Review Paper

Janus-kinase Inhibitors in Pathogenesis and Management of Chronic Urticaria: A Review of the Literature

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ABSTRACT

Background: Chronic urticaria is a long-lasting condition, sometimes with serious comorbidities, severely affecting the quality of life, which makes the patients seek efficient therapies to achieve sustained remissions. The complex nature of urticaria greatly complicates the patients' responses to appropriate treatments.

Objectives: This review was conducted to focus on the Janus kinase (JAK) pathway, evaluate its role as a new biomarker, and discover the efficacy of its inhibitors as novel therapeutic agents in the treatment of refractory chronic urticaria.

Methods: Electronic databases of PubMed and SCOPUS were searched to find and evaluate all the reports describing "Janus kinase," "JAK-STAT pathway," "chronic urticaria," "JAK inhibitors," and "pruritus." Because itching is the most annoying symptom of chronic urticaria and due to the scarcity of articles conducted on the use of JAK inhibitors in the treatment of this disease, we also reviewed quite a few articles performed on applying JAK inhibitors in the treatment of dermatologic disorders and also pruritus in atopic dermatitis.

Results: From the initially retrieved articles, only five were exclusively about the use of JAK inhibitors in the treatment of chronic urticaria.

Conclusions: Although JAK inhibitors are widely known as effective therapies in the treatment of some dermatological diseases, we found out that there are not currently sufficient eligible studies confirming the role of JAK inhibitors in the treatment of chronic urticaria. There is therefore a need for more studies regarding the efficacy and safety of these medications in the treatment of refractory chronic urticaria.

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Introduction

Urticaria, by definition, is the rapid development of wheals, angioedema, or both. Wheals have three typical features including a central swelling surrounded by erythema, itching, or sometimes burning sensation, and a fleeting nature [1, 2]. When the above changes appear at least twice a week and last for more than six weeks, the condition is called chronic urticaria [3-5].

Chronic urticaria is a long-lasting condition, sometimes with serious comorbidities, which makes the patients seek efficient therapies to achieve sustained remissions [6]. Chronic urticaria falls into the spontaneous (nonspecific eliciting factor) or inducible (specific eliciting factor) category [1], with the former being more frequent.

The prevalence of CSU is estimated to be between 0.5% and 1% in the general population, predominantly affecting females between 20 and 40 years [7]. More than 70% of the patients may suffer from this disease for more than a year, which may continue to five years in 14% of them [6]. In a recent report, it was demonstrated that the younger the patients, the longer the course of the disease [8]. Chronic urticaria severely affects the quality of life and is associated with co-morbidities such as lack of sleep, impairment in performance, and productivity, as well as psychosomatic disorders [9, 10].

The pathologic changes are induced by cytokines released from over-activated skin mast cells and basophils, which result in sensory nerve activation, vasodilation, and plasma extravasation. Although urticaria is a disease driven by mast cells and their mediators such as histamine, platelet-activating factor, and specific cytokines, the affected skin also exhibits a mixed inflammatory perivascular infiltration of neutrophils, eosinophils, basophils, macrophages, and T cells along with upregulation of endothelial cell adhesion molecules, neuropeptides, and growth factors [11-13]. These features indicate the complex nature of the urticaria, which greatly complicates the patients' favorable responses to appropriate treatments. Many patients with chronic urticaria may still suffer from this disease despite the administration of the proper doses of (approximately up to four times more than routinely recommended doses) second-generation antihistamines and short courses of steroids.

Therefore, identifying the immunological profile and understanding the underlying mechanisms of cell biology in the induction of inflammation in chronic urticaria may offer new therapeutic opportunities in the management of refractory chronic urticaria, unresponsive to the existing conventional medications. Biological medications are considered a novel field of therapy with a high potential to treat refractory chronic urticaria [14].

Considering the molecular biology of cells in disease pathogenesis, the role of the JAK-STAT pathway and its signal transduction in cell proliferation, differentiation, migration, and apoptosis appears to be of paramount importance, particularly by benefiting from new therapeutic inhibitors to control the inflammatory process [15]. Many immune and inflammatory diseases are closely related to the persistent activation of the JAK-STAT signaling pathway [16]. Furthermore, possible disturbances in the JAK-STAT pathway may result in various inflammatory and autoimmune skin diseases [17, 18]. Inhibiting JAK function, on the other hand, has been shown to efficiently restrain overly active immune cells [16, 19].

JAK inhibitors are small molecules with short half-lives and steroid-sparing effects that can be applied either orally or topically [20, 21], and are widely known to have anti-inflammatory, immunomodulatory, and antiproliferative effects [22]. They represent a targeted therapeutic approach for some diseases including skin disorders, yet their application is approved for some of these diseases, and for some others, their effectiveness is still under clinical trials [23]. JAK inhibitors are recognized to function either selectively or less selectively, such as abrocitinib for the former and Tofacitinib for the latter. Since the use of antipruritic therapeutic agents is not effective in relieving the constant itching of refractory chronic urticaria as an unpleasant sensation, the treatment has remained challenging in many patients. Therefore, a couple of experimental and clinical research has been conducted to evaluate the efficacy possibility of JAK inhibitors in the treatment of chronic urticaria unresponsive to conventional therapies.

This review was conducted to appraise the existing literature on drugs targeting the Janus kinase pathway in the treatment of chronic urticaria.

Methods

We aimed to assess the effects of JAK inhibitors as a novel treatment of chronic urticaria unresponsive to conventional therapies. Table 1 demonstrates how we started and accomplished this study.

Table 1. The review process of the evaluated articles

No.	Items	Considerations
1	Research question	To explore the strength of evidence for the application of JAK inhibitors to manage refractory chronic urticaria
2	Purpose of the review	To review the existing evidence of indications for the drugs that inhibit the JAK-STAT pathway in the treatment of refractory chronic urticaria To review the evidence for drugs efficacy that act on the JAK-STAT pathway in the treatment of refractory chronic urticaria To review the safety of the drugs that act on the JAK-STAT pathway in the treatment of refractory chronic urticaria To consider the research questions that may arise and can be answered throughout the research
3	Performing a two-step research	An initial search of databases for the keywords in the titles Checking the reference list of all the identified articles found in the first step
4	Identifying the relevant literature	Reviewing the full text of the selected published articles in English until the end of 2022
5	Inclusion criteria of relevant studies after reviewing	Including the studies on the human use of JAK-STAT pathway inhibitors from different aspects, such as indication, epidemiology, efficacy, and safety Excluding *in vitro* or animal studies
6	Reporting the results	Summarizing the results in the form of a review article

Journal of Pediatrics Review

Inclusion criteria

All the articles concerning the use of JAK inhibitors in the treatment of refractory chronic urticaria in human patients-not limited to any particular settings, countries, or ethnicities were reviewed.

Results

Identifying relevant literature

To review the pertinent articles in literature, all those published on PubMed and Scopus up to 2023 were extracted using a combination of "urticaria," "chronic," "Janus-kinase," "pruritus," and "JAK inhibitors" keywords. In addition, we reviewed several other relevant articles cited in the published articles on PubMed and Scopus. After reviewing these articles, we only found a few using JAK inhibitors in the treatment of chronic urticaria (Table 2).

Therefore, because itching is the most annoying symptom of chronic urticaria and due to the scarcity of articles conducted on the use of JAK inhibitors in the treatment of this disease, we also reviewed quite a few articles performed on applying JAK inhibitors in the treatment of dermatologic disorders and also pruritus in atopic dermatitis. A total of 70 articles were found and analyzed in this review.

Discussion

Pathogenesis of chronic urticaria

Urticaria is a mast cell-driven disease, where mast cells are the mediators of allergic diseases. Mast cells may cause profound inflammation and vasodilation by releasing their preformed and newly synthesized mediators [47] such as histamine, platelet-activating factor, and cytokines. These mediators may result in sensory nerve activation, vasodilation, and plasma extravasation leading to the leakage of the serum into the upper and mid-dermis with subsequent formation of wheals [1]. IgE-mediated inflammation is regulated by signaling molecules including IL-6 with a significant role in the survival and maturation of mast cells [48]. The regulation of mast cells plays an important role in the management of allergic disorders. STAT5 contributes to mast cell hemostasis [47].

Four decades ago, chronic urticaria was considered a T-cell-mediated disorder because of CD4+T-cell infiltration in the skin of the affected patients [6]. Increased expression of CD40 ligand on T-cells, as seen in autoimmune diseases, was another finding in the peripheral blood of patients with chronic urticaria. Another finding back then was that along with an increase in the switch of Th1 to Th17, there would be an increase in serum IL-17 concentration correlated with the severity of the

Table 2. Relevant articles on the application of jak inhibitors in the treatment of pruritus in refractory chronic urticaria

No	Author(s) Year	Origin	Type of Source	Articles/Patients No.	Purpose	Exclusively Conducted on Chronic Urticaria
1	Kocarturk et al. 2022 [23]	Turkey	Review	91 articles	Medications for the treatment of chronic spontaneous urticaria	Yes
2	Chapman et al. 2022 [24]	The USA	Review	37 articles	JAK inhibitors in dermatology	No
3	Filippo et al. 2022 [25]	Italy	Review	108 articles	Biologic drugs in allergic skin diseases	No
4	Shalabi et al. 2022 [26]	The USA	Review	-	JAK inhibitors in dermatology	No
5	Mansouri et al. 2022 [27]	Iran	Case series	5 patients	Oral Tofacitinib in refractory chronic urticaria	Yes
6	Zhang et al. 2021 [28]	China	Review	151 articles	Therapeutic and diagnostic targets in urticaria	Yes
7	Gimenez-Arnau et al. 2021 [29]	Spain	Review	189 articles	Pathogenesis of chronic spontaneous urticaria	Yes
8	Reszka et al. 2020 [30]	Poland	Review	254 articles	Therapeutic options for pruritus	No
9	Kim et al. 2020 [31]	Canada and the USA	Research Article	307 patients	The effects of ruxolitinib on itch and quality of life	No
10	Kim et al. 2020 [32]	Canada and the USA	Research Article	307 patients	The efficacy of ruxolitinib on itching	No
11	Arora et al. 2020 [33]	Australia	Review	413 articles	The efficacy of JAK inhibitors in treating atopic dermatitis	No
12	Singh et al. 2020 [34]	The USA	Review	101 articles	Role of JAK inhibitors in the treatment of atopic dermatitis	No
13	Ciechanowicz et al. 2019 [35]	Poland	Review	11 articles	JAK inhibitors in dermatology	No
14	Nakagawa et al. 2019 [36]	Japan	Research article	327 patients	The efficacy and safety of JTE-052 in night-time pruritus	No
15	Cinats et al. 2018 [37]	Canada	Review	-	JAK inhibitors in dermatology	No
16	Fukunaga et al. 2018 [38]	Japan	Case report	1 patient	Efficacy of ruxolitinib in refractory CU	Yes
17	Shreberk-Hassidim et al. 2017 [39]	Israel	Review	134 articles	JAK inhibitors in the treatment of cutaneous disorders	No
18	Damsky & King 2017 [40]	The USA	Review	100 articles	JAK inhibitors in dermatology	No
19	Kostovic et al. 2017 [41]	Croatia	Review	43 articles	Tofacitinib perspective in dermatology	No
20	Welsh et al. 2017 [17]	Germany and the UK	Review	119 articles	Targeting JAK-STAT signaling in inflammatory skin diseases	No
21	Yacoub & Prochaska 2016 [42]	The USA	Case report	1 patient	Efficacy of ruxolitinib in systemic mastocytosis	No
22	Bissonnette et al. 2016 [43]	Canada	Randomized trial	69 patients	Efficacy of Tofacitinib in improving the pruritus of atopic dermatitis	No
23	O'Shea et al. 2015 [44]	The USA	Review	81 articles	Relevance of the JAK-STAT pathway in the treatment of inflammatory disorders	No

No	Author(s) Year	Origin	Type of Source	Articles/Patients No.	Purpose	Exclusively Conducted on Chronic Urticaria
24	Clark et al. 2014 [45]	The USA	Review	100 articles	Evaluation of JAK inhibitors in the treatment of inflammatory diseases	No
25	Bao et al. 2013 [46]	The USA	Review	98 articles	JAK-STAT pathway in atopic dermatitis	No

Journal of Pediatrics Review

disease [6]. IL-10, released by several cell types such as T helper cells, monocytes, macrophages, dendritic cells, B cells, NK cells, cytotoxic T cells, mast cells, and granulocytes, also plays a critical role in inducing and maintaining immune tolerance [49]. Therefore, any deficiency in IL-10 may become associated with autoimmune disorders. IL-9, initially identified as a Th2 cytokine and mast cell growth factor, is now attributed to the Th9 subset of CD4+ T cells and is identified as a mediator of allergic inflammation [49]. IL-9 enhances the production of IgE from B cells [49]. In chronic urticaria, Th9 cells are significantly increased in peripheral blood and therefore an increase in IL-9 is anticipated.

Overexpression of these two cytokines leads to an increase in the number of eosinophils (producing IL-3, IL-5, and GM-CSF), an increase in the proportion of CD8+ cells, and an increase in inflammatory cytokine expression [49], but a decrease in the proportion of CD4+ cells.

It has been demonstrated that JAK/STAT pathway plays a major role in transducing extracellular signal transduction involved in cell differentiation, proliferation, migration, and apoptosis [15]. This pathway allows quick signaling from the membrane to the nucleus [38, 50, 51]. The JAK family is comprised of four types of cytoplasmic tyrosine kinases; JAK1, JAK2, JAK3, and Tyk2. STAT is the other component of this cascade, which is translocated to the nucleus after being phosphorylated by JAK and then participates in the transcription of specific genes. JAKs transduce the signaling of IL-2R, IL-4R, IL-5R, IL-6R, IL-13R, and type 1 interferon, which are all known as pathogenic pathways in different diseases [52]. Production of JAK/STAT-mediated cytokines such as IL-4, IL-13, IL-31, and TSLP inhibits the expression of skin barrier proteins, which may trigger pruritus in atopic dermatitis [53, 54]. Furthermore, several types of ligands including cytokines, interleukins, hormones, and growth factors may activate this pathway and affect tissue physiology [55]. Some examples are IL-2 and its family, interferon alpha, Il-23, and IL-17. Some of these molecules have important roles in the development of dermatological disorders including chronic hives [15]. Oncostatin M (OSM) is a member of the IL-6 family, synthesized by activated T cells, neutrophils, and macrophages [56, 57], which plays an important role as a keratinocyte activator [56]. The biological functions of OSM are mediated by the OSM receptor (OSMR) gene [51]. The mRNA expression of the OSMR is elevated in chronic autoimmune urticaria skin tissues showing a higher level of vascular markers with eosinophil and neutrophil infiltration, contributing to tissue edema [58]. It has been shown that OSMR leads to the activation of Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [57, 59, 60]. The JAK/STAT signaling pathway interacts with other pathways including MAPK and NF-kB to promote the expression of the inflammatory genes [49]. IL-6 is potentially able to activate JAK/STAT signaling pathway through the transmembrane receptor gp130. Activated JAK receptor tyrosine kinase can phosphorylate STATs to form dimers. Then, after translocation to the nucleus, where binding with nuclear DNA occurs, JAK receptor tyrosine kinase regulates downstream inflammatory genes [55]. The disease activity in chronic urticaria is related to the inflammatory cytokines released by Th1, Th2, Th17, and Th22 cells [61]. In patients with chronic urticaria, the expressions of Il-9, IL-10, STAT3, and JAK is increased while the expression of INF-γ is decreased in the skin tissues [49]. On the contrary, the downregulation of IL-9 and IL-10 inhibits the JAK/STAT signaling pathway [49]. Therefore, higher levels of eosinophils, cytokine expression, and activated JAK/STAT pathway signaling are associated with higher duration and intensity of pruritus in the patients [49].

Autoimmunity also contributes to the development of chronic spontaneous urticaria and is found in 50% of patients. There are two types of autoimmunity in this regard. The first type is characterized by IgE auto-antibodies against auto allergens and or thyroid antigens, namely anti-TPO antibodies, and the second type by autoantibodies against IgE and/or FcεRIα on mast cells.

Another important factor in the pathogenesis of chronic urticaria is the role of the neuroendocrine system. Psychological stress has a two-way interaction

with chronic urticaria; chronic urticaria induces psychological stress and chronic stress is a trigger of chronic urticaria. Chronic stress has the potential to increase the tone of the hypothalamic-pituitary-adrenal (HPA) axis, and hence the secretion of corticotropin-releasing hormone, which in the long term will be associated with decreased secretion of the aforementioned hormone because of fatigue in the HPA axis with resultant hypocortisolism [55].

In addition, chronic stress in association with the activation of the HPA axis results in the secretion of IL-18 with immune-modulatory and pro-inflammatory properties. IL-18 along with cortisol set up a negative feedback mechanism and together inhibit CRH secretion. However, prolonged periods of stress can shift the cytokine milieu toward increased production of proinflammatory cytokines including IL-6 and IL-18. Because of fatigue in the axis of HPA, the increased level of IL-18 results in increased CRH production with proinflammatory properties such as mast cell degranulation and increased vascular permeability. It has been shown that a peripheral HPA axis exists in the human skin with the epidermal and hair follicle keratinocytes, sebocytes, and mast cells with the potential to secrete CRH in stress response [55]. Keratinocytes also secrete IL-18 in response to stress leading to severe skin inflammation.

Treatment

Treatment strategies not only consist of relieving symptoms and reducing inflammation but also targeting the cytokines with central roles as inflammatory mediators to arrest the pathogenic pathways of the skin disease.

Chronic urticaria is a major problem in terms of management. It may last for a long period and may cause significant distress leading to low quality of life. The main goal of treatment in chronic urticaria is reducing the symptoms with invasive therapy by carefully balancing risk and benefit. However, most of the time, the treatment is challenging for both the physician and the patient as the therapy response is often disappointing. Since histamines are the main mediators of urticaria, newer generation antihistamines with less sedative and anticholinergic side effects are the preferred recommended therapy as the initial step. These medications should be taken daily and not as demanded or when the patient becomes symptomatic. For the patients with poor response to the above-mentioned therapy, the daily dose could be increased fourfold to the normal recommended dose. Other suggested therapies include corticosteroids, omalizumab, and cyclosporine Although, the fear of side effects associated with cyclosporine A has limited its usage, and it is therefore used only under omalizumab failure circumstances.

Currently, molecularly targeted therapies seem to have promising results in several human inflammatory and autoimmune conditions. Because many disease-causing cytokines depend on JAK-STAT signaling to elicit their pathologic effect, JAK inhibitors appear to play an important role in the treatment of these conditions. Even in the cases of other cytokines, such as TNF-α, IL-1, and IL-17, which do not rely on the JAK/STAT pathway, JAK inhibitors can indirectly suppress them by restricting other STAT-dependent cytokines [40, 62].

Newly developed JAK inhibitors including selective and pan-JAK inhibitors (JAK1, JAK2, JAK3, TYK2) appear to have the potential to advance the treatment strategies against autoimmune and inflammatory disorders, which cannot be easily controlled by the traditional available therapies. These are preferred over biologics because of their potential ability to inhibit signaling from multiple cytokines and their ease of administration (oral or topical) [63]. JAK inhibitors modulate the inflammatory process by activating STATs, which are intracytoplasmic transcription factors. After being activated, STATs form dimers and translocate into the nucleus where they modulate the expression of several genes [64].

A recent study in Japan was conducted to evaluate the efficacy of topical JAK inhibitors in the treatment of atopic dermatitis, the results of which showed that delgocitinib can lead to a significant clinical improvement (61.8% vs 0.5%) after 4 weeks of treatment, which indicated the effect of this pan-JAK inhibitor on treating moderate-to-severe atopic dermatitis [34]. Ruxolitinib is a selective JAK1 and high-potency JAK2 inhibitor, which was specifically effective in relieving pruritus in atopic dermatitis after eight weeks of treatment [31, 32]. Another topical JAK3 and JAK1 inhibitor demonstrated significant improvement in pruritus within 2 days of treatment in severe debilitating pruritus in another study [43]. Even though oral JAK inhibitors, such as abrocitinib, baricitinib, gusacitinib, and upadacitinib, with rapid efficacy and good tolerability, are currently under clinical trials to be validated for use in pruritus of atopic dermatitis [65], there are not sufficient experiments regarding their use in the treatment of the constant itching in refractory chronic urticaria. Although these inhibitors may act similarly in the treatment of the itching of chronic urticaria, their safety needs further evaluation to be approved.

In addition to the lack of sufficient data in the treatment of chronic urticaria with JAK inhibitors, they may also result in major side effects such as serious, opportunistic infections, Herpes zoster [66-69], hematologic complications (most often cytopenias) [62], venous thrombosis [51], and hyperlipidemia [70]. Other major issues are the dose and half-life of JAK inhibitors. Lowering, but not permanently blocking, JAK/STAT activation is another crucial issue to be taken into consideration [64]. All the aforementioned concerns are the reasons why the real-world safety and efficacy of JAK inhibitors in the management of chronic urticaria are still under question.

Conclusion

It is noteworthy that the lack of sufficient published articles for our topic of interest was one major challenge in this review. Although JAK inhibitors are widely known as effective therapies in the treatment of some dermatological diseases (including allergic dermatitis, alopecia areata, vitiligo, and psoriasis), we found out that there are currently not sufficient eligible studies confirming the role of JAK inhibitors, specifically in the treatment of chronic urticaria. Particularly, the safety concerns of these medications should not be ignored. However, more studies are required to approve the use of these novel medications for chronic urticaria, not responding to conventional therapies.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

All three authors were involved in data collection, and writing the article.

Conflicts of interest

The authors declared no conflict of interest.

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