BMJ Open

Risk of infections and cardiovascular and venous thromboembolic events associated with JAK inhibitors in rheumatoid arthritis: protocols of two systematic reviews and network meta-analyses

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To cite: Alves C, Penedones A, Mendes D, *et al*. Risk of infections and cardiovascular and venous thromboembolic events associated with JAK inhibitors in rheumatoid arthritis: protocols of two systematic reviews and network meta-analyses. *BMJ Open* 2020;**10**:e041420. doi:10.1136/bmjopen-2020-041420

► Prepublication history and supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-041420).

Received 05 September 2020
Revised 29 October 2020
Accepted 09 November 2020

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ABSTRACT

Introduction Janus kinases (JAK) inhibitors demonstrated to be effective in the treatment of adult patients with moderate-to-severe active rheumatoid arthritis (RA) but have been associated with serious cardiovascular and serious events. Two systematic reviews and network meta-analyses will be carried aiming to compare the relative safety of the different JAK inhibitors with regard to the risk of (1) cardiovascular and thromboembolic events and (2) serious infections in patients with RA.

Methods and analysis PUBMED, Embase, Cochrane Controlled Register of Trials and ClinicalTrials.gov will be searched in order to identify randomised controlled trials evaluating the efficacy and safety of JAK inhibitors in patients with RA. The following events will be assessed: (1) any cardiovascular event; major adverse cardiovascular events and venous thromboembolism and (2) any infection; serious infections; herpes zoster infection and tuberculosis. Search terms will comprise RA and drugs names, including the thesaurus terms and the International Nonproprietary Names. The assessment of the methodological quality of the included studies will be performed through the RoB 2 tool: a revised Cochrane risk of bias tool for randomised trials. Network meta-analyses will be performed using STATA V.13.0. For each outcome, treatments will be ranked according to the probability of being the safest (best) alternative using the surface under the cumulative ranking curve.

Ethics and dissemination Ethical approval is not required as no primary data are collected. This systematic review will be disseminated through peer-reviewed publications and at conference meetings.

Strengths and limitations of this study

- The Preferred Reporting Items for Systematic Review and Meta-Analysis for Network Meta-Analysis statement and the Centre for Reviews and Dissemination's guidance will be followed.
- The relative risk of cardiovascular and thromboembolic events will be assessed for the first time among the Janus kinases (JAK) inhibitors class.
- Although an increased risk of herpes zoster was identified for baricitinib in a previous network meta-analysis, further randomised controlled trials have been published, which can provide new evidence regarding the differential risk of infections among JAK inhibitors.
- The rare nature of serious cardiovascular events and opportunistic infections may limit the number and type of sensitivity analyses that can be conducted.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease, causing symmetrical polyarthritis, typically resulting in swollen, stiff and painful joints.[1] The pharmacological treatment of RA should start as soon as the diagnosis is made.[2] Methotrexate is an effective conventional synthetic (cs) disease-modifying antirheumatic drug (DMARD) and it is the first-line treatment option.[2] If the disease activity remains moderate to high, additional treatment with csDMARDs, biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) should be considered.[2]

Janus kinases (JAK1–3 and tyrosine kinase 2) inhibitors are tsDMARDs that target the JAK–STAT pathway with proven efficacy in the treatment of adult patients with moderate-to-severe active RA, who have not responded or are intolerant to either cs or bDMARDs.[3] Though two main safety concerns have been associated with the use of JAK inhibitors, namely cardiovascular adverse events and serious infections.[4–7]

The cardiovascular risk of JAK inhibitors has been under scrutiny by regulatory authorities. US Food and Drug Administration (US FDA) concluded that the benefit–risk profile of baricitinib was adequate to support the approval of the 2 mg dose, but not the 4 mg dose due to an increased risk of thrombosis.[4] Preliminary results from an ongoing postapproval study revealed an increased risk of blood clots and death when the approved dose of tofacitinib was doubled in patients with RA, leading the authorities to add warnings to the label.[8 9] A few cases of cardiovascular events were further reported in patients treated with upadacitinib in the Subjects with Moderately to Severely Active Rheumatoid Arthritis (SELECT) trials programme.[5] The change in the serum lipid profile seems to be a class effect.[3] Despite a previous meta-analysis of randomised controlled trials (RCTs) did not reveal a significant change in the risks of cardiovascular events and venous thromboembolism in patients with RA treated with JAK inhibitors,[6] the relative cardiovascular safety of JAK inhibitors compared with every other remains unclear due to lack of head-to-head comparisons.

Another important safety concern with JAK inhibitors are serious infections, such as reactivation of herpes zoster, pneumonia, tuberculosis, upper respiratory infection and urinary tract infections.[7 10 11] In 2013, European Medicines Agency (EMA) adopted a negative opinion on the approval of tofacitinib mainly due to safety concerns, including the risk of serious infections.[12] Tofacitinib was later approved in 2017 but, as baricitinib and upadacitinib, it was put under additional monitoring.[13 14] The risk of serious infections has also been described for JAK inhibitors under clinical development (decernotinib, filgotinib and peficitinib).[7 15] An increased risk of herpes zoster was identified for baricitinib in a network meta-analysis, but significant differences between the approved JAK inhibitors were not found.[7] Nevertheless, further RCTs may provide new evidence regarding the differential risk of infections with JAK inhibition.[16–18]

Two systematic reviews and network meta-analyses will be carried out to compare the relative safety of the different JAK inhibitors with regard to the risk of (1) cardiovascular and thromboembolic events and (2) serious infections in patients with RA.

METHODS

The protocols are in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement (online supplemental file).[19] Both systematic reviews and network meta-analyses will be reported in accordance to the PRISMA extension statement for reporting systematic reviews incorporating network meta-analyses of healthcare interventions (PRISMA-NMA) and will follow the Centre for Reviews and Dissemination's guidance for undertaking reviews in healthcare.[20 21] The systematic review on the risk of (1) cardiovascular and thromboembolic events and (2) the one about the risk of infections are both registered at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS35534 and EUPAS35531, respectively).

Eligibility criteria

Studies will be considered for inclusion if they fulfil the following criteria (with the exception of outcomes, the other inclusion criteria will be the same in both systematic reviews):

- Study design: Phase II and phase III RCTs.
- Population: Studies evaluating patients diagnosed with RA based on the American College of Rheumatology/European League Against Rheumatism criteria will be included.[22]
- Intervention: Only studies assessing the effects of JAK inhibitors (baricitinib, decernotinib, filgotinib, peficitinib, tofacitinib, upadacitinib) in the treatment of RA will be included.
- Comparators: Studies comparing the intervention against placebo, active treatment (DMARD) or no treatment.
- Outcomes: (1) any cardiovascular event: angina pectoris, myocardial infarction, congestive heart failure, carotid artery disease, aortic aneurysm, cerebral vascular diseases (stroke and transient ischaemic attack), venous thromboembolic events (VTEs) and cardiovascular death; major adverse cardiovascular events (MACE): myocardial infarction, cerebrovascular accident (ischaemic and haemorrhagic strokes) or cardiovascular death and VTEs: pulmonary embolism and deep vein thrombosis.
- Outcomes: (2) any infection; serious infections: events leading to death, hospitalisation or need for antibiotic therapy; herpes zoster infection and tuberculosis.
- Timing: No restrictions will be applied to the length of follow-up.
- Language: Only studies reported in English will be included.

Information sources

PUBMED (https://www.ncbi.nlm.nih.gov/pubmed/), Embase (https://www.embase.com/), Cochrane Controlled Register of Trials (https://www.cochranelibrary.com/central) and ClinicalTrials.gov (https://clinicaltrials.gov/) will be searched from the inception until June 2020. Bibliographic references list of all relevant studies, systematic reviews and meta-analyses will be hand searched in order to identify additional eligible studies.

Search strategy

Search terms will comprise RA and drugs names, including the thesaurus terms (MeSH (Medical Subject Headings) and Emtree terms) and the International Nonproprietary Names. No language filters will be applied. The search will be updated at the end of the systematic review. A search strategy (PUBMED) is presented in table 1.

Table 1 PUBMED search strategy

1	"Janus Kinase Inhibitors"[Mesh]	303
2	"Janus Kinase Inhibitors" [Pharmacological Action]	315
3	janus kinase inhibitor	6526
4	janus kinase inhibitors	5178
5	1 OR 2 OR 3 OR 4	6526
6	"upadacitinib"[Supplementary Concept]	26
7	upadacitinib	92
8	6 OR 7	92
9	"tofacitinib"[Supplementary Concept]	722
10	tofacitinib	1328
11	9 OR 10	1328
12	baricitinib	289
13	"baricitinib"[Supplementary Concept]	115
14	12 OR 13	289
15	peficitinib	50
16	"peficitinib"[Supplementary Concept]	21
17	15 OR 16	50
18	"GLPG0634"[Supplementary Concept]	30
19	filgotinib	91
20	18 OR 19	91
21	decernotinib	21
22	"2-((2-(1H-pyrrolo(2,3-b)pyridin-3-yl)pyrimidin-4-yl)amino)–2-methyl-N-(2,2,2-trifluoroethyl)butanamide"[Supplementary Concept]	8
23	21 OR 22	21
24	5 OR 8 OR 11 OR 14 OR 17 OR 20 OR 23	7249
25	"Arthritis, Rheumatoid"[Mesh]	112224
26	rheumatoid arthritis	148408
27	arthritis, rheumatoid	148408
28	21 OR 22 OR 23	148408
27	21 AND 25	919

Study records

Two researchers will independently screen by hand the titles and abstracts and selected full articles for inclusion in accordance with the prespecified eligibility criteria. Disagreements will be resolved by discussion and consensus with a third researcher.

Data items

The following data will be extracted from each study: reference, year of publication, RCT phase (II or III), sample sizes, follow-up length, intervention (name, dosage, frequency and duration of treatment), comparators and data on the safety outcomes. Data will be extracted from each included study by two researchers independently to a predeveloped form.

Methodological quality assessment of the included studies

The assessment of the methodological quality of the included studies will be performed through the RoB2 tool: a revised Cochrane risk of bias tool for randomised trials.[23] The value of trial data on adverse effects relies on two major characteristics: the rigour of monitoring for the adverse effects during the study and the completeness of reporting. Allocation concealment and withdrawal rates will also be evaluated.

Data synthesis

ORs and their 95% CIs will be pooled. The risk estimates will be considered statistically significant if the 95% CI do not contain the value 1. When no events are reported in one or both groups, a continuity correction of 0.5 will be added to each cell.

A network map linking all the pharmacological treatments will be formed.[24] The nodes of the network plot will show the pharmacologic treatments being compared and the edges will show the available direct comparisons between the treatments. Nodes and edges will be

weighted according to the number of patients and RCTs, respectively.

The network meta-analyses will be designed using a random-effect model.[24] The 95% predictive intervals will accompany the 95% CIs in the plot diagrams to facilitate the interpretation of the results in the light of the magnitude of heterogeneity.

Sensitivity analyses will be conducted to assess the impact of studies' methodological quality in the results and to compare the risk estimates under both random-effect and fixed-effect models. Further, subgroup analysis will be performed where the risk estimates will be disaggregated according to the background antirheumatic drugs used in the RCTs.

The inconsistency test will be conducted in order to assess the extent of disagreement between the direct and indirect evidence. Two levels of inconsistency will be evaluated. The first approach will test for the overall inconsistency, via Wald test.[24] In the second approach, each closed loop in the network will be examined (nodesplitting) in order to assess the local inconsistency between the risk estimates from direct and indirect evidence.[24]

A comparison-adjusted funnel plot will be used to test small-study effect and publication bias.[25]

For each outcome, treatments will be ranked according to the probability of being the safest (best) alternative using the surface under the cumulative ranking curve (SUCRA), expressed as a percentage.[26] A higher SUCRA value is regarded as a better result for an individual intervention. When ranking the treatments, the closer the SUCRA value is to 100%, the higher the treatment ranking is. A SUCRA value of 0% suggests the treatment is certainly the worst.[26] The league tables arrange the presentation of the summary estimates by ranking the treatments in the order of the most pronounced impact on the outcome under consideration, according to the SUCRA value.[27] All the statistics will be performed using STATA V.13.1. (StataCorp LP, College Station, Texas, USA).

Ethics and dissemination

The data that support the findings of this study are openly available in Medline, Embase, Cochrane Library and ClinicalTrials.gov. This systematic review will be disseminated through a peer-reviewed publication and at conference meetings.

DISCUSSION

This paper reports protocols of two systematic reviews with network meta-analyses that will be carried out to clarify if the use of JAK inhibitors increases the risk of cardiovascular adverse events or serious infections in patients with RA.

Such patients must be managed with regard to the cardiovascular risk in clinical practice.[2 28] Treatment with DMARDs, namely methotrexate and tumour necrosis factor (TNF) inhibitors, has been associated with a reduced risk of cardiovascular events.[29] Therefore, it is important to continuously assess the effect of antirheumatic therapies on cardiovascular outcomes. The incidence of thromboembolic events in patients treated with JAK inhibitors during clinical trials led regulatory authorities to recommend special precautions, particularly in those who have risk factors, such as previous medical history, hypertension, diabetes, older age, obesity or immobilisation due to surgery.[30–32] Moreover, the lipid profile should be monitored during the early weeks after initiating treatment with JAK inhibitors due to the risk of hypercholesterolemia.[30–32] Nonetheless, the cardiovascular risk associated with JAK inhibitors is still under assessment, as further information is accruing. Despite previous meta-analyses have evaluated the cardiovascular safety of different JAK inhibitors,[6 33] none has yet established adjusted indirect comparisons regarding the risk of MACE and thromboembolic events among the drugs in this class. To our knowledge, this will be the first network meta-analysis comparing the risk of MACE and thromboembolic events among drugs of this new class.

JAK inhibitors have also been associated with an increased risk of serious infections compared with other therapeutic options.[7] These findings should be analysed in the light that patients with RA are themselves at a higher risk for infections than the general population.[11] The risk of serious infections seems to be a class effect.[7 15] However, each JAK inhibitor is expected to selectively with JAK family proteins within the cell. This may lead to differences in their safety profiles, since each JAK member plays a given role in the immune response.[15] Therefore, it is important to better characterise the safety profile of JAK inhibitors, particularly with regard to the risk of infections.

Several risk minimisation measures and clinical studies, including postauthorisation safety studies, are currently ongoing as part of the pharmacovigilance activities planned for JAK inhibitors.[14 34 35] The ongoing study A3921133 is aimed at evaluating the cardiovascular safety of tofacitinib 5 mg two times per day and tofacitinib 10 mg two times per day, compared with a TNF inhibitor therapy, in patients with RA who are ≥50 years of age and with at least one cardiovascular risk factor.[36] Beyond the increased risk for thromboembolic events, the interim results showed an increased rate of non-fatal serious infections among patients taking tofacitinib, especially in those older than 65 years.[36] Based on these findings, tofacitinib's holder company sent a letter to healthcare professionals with new usage recommendations and EMA and FDA issued safety alerts.[8 36 37]

The following limitations are expected. First, not only the efficacy but also some adverse effects from JAK inhibitors seem to be dose dependent.[38 39] The cardiovascular risks may be affected by a dose-related trend as well, eventually requiring additional sensitivity analyses. Further, since the immune system response is mediated by the JAK–STAT pathway, a dose-dependent risk of infections may affect the results of this meta-analysis and subgroup

analyses may be required. Second, the short duration and relatively reduced sample size of RCTs may not allow to capture events of rare nature, such as cardiovascular events or opportunistic serious infections and limiting the number and type of analyses that can be conducted. Lastly, the risk of cardiovascular events and serious infections associated with the background antirheumatic drugs used in the RCTs may be different and can eventually increase the confounding among the results. Therefore, the disaggregation of the risk estimates according to the background antirheumatic therapy will be performed. Though the results of this network meta-analysis are expected to provide further clarification about the cardiovascular and infections risks of the different JAK inhibitors.

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Contributors CA designed the study, drafted the paper and approved the final version to be published. AP wrote and reviewed the draft paper. DM and FB-M reviewed and approved the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable (NA)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3/4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-9

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5-9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.