Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review

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Keywords:	Protocol, scoping review, JAK/STAT pathway, immune-mediated inflammatory skin diseases, PRISMA

Protocol

BMJ Open

Title: Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review

Short title: Scoping review of JAK/STAT blockade in dermatology

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ABSTRACT

Introduction. The JAK/STAT pathway is known to be involved in inflammatory and neoplastic skin diseases, like psoriasis, atopic dermatitis, alopecia areata, vitiligo, and melanoma. Improved knowledge of the components of this pathway has allowed the development of drugs, which act by inhibiting the pathway, blocking specific components. This offers new therapeutic opportunities. Although evidence on the use of JAK/STAT blockades in dermatological diseases is growing, none have been approved for use in treating skin diseases. The aim of this study is to develop an *a priori* protocol to broadly review the available evidence on the use of drugs targeting the JAK/STAT pathway in the treatment of dermatological diseases.

Methods and analysis. For the conduction of the scoping review protocol, we will employ an established scoping review methodology described in the Joanna Briggs Institute manual. This methodology outlines a 5-stage approach: 1) identify the research question; 2) identify relevant studies; 3) select studies; 4) chart the data; and 5) collate, summarize, and report the results, with an optional consultation exercise. Finally, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) to present the results.

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Keywords: Protocol; scoping review; JAK/STAT pathway; immune-mediated inflammatory skin diseases; PRISMA.

Article summary

Strengths and limitations of this study

- Strengths of this study include the importance of unrevealing uncertainty about evidence of using drugs targeting JAK/STAT pathway when prescribed as *off-label* for dermatological diseases in the clinical setting.

- We will use an established scoping review methodology, a systematic search developed by two health sciences librarians, and systematic screening and data abstraction carried out in duplicate.

- A limitation of this review is the potential to miss relevant articles, especially in the grey literature. To mitigate this, we will screen meeting abstracts to identify any missed articles describing case reports not published in journals and scaning reference lists of included articles and similar reviews.

INTRODUCTION

Improving knowledge of the molecular biology of the cell, and its adaptation to the disease pathogenesis, have allowed the design of new drugs directed against key targets in signaling pathway regulation. In this sense, the Janus kinases (JAKs) and Signal Transducer and Activator of Transcription (STATs) proteins (JAK/STAT) pathway is one of a handful of pleiotropic routes used to transduce multiple extracellular signals involved in cell proliferation, differentiation, migration, and apoptosis.[1] Alterations in the regulation of this process have been associated with pathological events fundamentally related to immunomodulatory and neoplastic (mainly hematological) disorders. In addition, they have been related to the pathophysiology of several dermatological diseases. Therefore, drugs that act on the JAK/STAT pathway represent an opportunity for the treatment of these disorders.[2]

The JAK family is comprised by four types of cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3, and Tyk2.[3] STAT, of which there are seven different subtypes (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT 5b, and STAT6), is the other fundamental component of the cascade[4]. After being phosphorylated by JAK, STAT translocates to the nucleus to induce the transcription of specific genes. Different types of ligands, from cytokines, such as interleukins (IL), to hormones, such as erythropoietin, activate this pathway to produce changes in the cell, and eventually in tissue physiology. Some of these molecules have been shown to be important, directly or indirectly, in the development of dermatological diseases. Examples of these are IL-2 and its family, IL-23, interferon alpha,[5] and IL-17.[6] The overall pathway has shown its implication in

the pathophysiology of diseases such as psoriasis, atopic dermatitis, lupus erythematous, melanoma, or pyoderma gangrenosum.[7]

This knowledge has led to the development of drugs that act on the JAK component of the pathway, by selectively inhibiting one (filgotinib, JAK1; pacritinib, JAK2; decernotinib, JAK3) or more than one (tofacitinib, JAK1 y JAK3; ruxolitinib, baricitinib, JAK1 and JAK2) JAK protein.[8] Ruxolitinib and tofacinib were the first drugs of this class to be approved by the FDA – in 2011 for myelofibrosis and in 2012 for rheumatoid arthritis, respectively.[9,10]

So far, no JAK/STAT inhibitors have been approved a license for the treatment of dermatological diseases. However, evidence exists resulting from the off-label use of these drugs, specifically tofacitinib and ruxolitinib, in different skin diseases. Knowing the efficacy and safety profile of each drug used in different dermatological diseases is essential to establish their risk-benefit balance.

Improving knowledge requires ordering evidence, establishing gaps in the evidence, and formulating questions that can be answered using systematic synthesis and analysis techniques. The aim of this is to develop guidelines that give support to physicians in making effective decisions in clinical practice. For this purpose, secondary scientific studies can develop methodologies that adapt to the specific needs of the formulated problem. The application of JAK inhibitors for the treatment of dermatological disorders is still in its early stages, and we consider it necessary to broadly review the knowledge available to date. Otherwise, the conduction of studies aimed at answering specific questions can lead to synthesis efforts that cannot be quantified.[11]

A scope review is a form of scientific synthesis that addresses an exploratory research question, with the aim of mapping key concepts and gaps in research related to a defined area or field.[12] The aim of this protocol was to define the methodology that will be used to broadly synthesize the available evidence on the use of inhibitors of the JAK/STAT pathway in dermatological diseases.

METHODS

Protocol design

The aim of the study is to broadly address the published evidence on drugs targeting JAK proteins in the treatment dermatological diseases, for three purposes: a) to structure the existing knowledge in this field; b) to establish areas where there may be gaps in the evidence; c) to formulate new questions that can be answered following the methodology of systematic reviews. With this intention, we used the methodology recently described to conduct scoping reviews.[13] This methodology outlines a 5-stage approach (**Table 1**): 1) identify the research question; 2) identify relevant studies; 3) select studies; 4) chart the data; and 5) collate, summarize, and report the results, with an optional consultation exercise. Finally, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) to present the results.[14]

Inclusion criteria

We will use PCC (participants, concept, context) mnemotechnic rule to define the inclusion criteria as follows:

Participants

All studies that include evidence on the use of JAK protein inhibitors in humans will be included. No restrictions regarding age, ethnicity, study design, or any other characteristics will be made.

Concept

We will review the existing literature on drugs targeting JAK~~s~~ proteins in the treatment of dermatological diseases: indications, epidemiology, genetics, efficacy and safety.

Context

We will not limit the context to a particular setting or country.

Research question

What are the indications, epidemiology, genetics, efficacy, and safety of drugs targeting proteins of STAT/JAK pathway for the treatment of dermatological diseases?

Identifying relevant literature

We will perform a three-step literature search. The first step will include an initial limited search of the MEDLINE and EMBASE databases. Then, we will carry out analyses of: the text contained in the titles, abstracts of retrieved papers, and the index terms used to describe the articles. In second step, we will search the same databases using the identified key words and index terms. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. We will contact authors of primary studies or reviews for further information, if relevant. We will include all studies published in English until October 2018. The process will be carried out by at least two researchers.

Identifying relevant studies~~.~~

We will apply the inclusion criteria, described previously, for the selection of studies. The process will be carried out by at least two researchers.

Charting the data.

We will develop a draft charting to record the information that will be relevant to the review.

Questions focusing on:

1) Mapping studies: Author(s), Year of publication, origin/country of origin (where the study was published or conducted), authors filiation, type of study, a priori design, registration, conflict of interest, funding;

2) Epidemiological and genetics aspects: Study population and sample size, genetic studies;

3) *Evaluation of the efficacy and safety of drugs for each disease*: Intervention type, comparator and details of these, duration of the intervention, dosage, outcomes and details of these and adverse events.

The data collection will be done by at least two reviewers.

5. Collating, summarizing and reporting results

The elements of the PCC inclusion criteria will guide the presentation of the data. Firstly, we will present the results of the search in the PRISMA flow chart. Secondly, we will organize the extracted data for topics defined as follows: indications, mechanism of action, efficacy safety and cost. For each category, a clear explanation was provided. The results of the scoping review will be presented as a map, in both diagrammatic and tabular form, and in a descriptive

format. A narrative summary will accompany the tabulated and/or charted results and will describe how the results relate to the review objective and question(s).

6. Differences between the protocol and the overview

Changes in the methodology that need to be carried out throughout the study will be detailed in the results section.

Compliance with Ethics Guidelines

This protocol relates to a search for previously conducted studies, and does not involve any new human or animal studies performed by the authors.

Patient and Public Involvement

Patients and or public were not involved in the development of this protocol.

CONCLUSION

Here, we have presented a protocol for systematically conducting a scoping review to broadly analyze the available evidence on the indications for and the mechanisms of action, efficacy, and safety of JAK/STAT pathway-targeting drugs in the use of dermatological therapy. Evidence-based medicine is intended to optimize decision-making by emphasizing the use of evidence derived from well-designed and well-conducted research. Currently, most reviews of treatments blocking the JAK/STAT pathway are narrative reviews, which lack the necessary methodological detail to promote reproducibility and reduce the risk of bias.[15,16] Secondary research methodologies are constantly being developed and must be adapted to the type of research question being asked and the urgency with which the question must be answered.[17]

We believe that the scoping review methodology is the one of the best suited protocols to answer the question posed in this study. The results will provide unique insights into the available evidence on the use of JAK/STAT pathway-targeting drugs in the treatment of dermatological diseases, facilitating the detection of knowledge gaps and the identification of new questions to address via additional systematic reviews.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity ofthe work as a whole, and have given theirapproval for this version to be published. The authors are also grateful to the reviewers fortheir helpful comments and suggestions. We would also like to thank Editage (www.editage.com) for performing English-language editing of this review.

Competing interests. None declared.

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Compliance with Ethics Guidelines. This protocol relates to a search for previously con-ducted studies, and does not involve any new human or animal subjects performed by the authors.

Data sharing statement. All the original data are presented in the text and tables of the protocol.

Contributors. FGG and JR conceived the study. FGG, PJGA, JH, AMM, JGM, MAL, IVP, AVGN, BIT, and JR contributed to the protocol design and plan. FGG, PJGA, and

JH developed the literature search. All the authors worked collaboratively to draft and revise the manuscript, and read and approved the final version. All the authors made substantive intellectual contributions to the development of this protocol.

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TABLES

Table 1.-Stages of the scoping reviews.

1. Research Question Identified	1.1. Overarching goal	To explore the depth and breadth of evidence for the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of patients with dermatological diseases
	1.2. Research question	What are the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of dermatological diseases?
	1.3. Purposes of this scoping review	1.3.1. Review the evidence of indications for drugs that act on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.2. Review the evidence of epidemiology of drugs acting on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.3. Review the evidence of genetics of drugs acting on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.4. Review the evidence on efficacy of the drugs that act on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.5. Review the evidence on safety of drugs that act on JAK/STAT pathway in the treatment of dermatogical diseases

		1.3.6. Obtain concrete research questions that can be answered through a systematic review
		1.3.7. Identify research gaps in the existing literature
2. Identifying relevant literature	2.1. We will perform a three steps-search	2.1.1. First search: an initial limited search of the MEDLINEand EMBASE databases to find keywords in the title, abstract, and the index terms used to describe the articles
		2.1.2. Second search: a search of MEDLINE and EMBASEusing all identified keywords
		2.1.3. Third search: the reference lists of all identified reports and articles are searched for additional studies
	2.2. We will include the studies published in full text in English until October 2018	
	2.3. We will contact authors, of primary studies or reviews, for further information, if this is relevant	
	2.4.The search and selection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
3. Selecting studies	3.1. Inclusion criteria	3.1.1. We will include in the review the studies on the human use of drugs inhibitors of JAK/STAT pathway published on the topics: indications, epidemiology, genetics, efficacy, and safety.

		3.1.2. Design of the studies: we will include guidelines, systematic reviews, randomized clinical trials, observational studies, cross sectional case report and series
	3.2. Exclusion criteria	3.2.1. We will exclude narrative reviews and studies performed *in vitro* or using animal models
4. Charting the data	4.1. We will extract the data in a predefined form.	
	4.2. From each study we will extract title, objective, main variables related to patients, intervention, comparator, outcomes (efficacy and safety) and bibliographic data	
	4.3. We will classify the studies by treatment indication	
	4.4. The list of studies, variables and data of there view will be published in an online-file	
	4.5. The data collection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
5. Collating, summarizing and reporting results	5.1. The results of comprehensive search will be presented using the PRISMA flow diagram	
	5.2. We will synthesize qualitatively the evidence obtained ordering it by topics: indications, mechanism of action, efficacy and safety of drugs that act on	

	JAK/STAT pathway to treat dermatological diseases and we will present it in a diagrammatic tabular form and in a descriptive format	
	5.3. We will use the extension of PRISMA for scoping review for the notification of the review	
6. Differences between the protocol and the overview	Any changes in the methodology that need to be carried out through out the study will be detailed together with the results publication.	

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the pathophysiology of diseases such as psoriasis, atopic dermatitis, lupus erythematous, melanoma, or pyoderma gangrenosum.[7]

This knowledge has led to the development of drugs that act on the JAK component of the pathway, by selectively inhibiting one (filgotinib, JAK1; pacritinib, JAK2; decernotinib, JAK3) or more than one (tofacitinib, JAK1 and JAK3; ruxolitinib, baricitinib, JAK1 and JAK2) JAK protein.[8] Ruxolitinib and tofacinib were the first drugs of this class to be approved by the FDA – in 2011 for myelofibrosis and in 2012 for rheumatoid arthritis, respectively.[9,10]

So far, no JAK/STAT inhibitors have been approved a license for the treatment of dermatological diseases. However, evidence exists resulting from the off-label use of these drugs, specifically tofacitinib and ruxolitinib, in different skin diseases. Knowing the efficacy and safety profile of each drug used in different dermatological diseases is essential to establish their risk-benefit balance.

Improving knowledge requires ordering evidence, establishing gaps in the evidence, and formulating questions that can be answered using systematic synthesis and analysis techniques. The aim of this is to develop guidelines that give support to physicians in making effective decisions in clinical practice. For this purpose, secondary scientific studies can develop methodologies that adapt to the specific needs of the formulated problem. The application of JAK inhibitors for the treatment of dermatological disorders is still in its early stages, and we consider it necessary to broadly review the knowledge available to date. Otherwise, the conduction of studies aimed at answering specific questions can lead to synthesis efforts that cannot be quantified.[11]

A scope review is a form of scientific synthesis that addresses an exploratory research question, with the aim of mapping key concepts and gaps in research related to a defined area or field.[12] The aim of this protocol is to define the methodology that will be used to broadly synthesize the available evidence on the use of inhibitors of the JAK/STAT pathway in dermatological diseases.

METHODS

Protocol design

The aim of the study is to broadly address the published evidence on drugs targeting JAK proteins in the treatment dermatological diseases, for three purposes: a) to structure the existing knowledge in this field; b) to establish areas where there may be gaps in the evidence; c) to formulate new questions that can be answered following the methodology of systematic reviews. With this intention, we will use the methodology recently described to conduct scoping reviews.[13] This methodology outlines a 5-stage approach (**Table 1**): 1) identify the research question; 2) identify relevant studies; 3) select studies; 4) chart the data; and 5) collate, summarize, and report the results, with an optional consultation exercise. Finally, we will use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) to present the results.[14] This protocol is reported following the recommendations of the PRISMA for protocols (PRISMA-P) statement. A checklist for this review protocol has been provided in a Supplementary file.

Inclusion criteria

We will use PCC (participants, concept, context) mnemotechnic rule to define the inclusion criteria as follows:

Participants

All studies that include evidence on the use of JAK protein inhibitors in humans will be included. No restrictions regarding age, ethnicity, study design, or any other characteristics will be made.

Concept

We will review the existing literature on drugs targeting JAK proteins in the treatment of dermatological diseases: indications, epidemiology, genetics, efficacy, and safety.

Context

We will not limit the context to a particular setting or country.

Research question

What are the indications, epidemiology, genetics, efficacy, and safety of drugs targeting proteins of STAT/JAK pathway for the treatment of dermatological diseases?

Identifying relevant literature

A systematic search developed by two health sciences librarians will perform using a three-step literature search. The first step will include an initial limited search of the MEDLINE and EMBASE databases (**Table 2**). Then, we will carry out analyses of: the text contained in the titles, abstracts of retrieved papers, and the index terms used to describe the articles. In second step, we will search the same databases using the identified key words and index terms.

Additionally, CINAHL, Scopus, and Web of Science to the search engines will be searched in this second step. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. We will contact authors of primary studies or reviews for further information, if relevant. We have established a time frame of four weeks after send authors a mail requesting information about their study or publicaction. We will include all studies published in English until October 2018. The process of searching, extracting key words, and filtering and excluding studies, will be carried out independently and by duplicate by at least two researchers and in case of disagreement will be decided by agreement with a third reviewer.

Identifying relevant studies

We will apply the inclusion criteria, described previously, for the selection of studies. The process will be carried out by at least two researchers and in case of disagreement will be decided by agreement with a third reviewer.

Charting the data.

We will develop a draft charting to record the information that will be relevant to the review.

Questions focusing on:

1) Mapping studies: Author(s), Year of publication, origin/country of origin (where the study was published or conducted), authors filiation, type of study, a priori design, registration, conflict of interest, funding;

2) Epidemiological and genetics aspects: Study population and sample size, genetic studies;

3) *Evaluation of the efficacy and safety of drugs for each disease*: Intervention type, comparator and details of these, duration of the intervention, dosage, outcomes and details of these and adverse events.

The data collection will be done by at least two reviewers using a piloting customized Google AppSheet form (https://www.appsheet.com/) and in case of disagreement will be decided by agreement with a third reviewer. We anticipate that we can start retrieving data in April 2019 and finalizing by September 2019.

5. Collating, summarizing and reporting results

The elements of the PCC inclusion criteria will guide the presentation of the data. Firstly, we will present the results of the search in the PRISMA flow chart. Secondly, we will organize the extracted data for topics defined as follows: indications, mechanism of action, efficacy safety and cost. For each category, a clear explanation will be provided. The results of the scoping review will be presented as a map, in both diagrammatic and tabular form, and in a descriptive format. A narrative summary will accompany the tabulated and/or charted results and will describe how the results relate to the review objective and question(s).

6. Differences between the protocol and the overview

Changes in the methodology that need to be carried out throughout the study will be detailed in the results section.

Compliance with Ethics Guidelines

This protocol relates to a search for previously conducted studies, and does not involve any new human or animal studies performed by the authors.

Patient and Public Involvement

Patients and or public were not involved in the development of this protocol.

CONCLUSION

Here, we have presented a protocol for systematically conducting a scoping review to broadly analyze the available evidence on the indications for and the mechanisms of action, efficacy, and safety of JAK/STAT pathway-targeting drugs in the use of dermatological therapy. Evidence-based medicine is intended to optimize decision-making by emphasizing the use of evidence derived from well-designed and well-conducted research. Currently, most reviews of treatments blocking the JAK/STAT pathway are narrative reviews, which lack the necessary methodological detail to promote reproducibility and reduce the risk of bias.[15,16] Secondary research methodologies are constantly being developed and must be adapted to the type of research question being asked and the urgency with which the question must be answered.[17]

Although we will try to analyse the quality of evidence per variable and disease using GRADE approach, probably most of the studies have produced documents communicating partial results following an observational design, which is associated with low or very low quality of evidence. However, we believe that the scoping review methodology is the one of the best suited protocols to answer the question posed in this study. The results will provide unique insights into the available evidence on the use of JAK/STAT pathway-targeting drugs in the treatment of dermatological diseases, facilitating the detection of knowledge gaps and the identification of new questions to address via additional systematic reviews.

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Provenance and peer review. Not commissioned; externally peer reviewed.

Compliance with Ethics Guidelines. This protocol relates to a search for previously conducted studies, and does not involve any new human or animal subjects performed by the authors.

Data sharing statement. All the original data are presented in the text and tables of the protocol.

Contributors. FGG and JR conceived the study. FGG, PJGA, JH, AMM, JGM, MAL, IVG, AVGN, BIT, and JR contributed to the protocol design and plan. FGG, PJGA, and

JH developed the literature search strategy. All the authors worked collaboratively to draft and revise the manuscript, and read and approved the final version. All the authors made substantive intellectual contributions to the development of this protocol. JR is the guarantor of the review.

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TABLES

Table 1. Stages of the scoping reviews.

1. Research Question Identified	1.1. Overarching goal	To explore the depth and breadth of evidence for the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of patients with dermatological diseases
	1.2. Research question	What are the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of dermatological diseases?
	1.3. Purposes of this scoping review	1.3.1. Review the evidence of indications for drugs that act on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.2. Review the evidence of epidemiology of drugs acting on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.3. Review the evidence of genetics of drugs acting on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.4. Review the evidence on efficacy of the drugs that act on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.5. Review the evidence on safety of drugs that act on JAK/STAT pathway in the treatment of dermatogical diseases

		1.3.6. Obtain concrete research questions that can be answered through a systematic review
		1.3.7. Identify research gaps in the existing literature
2. Identifying relevant literature	2.1. We will perform a three steps-search	2.1.1. First search: an initial limited search of the MEDLINE and EMBASE databases to find keywords in the title, abstract, and the index terms used to describe the articles
		2.1.2. Second search: search of MEDLINE and EMBASE using all identified keywords. A*dditionally, CINAHL, Scopus, and Web of Science to the search engines will be searched in this second step.*
		2.1.3. Third search: the reference lists of all identified reports and articles will be searched for additional studies
	2.2. We will include the studies published in full text in English until October 2018	
	2.3. We will contact authors, of primary studies or reviews, for further information, if this is relevant	
	2.4.The search and selection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
3. Selecting studies	3.1. Inclusion criteria	3.1.1. We will include in the review the studies on the human use of drugs inhibitors of JAK/STAT pathway published on the topics: indications, epidemiology, genetics, efficacy, and safety.

		3.1.2. Design of the studies: we will include guidelines, systematic reviews, randomized clinical trials, observational studies, cross sectional case report and series
	3.2. Exclusion criteria	3.2.1. We will exclude narrative reviews and studies performed *in vitro* or using animal models
4. Charting the data	4.1. We will extract the data in a predefined form.	
	4.2. From each study we will extract title, objective, main variables related to patients, intervention, comparator, outcomes (efficacy and safety) and bibliographic data	
	4.3. We will classify the studies by treatment indication	
	4.4. The list of studies, variables and data of there view will be published in an online-file	
	4.5. The data collection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
5. Collating, summarizing and reporting results	5.1. The results of comprehensive search will be presented using the PRISMA flow diagram	
	5.2. We will synthesize qualitatively the evidence obtained ordering it by topics: indications, mechanism of action, efficacy and safety of drugs that act on	

	JAK/STAT pathway to treat dermatological diseases and we will present it in a diagrammatic tabular form and in a descriptive format	
	5.3. We will use the extension of PRISMA for scoping review for the notification of the review	
6. Differences between the protocol and the overview	Any changes in the methodology that need to be carried out through out the study will be detailed together with the results publication.	

Table 2. Draft of first step of search strategy to be used for at least two electronic databases.

MEDLINE (Ovid), Embase (Ovid)

search	
#1	(('tofacitinib' OR 'baricitinib' OR 'ruxolitinib' OR 'oclacitinib' OR 'upadacitinib' OR 'delgocitinib' OR 'itacitinib' OR 'momelotinib' OR peficitinib OR 'decernotinib' OR 'fedratinib' OR 'pacritinib' OR 'filgotinib' OR 'gandotinib' OR 'solcitinib' OR 'lestaurtinib' OR 'janus kinase inhibitor')
#2	(('psoriasis'/exp OR psoriasis) OR 'atopic dermatitis' OR 'alopecia' OR 'contact dermatitis' OR 'vitiligo' OR 'graft versus host reaction' OR 'lichen planus' OR 'pyoderma gangrenosum' OR 'pruritus' OR (eosinofilic AND annulare AND erythema) OR 'male pattern alopecia' OR 'proteasome associated autoinflammatory syndrome' OR 'sting associated vasculopathy with onset in infancy' OR 'chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome' OR 'hand dermatitis' OR 'discoid lupus erythematosus' OR 'mucocutaneous candidiasis' OR (urticaria AND chronic) OR 'suppurative hidradenitis' OR 'melanoma' OR 'non melanoma skin cancer' OR 'cancer' OR 'lichen sclerosus et atrophicus' OR 'pityriasis rubra pilaris' OR 'pemphigus' OR 'skin disease' OR 'rosaceae' OR 'scleroderma' OR 'cinca syndrome' OR 'hyperhidrosis' OR 'erythropoietic protoporphyria' OR 'anca associated vasculitis' OR 'seborrheic dermatitis' OR 'herpes simplex' OR 'sjoegren syndrome'))
#3	#1 AND #2

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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 No.#)
ADMINISTRATIVE INFORMATION			
Title:		**Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review**	
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	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	13,14
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
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	4-5
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	9-11
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	Table 2

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
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)	10
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	10
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	10-11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
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	NA
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA/11/NA/11
	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)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** 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.

BMJ Open

Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review

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Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Immunology (including allergy), Pharmacology and therapeutics
Keywords:	Protocol, scoping review, JAK/STAT pathway, immune-mediated inflammatory skin diseases, PRISMA

Protocol

BMJ Open

Title: Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review

Short title: Scoping review of JAK/STAT blockade in dermatology

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World count: 1,450; **Tables**: 2; **Figures**: 0.

ABSTRACT

Introduction. The JAK/STAT pathway is known to be involved in inflammatory and neoplastic skin diseases, like psoriasis, atopic dermatitis, alopecia areata, vitiligo, and melanoma. Improved knowledge of the components of this pathway has allowed the development of drugs, which act by inhibiting the pathway, blocking specific components. This offers new therapeutic opportunities. Although evidence on the use of JAK/STAT blockades in dermatological diseases is growing, none have been approved for use in treating skin diseases. The aim of this study is to develop an *a priori* protocol to broadly review the available evidence on the use of drugs targeting the JAK/STAT pathway in the treatment of dermatological diseases.

Methods and analysis. For the conduction of the scoping review protocol, we will employ an established scoping review methodology described in the Joanna Briggs Institute manual. This methodology outlines a 5-stage approach: 1) identify the research question; 2) identify relevant studies; 3) select studies; 4) chart the data; and 5) collate, summarize, and report the results, with an optional consultation exercise. Finally, we will use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) to present the results.

Ethics and dissemination. Since this is a review of the literature, ethics approval is not indicated. We will disseminate the findings from this study in publications in peer-reviewed journals as well as presentations at relevant national and international conferences.

Keywords: Protocol; scoping review; JAK/STAT pathway; immune-mediated inflammatory skin diseases; PRISMA.

Article summary

Strengths and limitations of this study

- Strengths of this study include the importance of unrevealing uncertainty about evidence of using drugs targeting JAK/STAT pathway when prescribed as *off-label* for dermatological diseases in the clinical setting.

- We will use an established scoping review methodology, a systematic search developed by two health sciences librarians, and systematic screening and data abstraction carried out in duplicate.

- A limitation of this review is the potential to miss relevant articles, especially in the grey literature. To mitigate this, we will screen meeting abstracts to identify any missed articles describing case reports not published in journals and scan reference lists of included articles and similar reviews.

INTRODUCTION

Improving knowledge of the molecular biology of the cell, and its adaptation to the disease pathogenesis, have allowed the design of new drugs directed against key targets in signaling pathway regulation. In this sense, the Janus kinases (JAKs) and Signal Transducer and Activator of Transcription (STATs) proteins (JAK/STAT) pathway is one of a handful of pleiotropic routes used to transduce multiple extracellular signals involved in cell proliferation, differentiation, migration, and apoptosis.[1] Alterations in the regulation of this process have been associated with pathological events fundamentally related to immunomodulatory and neoplastic (mainly hematological) disorders. In addition, they have been related to the pathophysiology of several dermatological diseases. Therefore, drugs that act on the JAK/STAT pathway represent an opportunity for the treatment of these disorders.[2]

The JAK family is comprised by four types of cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3, and Tyk2.[3] STAT, of which there are seven different subtypes (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT 5b, and STAT6), is the other fundamental component of the cascade[4]. After being phosphorylated by JAK, STAT translocates to the nucleus to induce the transcription of specific genes. Different types of ligands, from cytokines, such as interleukins (IL), to hormones, such as erythropoietin, activate this pathway to produce changes in the cell, and eventually in tissue physiology. Some of these molecules have been shown to be important, directly or indirectly, in the development of dermatological diseases. Examples of these are IL-2 and its family, IL-23, interferon alpha,[5] and IL-17.[6] The overall pathway has shown its implication in

the pathophysiology of diseases such as psoriasis, atopic dermatitis, lupus erythematous, melanoma, or pyoderma gangrenosum.[7]

This knowledge has led to the development of drugs that act on the JAK component of the pathway, by selectively inhibiting one (filgotinib, JAK1; pacritinib, JAK2; decernotinib, JAK3) or more than one (tofacitinib, JAK1 and JAK3; ruxolitinib, baricitinib, JAK1 and JAK2) JAK protein.[8] Ruxolitinib and tofacinib were the first drugs of this class to be approved by the FDA – in 2011 for myelofibrosis and in 2012 for rheumatoid arthritis, respectively.[9,10]

So far, no JAK/STAT inhibitors have been approved a license for the treatment of dermatological diseases. However, evidence exists resulting from the off-label use of these drugs, specifically tofacitinib and ruxolitinib, in different skin diseases. Knowing the efficacy and safety profile of each drug used in different dermatological diseases is essential to establish their risk-benefit balance.

Improving knowledge requires ordering evidence, establishing gaps in the evidence, and formulating questions that can be answered using systematic synthesis and analysis techniques. The aim of this is to develop guidelines that give support to physicians in making effective decisions in clinical practice. For this purpose, secondary scientific studies can develop methodologies that adapt to the specific needs of the formulated problem. The application of JAK inhibitors for the treatment of dermatological disorders is still in its early stages, and we consider it necessary to broadly review the knowledge available to date. Otherwise, the conduction of studies aimed at answering specific questions can lead to synthesis efforts that cannot be quantified.[11]

A scope review is a form of scientific synthesis that addresses an exploratory research question, with the aim of mapping key concepts and gaps in research related to a defined area or field.[12] The aim of this protocol is to define the methodology that will be used to broadly synthesize the available evidence on the use of inhibitors of the JAK/STAT pathway in dermatological diseases.

METHODS

Protocol design

The aim of the study is to broadly address the published evidence on drugs targeting JAK proteins in the treatment dermatological diseases, for three purposes: a) to structure the existing knowledge in this field; b) to establish areas where there may be gaps in the evidence; c) to formulate new questions that can be answered following the methodology of systematic reviews. With this intention, we will use the methodology recently described to conduct scoping reviews.[13] This methodology outlines a 5-stage approach (**Table 1**): 1) identify the research question; 2) identify relevant studies; 3) select studies; 4) chart the data; and 5) collate, summarize, and report the results, with an optional consultation exercise. Finally, we will use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) to present the results.[14] This protocol is reported following the recommendations of the PRISMA for protocols (PRISMA-P) statement. A checklist for this review protocol has been provided in a Supplementary file.

Inclusion criteria

We will use PCC (participants, concept, context) mnemotechnic rule to define the inclusion criteria as follows:

Participants

All studies that include evidence on the use of JAK protein inhibitors in humans will be included. No restrictions regarding age, ethnicity, study design, or any other characteristics will be made.

Concept

We will review the existing literature on drugs targeting JAK proteins in the treatment of dermatological diseases: indications, epidemiology, genetics, efficacy, and safety.

Context

We will not limit the context to a particular setting or country.

Research question

What are the indications, epidemiology, genetics, efficacy, and safety of drugs targeting proteins of STAT/JAK pathway for the treatment of dermatological diseases?

Identifying relevant literature

A systematic search developed by two health sciences librarians will perform using a three-step literature search. The first step will include an initial limited search of the MEDLINE and EMBASE databases (**Table 2**). Then, we will carry out analyses of: the text contained in the titles, abstracts of retrieved papers, and the index terms used to describe the articles. In second step, we will search the same databases using the identified key words and index terms.

Additionally, CINAHL, Scopus, and Web of Science to the search engines will be searched in this second step. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. We will contact authors of primary studies or reviews for further information, if relevant. We have established a time frame of four weeks after send authors a mail requesting information about their study or publicaction. We will include all studies published in English until October 2018. The process of searching, extracting key words, and filtering and excluding studies, will be carried out independently and by duplicate by at least two researchers and in case of disagreement will be decided by agreement with a third reviewer.

Identifying relevant studies

We will apply the inclusion criteria, described previously, for the selection of studies. The process will be carried out by at least two researchers and in case of disagreement will be decided by agreement with a third reviewer.

Charting the data.

We will develop a draft charting to record the information that will be relevant to the review.

Questions focusing on:

1) Mapping studies: Author(s), Year of publication, origin/country of origin (where the study was published or conducted), authors filiation, type of study, a priori design, registration, conflict of interest, funding;

2) Epidemiological and genetics aspects: Study population and sample size, genetic studies;

3) *Evaluation of the efficacy and safety of drugs for each disease*: Intervention type, comparator and details of these, duration of the intervention, dosage, outcomes and details of these and adverse events.

The data collection will be done by at least two reviewers using a piloting customized Google AppSheet form (https://www.appsheet.com/) and in case of disagreement will be decided by agreement with a third reviewer. We anticipate that we can start retrieving data in April 2019 and finalizing by September 2019.

5. Collating, summarizing and reporting results

The elements of the PCC inclusion criteria will guide the presentation of the data. Firstly, we will present the results of the search in the PRISMA flow chart. Secondly, we will organize the extracted data for topics defined as follows: indications, mechanism of action, efficacy safety and cost. For each category, a clear explanation will be provided. The results of the scoping review will be presented as a map, in both diagrammatic and tabular form, and in a descriptive format. A narrative summary will accompany the tabulated and/or charted results and will describe how the results relate to the review objective and question(s).

6. Differences between the protocol and the overview

Changes in the methodology that need to be carried out throughout the study will be detailed in the results section.

Ethics and dissemination

This study will analyse only anonymised public data of previously conducted studies, and will not involve any new human or animal studies performed by the authors. We will prepare the publication in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline and its adaptation for scoping reviews. We will publish our findings in peer-reviewed journals and also may present them at conferences.

Patient and Public Involvement

Patients and or public were not involved in the development of this protocol. The study group developed this study protocol without patient involvement.

CONCLUSION

Here, we have presented a protocol for systematically conducting a scoping review to broadly analyze the available evidence on the indications for and the mechanisms of action, efficacy, and safety of JAK/STAT pathway-targeting drugs in the use of dermatological therapy. Evidence-based medicine is intended to optimize decision-making by emphasizing the use of evidence derived from well-designed and well-conducted research. Currently, most reviews of treatments blocking the JAK/STAT pathway are narrative reviews, which lack the necessary methodological detail to promote reproducibility and reduce the risk of bias.[15,16] Secondary research methodologies are constantly being developed and must be adapted to the type of research question being asked and the urgency with which the question must be answered.[17]

Although we will try to analyse the quality of evidence per variable and disease using GRADE approach, probably most of the studies have produced documents communicating partial results following an observational design, which is associated with low or very low quality of evidence. However, we believe that the scoping review methodology is the one of the best suited protocols to answer the question posed in this study. The results will provide unique insights into the available evidence on the use of JAK/STAT pathway-targeting drugs in the treatment of dermatological diseases, facilitating the detection of knowledge gaps and the identification of new questions to address via additional systematic reviews.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. The authors are also grateful to the reviewers for their helpful comments and suggestions. We would also like to thank Editage (www.editage.com) for performing English-language editing of this review.

Competing interests. None declared.

Provenance and peer review. Not commissioned; externally peer reviewed.

Compliance with Ethics Guidelines. This protocol relates to a search for previously conducted studies, and does not involve any new human or animal subjects performed by the authors.

Data sharing statement. All the original data are presented in the text and tables of the protocol.

Contributors. FGG and JR conceived the study. FGG, PJGA, JH, AMM, JGM, MAL, IVG, AVGN, BIT, and JR contributed to the protocol design and plan. FGG, PJGA, and

JH developed the literature search strategy. All the authors worked collaboratively to draft and revise the manuscript, and read and approved the final version. All the authors made substantive intellectual contributions to the development of this protocol. JR is the guarantor of the review.

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TABLES

Table 1. Stages of the scoping reviews.

1. Research Question Identified	1.1. Overarching goal	To explore the depth and breadth of evidence for the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of patients with dermatological diseases
	1.2. Research question	What are the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of dermatological diseases?
	1.3. Purposes of this scoping review	1.3.1. Review the evidence of indications for drugs that act on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.2. Review the evidence of epidemiology of drugs acting on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.3. Review the evidence of genetics of drugs acting on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.4. Review the evidence on efficacy of the drugs that act on JAK/STAT pathway in the treatment of dermatogical diseases
		1.3.5. Review the evidence on safety of drugs that act on JAK/STAT pathway in the treatment of dermatogical diseases

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		1.3.6. Obtain concrete research questions that can be answered through a systematic review
		1.3.7. Identify research gaps in the existing literature
2. Identifying relevant literature	2.1. We will perform a three steps-search	2.1.1. First search: an initial limited search of the MEDLINE and EMBASE databases to find keywords in the title, abstract, and the index terms used to describe the articles
		2.1.2. Second search: search of MEDLINE and EMBASE using all identified keywords. A*dditionally, CINAHL, Scopus, and Web of Science to the search engines will be searched in this second step.*
		2.1.3. Third search: the reference lists of all identified reports and articles will be searched for additional studies
	2.2. We will include the studies published in full text in English until October 2018	
	2.3. We will contact authors, of primary studies or reviews, for further information, if this is relevant	
	2.4.The search and selection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
3. Selecting studies	3.1. Inclusion criteria	3.1.1. We will include in the review the studies on the human use of drugs inhibitors of JAK/STAT pathway published on the topics: indications, epidemiology, genetics, efficacy, and safety.

		3.1.2. Design of the studies: we will include guidelines, systematic reviews, randomized clinical trials, observational studies, cross sectional case report and series
	3.2. Exclusion criteria	3.2.1. We will exclude narrative reviews and studies performed *in vitro* or using animal models
4. Charting the data	4.1. We will extract the data in a predefined form.	
	4.2. From each study we will extract title, objective, main variables related to patients, intervention, comparator, outcomes (efficacy and safety) and bibliographic data	
	4.3. We will classify the studies by treatment indication	
	4.4. The list of studies, variables and data of there view will be published in an online-file	
	4.5. The data collection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
5. Collating, summarizing and reporting results	5.1. The results of comprehensive search will be presented using the PRISMA flow diagram	
	5.2. We will synthesize qualitatively the evidence obtained ordering it by topics: indications, mechanism of action, efficacy and safety of drugs that act on	

	JAK/STAT pathway to treat dermatological diseases and we will present it in a diagrammatic tabular form and in a descriptive format	
	5.3. We will use the extension of PRISMA for scoping review for the notification of the review	
6. Differences between the protocol and the overview	Any changes in the methodology that need to be carried out through out the study will be detailed together with the results publication.	

Table 2. Draft of first step of search strategy to be used for at least two electronic databases.

MEDLINE (Ovid), Embase (Ovid)

search	
#1	(('tofacitinib' OR 'baricitinib' OR 'ruxolitinib' OR 'oclacitinib' OR 'upadacitinib' OR 'delgocitinib' OR 'itacitinib' OR 'momelotinib' OR peficitinib OR 'decernotinib' OR 'fedratinib' OR 'pacritinib' OR 'filgotinib' OR 'gandotinib' OR 'solcitinib' OR 'lestaurtinib' OR 'janus kinase inhibitor')
#2	(('psoriasis'/exp OR psoriasis) OR 'atopic dermatitis' OR 'alopecia' OR 'contact dermatitis' OR 'vitiligo' OR 'graft versus host reaction' OR 'lichen planus' OR 'pyoderma gangrenosum' OR 'pruritus' OR (eosinofilic AND annulare AND erythema) OR 'male pattern alopecia' OR 'proteasome associated autoinflammatory syndrome' OR 'sting associated vasculopathy with onset in infancy' OR 'chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome' OR 'hand dermatitis' OR 'discoid lupus erythematosus' OR 'mucocutaneous candidiasis' OR (urticaria AND chronic) OR 'suppurative hidradenitis' OR 'melanoma' OR 'non melanoma skin cancer' OR 'cicatrix' OR 'lichen sclerosus et atrophicus' OR 'pityriasis rubra pilaris' OR 'pemphigus' OR 'skin disease' OR 'rosaceae' OR 'scleroderma' OR 'cinca syndrome' OR 'hyperhidrosis' OR 'erythropoietic protoporphyria' OR 'anca associated vasculitis' OR 'seborrheic dermatitis' OR 'herpes simplex' OR 'sjoegren syndrome'))
#3	#1 AND #2

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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 No.#)
ADMINISTRATIVE INFORMATION			
Title:		**Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review**	
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	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	13,14
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
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	4-5
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	9-11
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	Table 2

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
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)	10
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	10
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	10-11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
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	NA
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA/11/NA/11
	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)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** 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.**

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