ORIGINAL ARTICLE

Itch and Janus Kinase Inhibitors

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Itch is a common skin symptom, with complex aetiology and pathogenesis. It is mediated by 2 pathways, the histaminergic and non-histaminergic pathways. Chronic itch is understood to be processed by the latter and is difficult to treat with traditional pruritus therapies. The Janus kinase and signal transducer and activator of transcription pathway is a signalling mechanism that regulates gene expression through various cytokines. Janus kinase inhibitors, which have been tested and used for several autoimmune diseases, have also been shown to be effective for itch through clinical trials and case reports. Janus kinase inhibitors could be a good choice for pruritus in atopic dermatitis, psoriasis, and other diseases, such as prurigo nodularis and lichen planus, with rapid itch relief compared with conventional treatments. The most common adverse effects reported include nasopharyngitis, acne, and elevated blood creatine phosphokinase levels. Janus kinase inhibitors are currently prescribed with warnings about a potential increase in malignancies and cardiovascular diseases and usage in people of older ages. This review aims to provide knowledge about itch and the Janus kinase and signal transducer and activator of transcription pathway and to analyse the current evidence for itch relief by Janus kinase inhibitors.

SIGNIFICANCE

Many patients report itch during dermatology examinations. Chronic itch is defined as itch lasting for more than 6 weeks and is often resistant to conventional treatments. Several inflammatory diseases are mediated by the Janus kinase and signal transducer and activator of transcription pathway, a signalling mechanism that controls gene expression. Recently, clinical trials and cases have reported that inhibitors of this pathway could reduce itch rapidly and effectively. This paper reviews the pathophysiology of itch and analyses the efficacy and safety of Janus kinase inhibitors for itch reduction in various dermatological diseases, including atopic dermatitis and psoriasis, as well as prurigo nodularis and chronic pruritus of unknown origin.

Itch, or pruritus, is one of the most common symptoms reported by patients visiting a dermatologist (1). It is defined as an unpleasant feeling that arouses a desire to scratch. Itch is a characteristic symptom of atopic dermatitis (AD) and also accompanies various other skin diseases. Some patients report severe pruritus without specific primary skin lesions. The pathophysiology of itch is complicated, involving numerous cells and cytokines, and is being actively studied. Many achieve symptom relief with medications including antihistamines, corticosteroids, and phototherapy, but some are bothered by severe or chronic itch that does not respond to conventional treatments (1).

The Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathway is an important signalling mechanism that regulates intracellular gene expression through cytokines and cell growth factors, such as interleukin (IL) and interferon (IFN) (2). The importance of the JAK-STAT pathway began to be elucidated through the association between gene mutations and haematological and immunological diseases, including gain-of-function mutations in JAK2 in polycythemia vera, essential thrombocytosis, and myelofibrosis, and loss-of-function mutation in STAT3 of autosomal dominant hyperimmunoglobulin E syndrome (3, 4). It is now known that JAK-dependent cytokines play an important role in the development of a number of inflammatory and autoimmune diseases (2).

JAK inhibitors are attracting attention as a novel treatment for various skin diseases, which includes AD, alopecia areata, and vitiligo. Notably, JAK inhibitors have been found to be effective not only for the skin lesions in patients with AD, but also for itch, raising the possibility of their application in various itchy conditions (3). The aim of this review was to analyse the current applications of JAK inhibitors in the management of pruritus.

METHODS

This narrative review was conducted after keyword searches of PubMed until July 2022, using the following terms: "itch AND JAK inhibitor" and "pruritus AND JAK inhibitor". Further searches were performed for diseases of special interest with itching, such as AD, psoriasis, prurigo nodularis, and chronic pruritus of unknown origin (CPUO). Only articles in English were included. Initially, papers were selected based on the title, and then on the abstract referring to JAK inhibitors and itch. After reviewing all the literature searched, the papers providing quantitative results for itch reduction were chosen. The articles chosen and the related references were thoroughly reviewed by the authors.

RESULTS

Pathophysiology of itch

Itch is induced by 2 separate and distinct pathways, histaminergic and non-histaminergic pathways (1). The histaminergic pathway is mediated by histamines released mainly from mast cells, but also from basophils and keratinocytes, and is associated with acute itch. The non-histaminergic pathway is activated by endogenous or exogenous pruritogens, such as protease, amines, and chemokines released from various immune cells including mast cells, macrophages, eosinophils, neutrophils, and neurones. This pathway is known to be responsible for the pathophysiology of chronic itch and explains why antihistamines are usually ineffective (1, 5).

Numerous pruritogens and their receptors have been studied. The cytokines best known to mediate chronic itch are T helper (Th) 2 cytokines, represented by IL-4, IL-13, and IL-31, which are important in diseases such as AD and prurigo nodularis (5). Thymic stromal lymphopoietin (TSLP) from keratinocytes also plays an important role in the pathogenesis of itch by promoting Th2 immune responses (1). Scratching causes keratinocytes to express more TSLPs, which leads to positive feedback, called the "itch-scratch cycle." Pruritus in psoriasis and the acute phase of AD is attributed to the Th17-related cytokines, IL-17 and IL-23. Uraemic pruritus is explained by IL-2 and IL-31. Besides the cytokines, proteases with their receptors, substance P with its receptor, neurokinin 1 receptors, and Mas-related G protein-coupled receptors are known to contribute to chronic itch (5).

By the binding of pruritogens to their receptors or directly activating ion channels, itch signals are transmitted from the skin to the spinal cord and, finally, to the brain through unmyelinated type C and myelinated type Aδ nerves (1). Itch perception stimulates several areas of the brain, such as the somatosensory cortex (links to itch localization, intensity, and recognition) and the cingulate cortex (links to perception, motivation, and unpleasant sensation) (5). Scratching induces itch-relief pleasure by inhibiting those areas and stimulates the brain's reward system promoting an addictive itch-scratch cycle.

Janus kinase and signal transducer and activator of transcription pathway and itch

JAK-STAT pathways are involved in the pathogenesis of itch. Following the engagement of cytokines and receptors, the downstream signalling mediators are activated, where the intracellular JAK-STAT pathway functions. The JAK-STAT pathway transmits signals from the cell membrane to the nucleus. The binding of extracellular cytokines to the receptor activates intracellular JAK proteins, phosphorylating STAT proteins, which dimerize and then translocate into the nucleus to modulate gene expression (2). Four JAK family members (JAK1, JAK2, JAK3, and TYK2) and 7 STAT family members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) are known. They work alone or together in various combinations. For example, IL-4 and its receptor, which consists of an IL-4 receptor-α and common γ-chain subunits, are associated with JAK1 and JAK3. TSLP binds to its receptor, which is dependent on JAK1 and JAK2.

IL-4 receptor-α, and JAK1 signalling in sensory neurones drive chronic itch (6). Among the chronic itch cytokines, IL-4 has been shown to enhance neuronal responsiveness to multiple pruritogens via JAK1 phosphorylation. Oetjen et al. (6) showed that mice lacking JAK1 in their sensory neurones scratched less despite MC903 (calcipotriol) exposure, which caused ample levels of AD-like skin inflammation. Also, the same mice placed under the condition of "chronic itch not associated with inflammation" (i.e. repeated application of acetone, ether, and water mixture) scratched significantly less, which suggests that JAK1 signalling in sensory neurones is necessary for chronic itch in both inflammatory and non-inflammatory settings. A number of clinical studies have demonstrated the efficacy of JAK inhibitors in chronic itch and are discussed in detail below.

Atopic dermatitis

Itch in atopic dermatitis. AD is a chronic inflammatory skin disorder with a complex and multifactorial pathogenesis. Its pathogenesis is based on the impairment of epidermal barrier function and immune dysregulation. The inflammatory environment drives an immune response with a bias toward Th2 cells that increases the levels of Th2 cytokines such as IL-4, IL-5, IL-13, IL-31, and IL-33 (7). Itch is known to be associated with IL-13, IL-31, and TSLP in AD and is a cardinal symptom causing physical and psychological burdens to patients and impairing their quality of life (8). Many studies have assessed the efficacy of treatment for itch relief using the Peak Pruritus Numerical Rating Scale (PP-NRS), which was developed to evaluate itch intensity in moderate-to-severe AD. It is a single, self-reported score representing the worst pruritic moment during the previous 24 h rated on a scale of 0 to 10, with 0 being "no itch" and 10 being "the worst itch imaginable". Some studies analysed itch relief as a decrease in the mean NRS score, and some analysed it by the proportion of patients whose NRS mean changed by 4 points or more from baseline.

Efficacy of Janus kinase inhibitors in itch. Previous studies in AD showed that the activation of JAK-STAT signalling within the atopic skin of patients and the inhibition of the pathway may reduce inflammation by improving skin barrier function (9). Herein, we focus on the efficacy of JAK inhibitors in itch relief rather than improvements in eczematous skin lesions. **Table I** summarizes the efficacy of topical and oral JAK inhibitors studied in various randomized trials. To evaluate the

efficacy of JAK inhibitors alone, monotherapy regimen trials were reviewed. Tofacitinib ointment showed significantly greater efficacy in pruritus compared with the vehicle with early onset (rapid itch reduction of approximately –3 NRS on day 2 and –4.4 NRS as the endpoint of week 4) (10). Ruxolitinib cream also showed significant improvement in itch compared with the vehicle (11). Delgocitinib ointment showed significant improvement in both adult and paediatric patients (12, 13). All regimens of brepocitinib showed significant reductions in itch scores of ≥ 4, but the higher dose groups showed a rapid response as early as day 2 and day 3 (14). For oral JAK inhibitors, upadacitinib and abrocitinib showed higher response rates than baricitinib, implying that selective JAK1 inhibitors are more effective for itch relief than JAK1/2 inhibitors (15–17). The result from systematic review and network meta-analysis of oral JAK inhibitors showed that oral upadacitinib was the most effective among the above agents (18). This result may be because the JAK1 pathway plays a more important role in itch in AD, and thus, the high affinity and selectivity of JAK1 inhibitors are more effective.

Comparison with other treatments. Many moderate-to-severe AD patients with insufficient responses to conventional treatment have been treated with dupilumab. Dupilumab targets the shared α-chain of IL-4 and IL-13 receptors, inhibiting Th2-driven inflammation. Patients are usually given 300 mg dupilumab subcutaneously

Table I. Janus kinase (JAK) inhibitors for itch relief in atopic dermatitis

JAK inhibitor	Study type Trial identifier	Patients n	Duration (weeks)	Regimen	Initial itch NRS mean±SD	Variable	Results
Topical							
Tofacitinib (JAK1/3)	Phase IIa NCT02001181 (10)	69 (18–60 years)	4	2% BID	6.5±2.5 (2% BID) 5.5±2.2 (vehicle)	NRS point	–4.4 vs –1.1 (vehicle) at week 4
Ruxolitinib (JAK1/2)	Phase III NCT03745638 (11)	631 (≥ 12 years)	8	0.75% BID 1.5% BID	5.1±2.3 (0.75%) 5.2±2.5 (1.5%) 5.1±2.5 (vehicle)	NRS-4	52.2% (0.75%), 40.4% (1.5%) vs 15.4% (vehicle) of participants at week 8
Delgocitinib (JAK 1/2/3, TYK2)	Phase III JapicCTI-173554 (12)	158 (≥ 16 years)	4	0.5% BID	5.3±2.2 (daytime) 4.6±2.4 (night-time)	NRS point NRS %	Daytime: –1.5 vs –0.5 (vehicle) at week 4 Night-time: –1.5 vs 0.3 (vehicle) at week 4
Delgocitinib (JAK 1/2/3, TYK2)	Phase III JapicCTI-184064 (13)	137 (2–15 years)	4	0.25% BID 0.5% BID (for extension)	2.3±0.7 (daytime) 1.8±0.7 (night-time)	NRS point NRS %	Daytime: –0.5 (0.25%) vs +0.1 (vehicle) at week 4 Night-time: –0.3 (0.25%) vs +0.2 (vehicle) at week 4
Brepocitinib (JAK1/TYK2)	Phase IIb NCT03903822 (14)	292 (12–75 years)	6	0.1% QD 0.3% QD, BID 1.0% QD, BID 3.0% QD	6.0±2.03	NRS-4	50% (3.0% QD), 45.2% (1.0% QD), 40.7% (1.0% BID) of participants at week 6
Oral							
Baricitinib (JAK1/2)	Phase III NCT03334422 (15)	615 (≥ 18 years)	16	1 mg QD, 2 mg QD, 4 mg QD	6.4±2.2 (1mg) 6.6±2.2 (2 mg, 4 mg) 6.8±2.2 (placebo)	NRS % NRS-4	47.2% (4 mg), 46.9% (2 mg) vs 16.6% (placebo) improvement at week 16 18.7% (4 mg), 15.1% (2 mg) of participants at week 16
Upadacitinib (JAK1)	Phase III NCT03569293 (16)	847 (12–75 years)	16	15 mg QD, 30 mg QD	7.2±1.6 (15 mg) 7.3±1.5 (30 mg) 7.3±1.7 (placebo)	NRS % NRS-4	62.8% (15 mg), 72% (30 mg) vs 26.1% (placebo) improvement at week 16 52.2% (15 mg), 60.0% (30 mg) vs 11.8% (placebo) of participants at week 16
Abrocitinib (JAK1)	Phase III NCT03575871 (17)	391 (≥ 12 years)	12	100 mg QD, 200 mg QD	7.1±1.6 (100 mg) 7.0±1.6 (200 mg) 6.7±1.9 (placebo)	NRS point NRS-4	–4 (200 mg), –3.2 (100 mg) vs –1.6 (placebo) at week 12 55.3% (200 mg), 45.2% (100 mg) vs 11.5% (placebo) of patients at week 12
Oral JAK inhibitors comparison (18)							
Baricitinib (JAK1/2)	Phase III NCT03334396 NCT03334422 (15) NCT03435081	392 248	16 16	2 mg QD 4 mg QD	6.8 6.5	NRS-4 NRS-4	8.0% at week 2 and 23.33% at week 16 12.0% at week 2 and 30.0% at week 16
Upadacitinib (JAK1)	Phase III NCT03569293 (16) NCT03607422	557 567	16 16	15 mg QD 30 mg QD	7.2 7.3	NRS-4 NRS-4	31.1% at week 2 and 41.9% at week 16 43.9% at week 2 and 55.2% at week 16
Abrocitinib (JAK1)	Phase III NCT03349060 NCT03575871 (17)	314 309	12 12	100 mg QD 200 mg QD	7.0 7.0	NRS-4 NRS-4	21.6% at week 2 and 30.5% at week 12 40.0% at week 2 and 44.3% at week 12
Comparison with dupilumab							
Upadacitinib (JAK1)	Phase III NCT03738397 (19)	692 (18–75 years)	16	30 mg QD	7.4±1.6 (upadacitinib) 7.5±1.7 (dupilumab)	NRS % NRS-4	66.9% (upadacitinib) vs 49.0% (dupilumab) improvement at week 16 55.3% (upadacitinib) vs 35.7% (dupilumab) of participants at week 16
Abrocitinib (JAK1)	Phase III NCT03720470 (20)	838 (≥ 18 years)	16	100 mg QD, 200 mg QD	7.1±1.7 (100 mg) 7.6±1.5 (200 mg) 7.3±1.7 (dupilumab)	NRS-4	49.1% (200 mg), 31.8% (100 mg) vs 26.4% (dupilumab) of participants at week 2 77% (200 mg, dupilumab) and 69% (100 mg) of participants at week 16

BID: twice daily; NRS: numerical rating scale; NRS-point: itch reduction evaluated as a decrease in score; NRS-%: itch reduction evaluated as a decrease in percentage from baseline; NRS-4: itch reduction evaluated as the proportion of participants achieving a ≥ 4-point reduction from baseline; QD: once daily.

every other week after a loading dose of 600 mg. The efficacy of the 2 oral JAK1 inhibitors seemed to be more effective in itch reduction compared with dupilumab (Table I). In addition, the response was more rapid in the upadacitinib group than in the dupilumab group: 31.4% (upadacitinib) vs 8.8% (dupilumab) improvement from baseline NRS scores at week 1 (19). This faster action may be because JAK inhibitors are small-molecule drugs. They are relatively simple chemical compounds that bind with targets such as G protein-coupled receptors, ligand-gated ion channels, and receptor tyrosine kinases on extracellular or intracellular domains, which lack high specificity compared with biologics. As mentioned above, selective JAK1 inhibitors affect the signalling of multiple inflammatory mediators, including IL-4, IL-13, IL-22, IL-31, IFN-γ, and TSLP, whereas dupilumab has higher specificity. Efficacy varies depending on the type and dosage of JAK inhibitor. For abrocitinib, only the 200 mg group showed effectiveness similar to that of dupilumab at week 16, although both the 100 mg and 200 mg groups had higher response rates than dupilumab at week 2 (20).

Psoriasis

Itch in psoriasis. Psoriasis is a chronic inflammatory skin disease with a complex and multifactorial aetiology. The pathogenesis of psoriasis is known to be associated with genetic susceptibility and immunological disturbances (21). Keratinocyte proliferation and psoriatic inflammatory processes are driven by T cells, especially Th17 cells, and mediated by various cytokines including IL-17, IL-23, and tumour necrosis factor (TNF). When IL-23 binds to the IL-23 receptor, a heterodimer of JAK2 and TYK2 is involved in signal transduction that promotes inflammation.

Although approximately 70–90% of the patients experience pruritus and at least 30% of them have generalized pruritus, itch in psoriasis has traditionally drawn less

attention than that in AD (22). The mechanism of itch in psoriasis needs further investigation, but the importance of impaired innervations and neuropeptide imbalances in psoriatic skin are most mentioned (23). The pruritogens and itch mediators involved in psoriasis include substance P, calcitonin gene-related peptide, IL-2, E-selectin, and vasoactive intestinal peptide (23). Histamine does not play a significant role in pruritus in psoriasis, and therefore oral antihistamines are not effective.

Efficacy of JAK inhibitors in itch. Several randomized controlled trials of JAK inhibitors for psoriasis have been conducted and the results of itch reduction are summarized in **Table II**. For topical tofacitinib, significant improvements in itch were maintained in patients treated with 2% twice daily, 1% twice daily, and 2% once daily regimens from week 2 through week 12, except for weeks 8 and 12 in the 2% once daily group (24). Topical ruxolitinib showed safety and clinical effectiveness in the treatment of psoriasis through a proof-of-concept study and open-label non-randomized phase II clinical trial, but there were no data on pruritus (25). Similarly, there are few results on itch reduction in psoriasis by oral JAK inhibitors. Oral tofacitinib has been shown to improve the Psoriatic Area and Severity Index (PASI) score, but no assessment of pruritus was performed. Oral solcitinib showed a dose-dependent decrease in visual analogue scale itch scores, but no data were provided (28). Interest in the use of JAK inhibitors for psoriasis seems to have shifted from others to TYK2 inhibitors. Deucravacitinib recently completed 2 large phase III trials (29), and PF-06826647 completed a phase II trial, and the study results are awaiting publication.

In general, however, JAK inhibitors have failed to show superiority in disease control over existing biologics (e.g. improvement in PASI scores) and pruritus in psoriasis is not an outcome of interest compared with AD. Thus, limited data are available.

Table II. Janus kinase (JAK) inhibitors for itch relief in psoriasis

JAK inhibitor	Study type Trial identifier	Patients *n*	Duration (weeks)	Regimen	Initial itch NRS Mean±SD	Variable	Results
Topical							
Tofacitinib (JAK1/3)	Phase IIb NCT01831466 (24)	435 (≥ 18 years)	12	1% QD, BID 2% QD, BID	5.8±2.6 (2% BID) 5.3±2.4 (1% BID) 5.4±2.6 (vehicle BID) 6.0±2.7 (2% QD) 5.7±2.9 (1% QD) 5.4±3.0 (vehicle QD)	NRS point	−2.6 (2% QD), −1.9 (1% QD) vs −1.7 (vehicle QD) at week 2 −3.2 (2% BID), −2.6 (1% BID) vs −1.5 (vehicle BID) at week 2
Oral							
Baricitinib (JAK1/2)	Phase IIb NCT01490632 (26)	238 (≥ 18 years)	12	2 mg QD 4 mg QD 8 mg QD 10 mg QD	No data provided	NRS point	−4.7 (10 mg), −3.8 (8 mg), −3.3 (4 mg), −2.8 (2 mg) vs −1.1 (placebo) at week 12
Abrocitinib (JAK1)	Phase IIb NCT02201524 (27)	59 (18–65 years)	4	200 mg QD, BID 400 mg QD	6.8 (200 mg QD) 7.7 (200 mg BID) 7.2 (400 mg QD) 6.4 (placebo)	NRS point	−6.0 (400 mg QD), −5.3 (200 mg BID), −4.0 (200 mg QD) vs −0.3 (placebo) at week 4
Deucravacitinib (TYK2)	Phase III NCT03624127, NCT03611751 (29)	666, 1020 (≥ 18 years)	52	6 mg QD	No data provided	NRS point	−3.6 (6 mg) vs −0.7 (placebo) at week 16 −3.6 (6 mg) vs −0.5 (placebo) at week 16

BID: twice daily; NRS: numerical rating scale; NRS-point: itch reduction evaluated as a decrease in score; QD: once daily.

Other conditions

Successful treatments using JAK inhibitors for refractory pruritus in various skin diseases have been reported. Some cases are introduced below and in **Table III.**

Chronic pruritus with or without systemic diseases. Chronic pruritus is defined as an itch that persists for longer than 6 weeks. Approximately 15% of the general population is affected, with a higher incidence in elderly people. Various systemic diseases accompany chronic and refractory pruritus. Wang et al. (30) reported that 5 rheumatoid arthritis patients with chronic pruritus who had not responded at all to prior anti-itch therapies, including gabapentin and prednisone, were successfully treated with oral tofacitinib. A 55-year-old male patient with polycythemia vera was completely relieved of itching after 2 months of treatment with oral ruxolitinib (4).

If there is generalized itching lasting longer than 6 weeks without skin lesions or systemic causes of pruritus, such as haematological diseases or chronic kidney diseases, the condition is referred to as CPUO (31). A phase II clinical trial (NCT05038982) evaluating the efficacy of abrocitinib for reducing pruritus in adults with CPUO and prurigo nodularis was recently completed and is awaiting publication of the results (32).

Prurigo nodularis. Prurigo nodularis is a chronic inflammatory disease that presents as multiple, severely pruritic nodules symmetrically distributed on the trunk or extremities. The recalcitrant itch of this disease is not relieved by conventional anti-pruritic therapies. Although the pathogenesis is not fully understood, 1 study reported that STAT 2 and 3 were upregulated in pruritic nodules, as well as the corresponding cytokines Th2, Th17, and Th22 (33). Two clinical trials have been conducted to evaluate the efficacy of JAK inhibitors in prurigo nodularis (32, 34). Several case reports showed that both oral and topical JAK1 inhibitors could be a good choice for treating refractory itch in patients with prurigo nodularis (35, 36).

Lichen planus. Lichen planus is an inflammatory skin disease that manifests as pruritic, purpuric, flat-topped papules. The pathogenesis is not completely known; however, the upregulation of JAK2/STAT1 in keratinocytes and dependent cytokines, such as IFN-γ, seem to play a role (37). The use of topical ruxolitinib for lichen planus was tested in a phase II trial (38), and 1 case report demonstrated that oral tofacitinib dramatically improved pruritus in patients with the disease (39).

Safety and adverse effects

Various adverse effects have been reported in the clinical trials reviewed in this paper and are summarized in **Table IV**. Most of the adverse effects in patients treated with topical JAK inhibitors were mild or moderate in severity, including nasopharyngitis and application site reactions. Increased creatine phosphokinase (CPK) and alanine aminotransferase levels were reported in a few participants, but they were considered unrelated to the treatment (14). For oral agents, CPK elevations with or without recent physical exertion were reported in several participants, some mild and transient, but some led to the discontinuation of the study. A few cases of opportunistic infections, herpes zoster, and cytopaenia (anaemia, neutropaenia, lymphopaenia, and thrombocytopaenia) were also reported. Acne and nausea were the most frequently reported adverse effects of oral JAK inhibitors. A few cases of malignancies and cardiovascular diseases were reported, most of which were unrelated to the study.

Table III. Janus kinase (JAK) inhibitors for itch relief in other diseases

JAK inhibitor	Diseases	Types of study	Patients n	Treatment duration	Regimen	Initial itch NRS Mean±SD	Variable	Results
Tofacitinib (JAK1/3)	Chronic pruritus with rheumatoid arthritis (30)	Case series	5 (65.0±12.4 years)	7.8±4.6 months	Oral 5 mg BID	9.8±0.4	NRS point	All patients responded 0 on the NRS after treatment.
Ruxolitinib (JAK1/2)	Chronic pruritus with polycythemia vera (4)	Case report	1 (55 years)	2 months	Oral 5 mg BID	No data	No data	Complete resolution of itching
Tofacitinib (JAK1/3)	Chronic pruritus including prurigo nodularis, CPUO (35)	Case series	19 (61.5±18.9 years)	No data	Topical 2% cream	7.8±2.2	NRS point NRS-4	NRS 4.47±3.55 after 24 h 68.4% of the patients after 24 h
Tofacitinib (JAK1/3)	Prurigo nodularis (36)	Case report	1 (65 years)	6 weeks	Oral 5 mg BID, QD, EOD for 2 weeks each	10	NRS point	NRS 7 at week 1, 0 at week 6
Abrocitinib (JAK1)	Prurigo nodularis and CPUO (32)	Phase II NCT05038982	20	12 weeks	Oral 200 mg QD	–	NRS point	Awaiting results
INCB054707 (JAK1)	Prurigo nodularis (34)	Phase II NCT05061693	140 (recruiting)	16 weeks	Oral	–	NRS point	–
Ruxolitinib (JAK1/2)	Lichen planus (38)	Phase II NCT03697460	12 (61.1±13.4 years)	8 weeks	Topical 1.5% cream	5.8±3.5	NRS point	NRS 1.3±2.0 at week 4
Tofacitinib (JAK1/3)	Lichen planus (39)	Case report	1 (51 years)	20 weeks	Oral 5 mg BID	10.0	NRS point	NRS 0 at week 12 and week 20

BID: twice daily; CPUO, chronic pruritus of unknown origin; EOD: every other day; NRS: numerical rating scale; NRS-point: itch reduction evaluated as a decrease in score; NRS-4: itch reduction evaluated as the proportion of participants achieving a ≥4-point reduction from baseline; QD: once daily.

Table IV. Adverse effects of Janus kinase (JAK) inhibitors used for itch

JAK inhibitor	Most frequently reported AEs	AEs of special interest
Topical		
Tofacitinib (10, 24, 35) (JAK1/3)	Nasopharyngitis, bronchitis, URI, gastroenteritis, furuncle, contact dermatitis, application site discomfort (pain, pruritus, burning sensation)	No deaths, severe, or serious AEs (except 1 death due to myocardial infarction considered unrelated to the treatment (24))
Ruxolitinib (11, 38) (JAK1/2)	Nasopharyngitis, URI, headache, application site discomfort (pruritus, burning sensation)	Abnormal taste (38) No deaths, severe, or serious AEs
Delgocitinib (12, 13) (JAK1/2/3, TYK2)	Nasopharyngitis, influenza, Kaposi varicelliform eruption, impetigo, acne, gastroenteritis, conjunctivitis, application site folliculitis, application site irritation	No deaths, severe, or serious AEs
Brepocitinib (14) (JAK1, TYK2)	Nasopharyngitis, worsening of AD, erythema, contact dermatitis	No deaths, severe, or serious AEs
Oral		
Baricitinib (15, 26) (JAK1/2)	Nasopharyngitis, URI, bronchitis, sinusitis, gastroenteritis, urinary tract infection, headache, herpes simplex	Herpes zoster, anaemia, lymphopenia, neutropenia, CPK elevation No deaths
Upadacitinib (16, 19) (JAK1)	Acne, URI, nasopharyngitis, conjunctivitis, headache, worsening of AD, CPK elevation	Eczema herpeticum, herpes zoster, anaemia, lymphopenia, neutropaenia, CPK elevation, AST/ALT elevation, Malignancies (skin cancer, breast cancer, gastric cancer; considered unrelated to the treatment (16)) No deaths
Abrocitinib (18, 20, 27) (JAK1)	Nausea, vomiting, nasopharyngitis, URI, headache, acne, folliculitis, conjunctivitis, CPK elevation, abdominal pain, worsening of AD	Herpangina, pneumonia, eczema herpeticum, herpes zoster, thrombocytopaenia, CPK elevation (1 cardiac death due to aortic valve sclerosis and hypertension considered unrelated to the treatment (18))
Deucravacitinib (29, 40) (TYK2)	Nasopharyngitis, URI, headache, diarrhoea, nausea, arthralgia, cough, psoriasis, acne, folliculitis	Herpes zoster, CPK elevation Venous thromboembolic event (considered unrelated to the treatment) Myocardial infarction Malignancies (basal cell carcinoma, malignant sweat gland neoplasm, Hodgkin's disease, breast cancer)

AD: atopic dermatitis; AE: adverse effect; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatine phosphokinase; URI: upper respiratory tract infection.

According to the reference papers, adverse events (regardless of its severity and cause) following upadacitinib 15 mg and 30 mg, were reported in 61.4% and 67.4% of the participants, respectively, compared with 55.8% in the placebo group (16). For abrocitinib 100 mg and 200 mg, the result was 62.7% and 65.8%, respectively, compared with 53.8% in the placebo group (17). For baricitinib 2 mg and 4 mg, the result was 57.7% and 56.0%, respectively, compared with 55.2% in the placebo group (15). Serious adverse effects were reported in 1–4% of the participants in both groups (JAK inhibitors and placebo) (15–17). Based on the results above, upadacitinib and abrocitinib appear to have a slightly higher risk of adverse effects than baricitinib, which correlates with the efficacy of the drug where upadacitinib and abrocitinib seem to have a slightly better efficacy profile compared with baricitinib. However, further studies are needed to accurately compare the safety profile between the JAK inhibitors.

Some JAK inhibitors are currently approved for autoimmune diseases, with warnings about use in elderly people and the potential for the increased incidence of cardiovascular diseases and malignancies. In general, the safety of JAK inhibitors seems to be comparable to that of other biologics, although more data on long-term safety need to be accumulated.

Conclusion

JAK inhibitors have strengths that include rapid therapeutic effects, convenient administration, and dosage flexibility. In particular, JAK inhibitors seem to provide considerable itch reduction (of more than half the baseline numerical scale points) in various dermatological diseases in a relatively short time (generally, a few days) compared with conventional pruritus treatments. JAK inhibitors could be a good option for patients with chronic and refractory pruritus. More data on long-term efficacy and safety are necessary to confirm the impact of JAK inhibitors in treating itch.

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