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REVIEW

A Scoping Review Protocol to Explore the Use of Interleukin-1-Targeting Drugs for the Treatment of Dermatological Diseases: Indications, Mechanism of Action, Efficacy, and Safety

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ABSTRACT

Introduction: The interleukin (IL)-1 pathway has been identified as being involved in inflammatory and neoplastic skin diseases such as psoriasis, atopic dermatitis, neutrophilic dermatosis, melanoma, and squamous cell carcinoma. Drugs developed to target the IL-1 pathway are currently used to treat these pathologies, and although they are becoming more selective, they are not exempt from adverse events and high costs. Integrating the best research evidence with clinical experience and patient needs has been shown to improve care, health, and cost outcomes. This is because evidence-based guidelines rank interventions according to cost-effectiveness. However, evidence on this topic is scarce for several reasons. First, although randomized clinical trials currently provide the best evidence, they are not always available. Second, there are no secondary scientific studies that summarize the use of IL-1-targeting agents in dermatology. We therefore sought to develop an a priori protocol for broadly reviewing the available evidence on the use of IL-1-targeting drugs in the treatment of dermatological diseases.

Methods: We used the latest methodology to perform a scoping review as described in the Joanna Briggs Institute manual.

Results/Discussion: Developing and applying a methodology for evidence synthesis promotes reproducibility and increases the validity of secondary scientific investigations, making it the optimal strategy for scientifically synthesizing a broad field such as the indications for and the mechanisms of action, efficacies, safety, and costs of IL-1-targeting drugs in the treatment of dermatological diseases. Quantitative synthesis facilitates the detection of knowledge gaps and the identification of new questions that can be addressed through systematic reviews. We present an a priori protocol for exploring the available evidence on this topic.

Keywords: Immune-mediated chronic inflammatory skin diseases; Interleukin-1-

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targeting drugs; PRISMA statement; Scoping review

INTRODUCTION

Research into inflammatory disease pathophysiology facilitates the development of increasingly selective pharmaceutical agents that are highly effective but may also be expensive and have serious side effects. Autoinflammation is driven by endogenous danger signals, metabolic mediators, as well as cells and cytokines of the innate immune system, including interleukin (IL)-1, IL-8, and tumor necrosis factor (TNF)-α [1]. IL-1 is a proinflammatory cytokine that is pathogenically involved in the development of skin diseases. The IL-1 pathway is balanced by activating/promoting agents such as the receptor I (IL-1RI) agonist isoforms IL-1α and IL-1β as well as natural inhibitors of excessive inflammatory responses such as IL-1Ra (a competitive inhibitor of IL-1α and IL-1β) and IL-1RII (which acts as a decoy receptor). While IL-1α initiates the inflammatory process, both isoforms are responsible for propagating and maintaining it [2].

IL-1 is a proinflammatory cytokine involved in skin homeostasis. In the skin, it is mainly expressed in keratinocytes [3], but it can also be found in melanocytes, Langerhans cells, and Merkel cells. Two agonist isoforms encoded by genes located at different loci on chromosome 2 target the IL-1 receptor: IL-1α and IL-1β [4]. These are secreted in the endoplasmic reticulum independently of the Golgi apparatus after inflammasome activation [5]. The precursor of IL-1α, pro-IL-1α, is biologically active, is expressed more with inflammation, and can reside in the cytoplasm, nucleus, or membrane of a producer cell. The precursor of IL-1β, pro-IL-1β, is biologically inactive until processed by intracellular caspase-1 in inflammasomes or by extracellular neutrophilic proteases such as elastase, chymase, granzyme A, cathepsin G, and proteinase [6]. IL-1 has two receptors: IL-1RI and IL-1RII. Signal transduction caused by IL-1 occurs exclusively through IL-1RI. IL-1α, IL-1β, and extracellular pro-IL-1α inhibit IL-1RI with the same affinity. Signal transduction is initiated by IRAK activation, which in turn activates transcription factors such as nuclear factor kappa B (NF-κB), c-Jun N-terminal kinase, and p38 mitogen-activated protein kinase (JNK-MAPK) signaling [7]. There are natural inhibitors of excessive inflammatory responses such as IL-1Ra and IL-1RII. IL-1Ra acts as a competitive inhibitor of IL-1α and IL-1β and exists in two isoforms: the soluble glycosylated extracellular isoform (sIL-1Ra), which is predominantly produced by activated macrophages and monocytes, and the nonglycosylated intracellular isoform (icIL-1Ra), which is produced mainly by Kupffer cells [8]. The nonglycosylated isoform regulates intracellular IL-1-dependent responses. IL-1RII functions as a decoy receptor since it lacks a Toll/IL-1R (TIR) domain [9].

With respect to their biological functions, IL-1 isoforms are generally active during stress responses, inflammation onset, and immune response activation, and they partake in gene expression regulation. They also intervene in carcinogenesis and tumor progression by regulating angiogenesis. These functions can be performed selectively by one isoform alone or can be initiated by one isoform and perpetuated by another, exerting effects at the local (IL-1α) or systemic (IL-1β) level [10]. The regulation of IL-1 can be affected by different factors, both genetic and acquired. Genetic factors include mutations such as IL-1β 511 (CT) polymorphism, IL-1α-889 (C → T) polymorphism, and melanocortin 1 receptor (MC1R) gene polymorphism. These can result in differences in immune response or susceptibility to different diseases. Alternatively, ultraviolet radiation A and B, human papillomavirus infection, skin barrier integrity alteration, and exposure to certain chemicals have been found to be related to dysregulation of the IL-1 pathway [4].

IL-1 pathway alterations have been associated with the onset and progression of several dermatological diseases, including psoriasis [11], atopic dermatitis [12], neutrophilic diseases (e.g., Sjögren's syndrome, pyoderma gangrenosum, Sweet syndrome, or subcorneal pustular dermatosis) [13], as well as the development of neoplastic diseases such as actinic keratosis, Bowen's disease, cutaneous

epidermoid carcinoma, or melanoma [14]. Research conducted regarding the pathophysiological mechanisms for these diseases has led to the development of selective pharmaceutical agents such as anakinra (a recombinant IL-1Ra that competes with IL-1R agonists for its receptor), rilonacept (which acts as a soluble decoy preventing the activation of IL-1RI [15]), canakinumab (a human monoclonal antibody targeting IL-1β [16]), or, more recently, MABp1 (an anti-IL-1α monoclonal antibody [17]). However, given the broad expression and systemic functions of IL-1β and IL-1R, it is questionable whether the long-term effects of these drugs are tolerable. Another drawback of these inhibitors is that they have been associated with bacterial infections, thus limiting their use. From this perspective, anti-IL-1α may have a clinical advantage since they are applied locally rather than systemically, thus potentially limiting adverse effects [10].

The available evidence on the use of IL-1 pathway-modulating agents for the treatment of dermatological diseases is scarce but growing. However, while randomized clinical trials currently represent the best source of evidence, they are not always available, thus making it necessary to obtain secondary evidence. Integrating the optimal research evidence available with clinical experience and patient values has been shown to improve care, health, and cost outcomes [18]. This is likely because evidence-based guidelines rank interventions based on cost-effectiveness, which allows us to discard ineffective alternatives, improve patient status over the long term, avoid complications and additional treatments, and identify measures for disease prevention. Thus, it is necessary to scientifically synthesize the breadth of studies derived from primary research. The secondary scientific research methodology applied depends on the type of research question being asked and the urgency of the response [19]. They can be divided into the following categories: (1) systematic reviews, which question the effectiveness of an intervention; (2) rapid reviews, when time is a critical factor; (3) scoping reviews, which provide an overview of a broad field; and (4) realistic reviews, which are designed to determine how and why complex social interventions function. Specifically, a scoping review is a form of scientific synthesis that addresses an exploratory research question aimed at mapping key concepts and identifying research gaps related to a defined area or field by systematically searching, selecting, and synthesizing existing knowledge [20]. These studies aim to synthesize and present the available evidence, to identify and make recommendations about specific areas of research, and finally to explore the possibility of carrying out systematic reviews on the specific questions formulated.

Here, we aimed to establish a methodology for broadly synthesizing the available evidence on the indications for and the mechanisms of action, efficacies, and safety of IL-1 pathway-targeting drugs that are used to treat dermatological diseases.

METHODS

Protocol Design

The aim of the study was to devise a protocol for broadly addressing the published evidence on IL-1-targeted drugs used in the treatment of dermatological diseases, with three goals in mind: to qualitatively synthesize the available data, to explore the opportunity to formulate questions that could be answered by performing systematic reviews, and to identify gaps in the existing literature. To achieve this aim, we used an existing methodology for conducting scoping reviews [21] that can be broken down into five stages (Table 1): (1) identify the research question; (2) identify the relevant studies; (3) select the studies; (4) chart the data; and (5) collate, summarize, and report the results, and—optionally—perform a consultation exercise. Any necessary alterations to this methodology will be outlined in the Results section of the scoping review.

Table 1 Stages of the scoping review

1. Identifying the research question	1.1. Overarching goal	To explore the depth and breadth of evidence for the indications for and the mechanisms of action, efficacies, and safety of drugs that act on interleukin-1 in the treatment of patients with dermatological diseases
	1.2. Research question	What are the indications for and the mechanisms of action, efficacies, and safety of drugs that act on interleukin-1 in the treatment of dermatological diseases?
	1.3. Purposes of this scoping review	1.3.1. Review the evidence for the indications for drugs that act on interleukin-1 in the treatment of dermatogical diseases
		1.3.2. Review the evidence for the mechanisms of action of drugs that act on interleukin-1 in the treatment of dermatogical diseases
		1.3.3. Review the evidence for the efficacies of the drugs that act on interleukin-1 in the treatment of dermatogical diseases
		1.3.4. Review the evidence for the safety of drugs that act on interleukin-1 in the treatment of dermatogical diseases
		1.3.5. Review the evidence for the costs of drugs that act on interleukin-1 in the treatment of dermatogical diseases
		1.3.6. Obtain concrete research questions that can be answered by performing systematic reviews
		1.3.7. Identify research gaps in the existing literature
2. Identifying relevant literature	2.1. We will perform a three-step 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—a search of MEDLINE and EMBASE using 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 in English until March 2018	
	2.3. We will contact the authors of primary studies or reviews for further information if this is relevant	
	2.4. The process of searching and selecting will be carried out by at least two reviewers; any disagreement between them will be resolved by referring to a third reviewer	

Table 1 continued

3. Selecting the studies	3.1. Inclusion criteria	3.1.1.We will include in the review published studies of interleukin-1 treatments that describe indications, mechanisms of action, efficacies, safety, and costs
		3.1.2. Study designs: we will include guidelines, systematic reviews, observational studies, cross-sectional case reports, series, and expert opinions
	3.2. Exclusion criteria	3.2.1. We will exclude narrative reviews and studies done in vitro or in animals
4. Charting the data	4.1. We will extract the data in a predefined form	
	4.2. From each study, we will extract the title, objective, and the main variables relating to patient, intervention, comparator, outcome (efficacy and safety), and bibliographic data. We will classify the studies by treatment indication	
	4.3. The list of studies, variables, and data of the review will be published in an online file	
	4.2. Data will be collected by at least two reviewers; any disagreement between them will be resolved by referring to a third reviewer	
5. Collating, summarizing, and reporting results	5.1. The results of the comprehensive search will be presented using a PRISMA flow diagram	
	5.2. We will qualitatively synthesize the evidence obtained, categorizing it by topic into indications, mechanisms of action, efficacies, and safety of drugs that act on interleukin-1 in the treatment of dermatological diseases, and we will present it in a diagrammatic tabular form and in a descriptive format	

Inclusion Criteria

We used the mnemonic "PCC" (participants, concept, context) to define the inclusion criteria.

Participants

The review should include all patients with dermatological diseases that could potentially be treated using IL-1-targeting drugs. No restrictions concerning age, ethnicity, study design, or any other characteristic should be imposed.

Concept

The existing literature on the usage of IL-1-targeting drugs in the treatment of dermatological diseases should be reviewed, focusing on indications, mechanisms of action, efficacies, safety, and costs.

Context

The context of the review should not be limited to a particular setting or country.

Research Question

The research question to be asked is: 'What are the indications for and the mechanisms of action, efficacies, and safety of IL-1-targeting drugs used in the treatment of dermatological diseases?'

Identifying Relevant Literature

A three-step literature search should be performed to identify and locate all relevant studies. The first step will entail a limited search of the MEDLINE and EMBASE databases. This will be followed by a keyword analysis of the titles, abstracts, and indexing categorizations used. The second step will be a second search of those two databases using the newly identified keywords and indexing terms. The third and final step will involve searching the reference lists of all the identified reports and articles for additional studies. Where necessary, authors of primary studies or reviews should be contacted for additional information. Due to time and funding limitations, only studies published in English prior to March 2018 will be included. The literature search and review should be carried out by at least two researchers.

Identifying Relevant Studies

The inclusion criteria listed previously will be applied to the literature in order to select relevant studies. This process should be carried out by at least two researchers.

Data Charting

The following relevant data should be recorded and charted: (a) author(s), (b) year of publication, (c) origin (where the study was published or conducted), (d) aims/purpose, (e) study population and sample size (if applicable), (f) methodology, (g) intervention type and comparator (with applicable details), (h) intervention duration (if applicable), (i) outcomes (with applicable details such as measurement criteria), and (j) key findings related to the scoping review question.

Data collection should be performed by at least two reviewers.

Collating, Summarizing, and Reporting Results

The PCC inclusion criteria will guide data presentation. First, search results will be presented in a PRISMA flow chart. Subsequently, extracted data will be categorized into topics such as mechanism of action, efficacy, safety, and cost. A clear explanation of each reported category should be provided. Scoping review results will be presented in diagrammatic (e.g., a map), tabular, and descriptive formats. 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).

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.

CONCLUSIONS

We have presented our protocol for systematically conducting a scoping review to broadly synthesize the available evidence on the indications for and the mechanisms of action, efficacies, and safety of interleukin-1 pathway-targeting drugs that are used to treat dermatological diseases. 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 anti-IL-1 treatments are narrative reviews which lack the necessary methodological detail to promote reproducibility and reduce the risk of bias. 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. We

believe that the scoping review methodology is the one that is best suited to the question posed in this study. The results will provide unique insights into the available evidence on the use of IL-1-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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