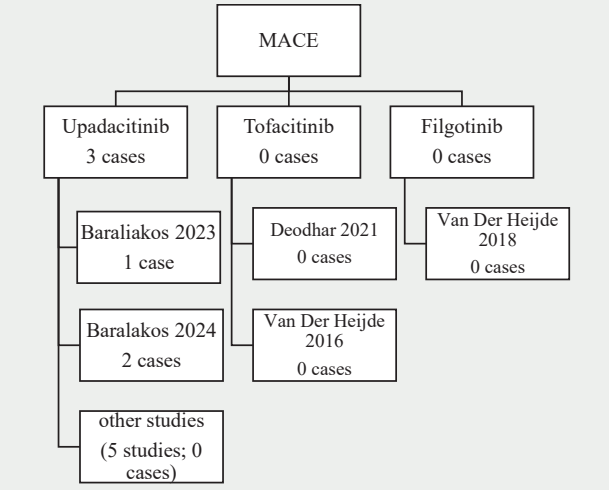

Figure 2. MACE incidence in JAK inhibitor trials for axial spondyloarthritis

Baraliakos et al. (18) reported a non-fatal haemorrhagic stroke after 52 weeks of treatment with upadacitinib in a patient with a history of smoking. He reported, one year later, in a second study (18), two additional cases of MACE over 104 weeks in the same population (upadacitinib 15 mg/day), an acute ST elevation in a 38-year-old man and a cerebral hemorrhage at left basal ganglia in a 47-year-old man, corresponding to an incidence rate of 0.3 per 100 patient-years (95% CI: 0.0–1.1).

All other studies, including those evaluating tofacitinib (2 mg, 5 mg and 10 mg twice daily) (20,23) and filgotinib (200 mg/day) (24), reported no MACE. The only other cardiovascular adverse event was a single case of hypertension in the high-dose tofacitinib group (10 mg twice daily), reported by van der Heijde et al. in 2017 (23).

MACE risk according to JAK inhibitor molecule

Upadacitinib, the most frequently evaluated JAK inhibitor, was featured in six studies (18,19,21,22,25,26) involving 1,688 patients in total.

Tofacitinib was evaluated in two studies (21,23), involving 478 patients.

Filgotinib was evaluated in one study (24), involving 116 patients.

Upadacitinib:

Seven RCTs examined the efficacy and safety of upadacitinib at a dose of 15 mg per day (18,19,21,22,25-27). The longest follow-up periods (52 and 104 weeks) were conducted by Baraliakos et al. (2023, 2024) (18,19) and involved 409 patients from 22 countries. These studies reported three major adverse cardiac events (MACEs): one non-fatal haemorrhagic stroke after 52 weeks and a myocardial infarction and a cerebral hemorrhage after 104 weeks, representing an incidence rate of 0.3 per 100 patient-years (95% confidence interval [CI]: 0.0–1.1).

Table 1. Characteristics of included studies

First author (ref) Year of publication	Study design/ Characteristics of the population studied	Inclusion and exclusion criteria	JAK inhibitor	Intervention	Study duration	Cardiovascular outcome
Baraliakos **et al 2023** **[17]**	RCT : 22 countries Total : 409 Continued on Upadacitinib 206 Switched from placebo to Upadacitinib 203	- Age ≥ 18 years - Meeting modified New York criteria for AS - Active AS (BASDAI score of ≥ 4 - Patient's assessment of total back pain score of ≥ 4) - Inadequate response to ≥ 2 NSAIDs and a bDMARD - Prior exposure to two bDMARDs was allowed for ≤ 30% of patients - Prior exposure to a JAK inhibitor was not permitted	Upadacitinib	Upadacitinib 15mg per day	52 weeks	1 case of adjusted MACE: non-fatal haemorrhagic stroke (history of smoking)
Baraliakos **et al 2024** **[18]**	RCT : 22 countries Total : 409 Continued on Upadacitinib 206 Switched from placebo to Upadacitinib 203	- Age ≥ 18 years - Meeting modified New York criteria for AS - Active AS (BASDAI score of ≥ 4 and - Patient's assessment of total back pain score of ≥ 4) - Inadequate response to ≥ 2 NSAIDs and a bDMARD - Prior exposure to two bDMARDs was allowed for ≤ 30% of patients - Prior exposure to a JAK inhibitor was not permitted	Upadacitinib	Upadacitinib 15mg per day	104 weeks	2 case of adjusted MACE: one acute ST elevation (myocardial infarction) and one cerebral hemorrhage at left basal ganglia E (E/100 [95% CI]) 2 (0.3 [0.0 , 1.1])
Deodhar et al 2021 **[19]**	RCT : 14 countries Total : 270 Tofacitinib 134 Placebo 136	- Age ≥ 18 years - Meeting modified New York criteria for AS - Active AS (BASDAI score ≥4 and NSAID inadequate response) - Excluded if treated with targeted synthetic DMARDs or current bDMARDs - Prior bDMARD treatment allowed if discontinued for ≥4 weeks	Tofacitinib	Tofacitinib 5mg twice a day vs placebo	16 weeks	No case of MACE
Deodhar et al 2022 **[20]**	RCT : 20 countries Total : 178 Continued on Upadacitinib 89 Switched from placebo to Upadacitinib 89	- Age ≥ 18 years - Meeting modified New York criteria for AS - Active AS (BASDAI score ≥4 and patient's assessment of back pain score of ≥ 4) and inadequate response to ≥2 NSAIDs or intolerance to or contraindication for NSAIDs - Prior exposure to JAK inhibitors or biologic DMARDs (such as tumor necrosis factor [TNF] inhibitors and interleukin-17A [IL-17A] inhibitors) were excluded - Patients with total spinal ankylosis were ineligible.	Upadacitinib	Upadacitinib 15mg	64 weeks	No case of MACE
Deodhar et al 2022 [21]	RCT : 23 countries Total : 314 Upadacitinib 156 Placebo 157	- Age ≥ 18 years - Non-radiographic axial spondyloarthritis meeting the 2009 ASAS classification criteria - Active disease (BASDAI and patient's assessment of total back pain score ≥4 and at least one objective sign of active inflammation at screening based on - MRI of the sacroiliac joints, high-sensitivity C-reactive protein greater than the upper limit of normal, or both) - Inadequate response to at least two NSAIDs or intolerance to or contraindication for NSAIDs - Prior exposure to two bDMARDs was allowed for for at least 20% but no more than 35% of patients - Exclusion included prior inflammatory arthritis other than axial spondyloarthritis - Previous treatment with a JAK inhibitor was also an exclusion criterion - Patients meeting modified New York criteria for ankylosing spondylitis were excluded - Patients who showed lack of efficacy for both a TNF inhibitor and IL-17 inhibitor were excluded from the study	Upadacitinib	Upadacitinib 15mg vs placebo	14 weeks	No case of MACE
Van der heijde 2016 [22]	RCT : total : 208 Tofacitinib 2mg 52 Tofacitinib 5mg 52 Tofacitinib 10mg 52 Placebo 136 51	- Age ≥18 years - Meting modified New York criteria for AS - Active disease r(BASDAI score ≥4 and back pain score ≥4) - Patients with normal CRP levels could be enrolled if other criteria were met - Exclusion criteria included prior biological DMARD treatment and tuberculosis infection	Tofacitinib	Tofacitinib 2mg or 5mg or 10 mg twice a day vs placebo	16 weeks	No case of MACE One case of hypertension with tofacitinib 10mg twice a day

Table 1. (following) Characteristics of included studies

First author (ref) Year of publication	Study design/ Characteristics of the population studied	Inclusion and exclusion criteria	JAK inhibitor	Intervention	Study duration	Cardiovascular outcome
Van der heijde 2018 [23]	RCT : 7 countries Total : 116 Filgotinib 58 Placebo 58	- Age ≥18 years - Meting modified New York criteria for AS - Active disease (BASDAI score ≥4 and back pain score ≥4, high-sensitivity C-reactive protein > 3·0 mg/l) - Inadequate response to two or more NSAIDs - Prior exposure to two bDMARDs was allowed for ≤ 30% of patients	Filgotinib	Filgotinib 200mg vs placebo	12 weeks	No case of MACE
Van der heijde 2019 [24]	RCT : 20 countries Total : 187 Upadacitinib 93 Placebo 94	- Age ≥ 18 years - Meeting modified New York criteria for AS - Active AS (BASDAI score ≥4 and patient's assessment of back pain score of ≥ 4) and inadequate response to ≥2 NSAIDs or intolerance to or contraindication for NSAIDs - Prior exposure to JAK inhibitors or biologic DMARDs (such as tumor necrosis factor [TNF] inhibitors and interleukin-17A [IL-17A] inhibitors) were excluded - Patients with total spinal ankylosis were ineligible.	Upadacitinib	Upadacitinib 15mg vs placebo	14 weeks	No case of MACE
Van der heijde 2022 [25]	RCT : 20 countries Total : 178 Continued on Upadacitinib 89 Switched from placebo to Upadacitinib 89	- Age ≥ 18 years - Meeting modified New York criteria for AS - Active AS (BASDAI score ≥4 and patient's assessment of back pain score of ≥ 4) and inadequate response to ≥2 NSAIDs or intolerance to or contraindication for NSAIDs - Prior exposure to JAK inhibitors or biologic DMARDs (such as tumor necrosis factor [TNF] inhibitors and interleukin-17A [IL-17A] inhibitors) were excluded - Patients with total spinal ankylosis were ineligible.	Upadacitinib	Upadacitinib 15mg	104 weeks	No case of MACE
Van der heijde 2022 [26]	RCT : 22 countries Totalal : 420 Upadacitinib 211 Placebo 209	- Age ≥ 18 years - Meeting modified New York criteria for AS - Active AS (BASDAI score of ≥ 4 and - Patient's assessment of total back pain score of ≥ 4) - Inadequate response to ≥ 2 NSAIDs and a bDMARD - Prior exposure to two bDMARDs was allowed for ≤ 30% of patients - Prior exposure to a JAK inhibitor was not permitted	Upadacitinib	Upadacitinib 15mg vs placebo	14 weeks	No case of MACE

Four other RCTs using upadacitinib (Deodhar 2022; Van der Heijde 2019, 2022), lasting 14, 64 and 104 weeks, and involving populations ranging from 178 to 420 patients, reported no MACEs. One of these studies focused specifically on SpAax-nr and required the presence of objective inflammatory markers (MRI or CRP) for inclusion.

Tofacitinib:
Two RCTs evaluated tofacitinib at doses of 2 mg, 5 mg and 10 mg twice daily (21,23). In Deodhar et al., 270 patients received 5 mg twice daily for 16 weeks and no cardiovascular events occurred. In the dose-finding study conducted by van der Heijde et al. (23), 208 patients were randomised to receive one of three doses of tofacitinib or a placebo. No major adverse cardiovascular events (MACE) were reported, although one case of hypertension was observed in the 10 mg group.

Filgotinib:
The study by van der Heijde et al. (24) included 116 patients who were treated with 200 mg per day for 12 weeks. No cardiovascular events were reported.

Summary of cardiovascular safety

These results suggest that JAK inhibitors have a favourable cardiovascular safety profile in patients with axial SpA when administered under controlled conditions. Although upadacitinib was the only molecule associated with MACEs (n = 3), these events were rare and occurred in the context of the long-term extension setting. No MACE were observed with tofacitinib or filgotinib in trials lasting up to 16 weeks. However, it is important to note that most trials excluded patients with known cardiovascular risk factors, which limits the generalisability of these findings. Further real-world studies and long-term post-marketing surveillance are required to evaluate the cardiovascular safety of JAK inhibitors in wider, higher-risk axSpA patient groups.

Discussion

We performed a systematic review of ten RCTs including 2,671 patients to assess the cardiovascular risk of JAK inhibitors used for treating SpA patients. In summary, the analyses revealed that JAK inhibitors have a favorable

cardiovascular safety profile in patients with SpA. One of our analysis' strengths is that it includes only RCTs and a relatively large number of patients with SpA.

The majority of included studies on Tofacitinib, Filgotinib and Upadacitinib show overall a low risk of bias. The Van der Heijde 2017 study (23) stands out as having a high overall risk of bias, mainly due to concerns in the randomization process and outcome measurement.

Although our analysis indicates a positive cardiovascular safety profile of JAK inhibitors, these findings should be considered in light of the methodological limitations of the included studies. A more detailed analyze reveals wide variability in trial design and reporting. Specifically, follow-up duration varied widely, ranging from 12 weeks (23) in some studies to 104 weeks in others (18,25).

Given that short-term trials might miss long-term cardiovascular events; this variation is an important factor to take into account.

Furthermore, the studies differed in sample size, with some including as few as 116 patients, which limits the ability to detect rare events such as MACE.

Many trials also employed strict inclusion criteria. This selective enrolment may have minimized the observed adverse events, suggesting that the safety profile could differ in a real-world patient's population.

Chronic systemic inflammation is a key driver of accelerated atherosclerosis and increased pulmonary (28) and CV risk (29). Suppressing inflammation through "Treat to Target" strategies and DMARDs, including csDMARDs, bDMARDs, and JAK inhibitors, has demonstrably improved cardiovascular outcomes in patients with chronic inflammatory rheumatic diseases (30).

Anti-JAK drugs may cause an increase in total cholesterol, LDL-cholesterol and HDL cholesterol levels and apolipoproteins (Apo) A1 and ApoB. These lipid abnormalities are generally observed in the first few weeks of treatment and stabilize thereafter (31).

JAK enzymes, a part of the tyrosine kinase family enzymes, play a crucial role in various cell signalling pathways involved in inflammation, immunity and other physiological functions. By blocking these enzymes, anti-JAKs modulate a wide range of pro-inflammatory cytokines. Although this is beneficial for reducing inflammation, this "pan-JAK" inhibition could have consequences for organ function, including the cardiovascular system (32) Increased risk of thromboembolism is suggested by data from numerous clinical trials on JAK inhibitors. Among the many mechanisms potentially involved in the increased risk of thrombosis with JAK inhibitors, transendothelial leukocyte migration and the JAK-STAT signaling pathway have been particularly highlighted.(33)

The current recommendations for using Janus kinase (JAK) inhibitors in SpA position them as a significant therapeutic option, particularly for patients who have not adequately responded to or are intolerant of other treatments (34). While non-steroidal anti-inflammatory drugs (NSAIDs) remain the first-line pharmacological treatment, followed by biologic disease-modifying antirheumatic drugs (bDMARDs) like tumor necrosis factor inhibitors (TNFi) or interleukin-17 inhibitors (IL-17i), many patients still do not achieve desired therapeutic goals (34).

EULAR include JAK inhibitors as an option for patients with an inadequate response or intolerance to NSAIDs (34). Furthermore, for patients who experience an inadequate response to their initial bDMARD, it is recommended to switch to another bDMARD or consider a JAK inhibitor (32). This addresses an unmet need for oral therapies with alternative mechanisms of action.

It's worth noting that the cardiovascular risk associated with anti-JAKs is significant in patients aged 65 and over, smokers (current or former), and those with other pre-existing cardiovascular risk factors (history of atherosclerotic cardiovascular disease, hypertension, etc.). For these patients, the use of anti-JAKs should be considered with caution. Regular monitoring of lipid parameters and vigilance for cardiovascular symptoms are recommended (32).

Conclusion:

This systematic review revealed that JAK inhibitors have a good cardiovascular safety profile in SpA patients, with a low incidence of major adverse cardiac events (MACE) reported in the included randomized controlled trials. However, these results should be interpreted with caution. Some of included studies mainly focused on patients with low baseline cardiovascular risk and were not designed to assess the long-term effects of these drugs.

Consequently, the observed safety profile cannot be generalized to patients in real life, particularly older people or those with significant pre-existing cardiovascular risk factors. Given these limitations, it is essential to conduct long-term observational studies and post-marketing surveillance to fully clarify the cardiovascular risk associated with JAK inhibitors in this population.

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