Review Article

A Literature Review of the Janus Kinase Inhibitors Used in the Treatment of Auto-Immune Dermatological Conditions

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Abstract

The signal transducer and activator of transcription (STAT) families and Janus kinase group (JAK) are important intracellular signalling components that affect more than 50 cytokines and growth elements. JAK inhibitors target distinct receptor-associated kinases, inhibiting the activation of inflammatory signals. With the expanding body of evidence supporting the use of targeted medicines, numerous JAK inhibitors, both topical and systemic, have been tested in the treatment of atopic dermatitis, with varying mechanisms of action, effectiveness, and safety. The efficacy and safety of JAK inhibitors used to treat inflammatory and atopic skin diseases are examined in this review study. Their application in the mentioned fields has been characterized by some excellent clinical responses, but wide variability in responses and some serious and even life-threatening side effects. While JAK inhibitors are now beneficial to many patients, further study is needed to better understand this complicated mechanism to improve treatment outcomes and minimize side effects.

Keywords: Janus kinase, Atopic dermatitis, Inflammatory signals, Topical applications, JAK inhibitors

Introduction

The Janus kinase signal transducer and transcription activator (JAK/STAT) signalling pathway are central to the control of intracellular functions affecting >50 cytokines and growth factors including hormones, interferons (IFN), interleukins (ILs), and colony-stimulating factors (CSF) [1]. Cellular systems controlled or mediated through the JAK/STAT pathways include immune function, inflammation, haematopoiesis, tissue repair, adipogenesis, and apoptosis. Changes in balance or loss of function within these pathways are linked to a range of diseases in humans. JAKs interact without covalent binding to cytokine receptors, to mediate the phosphorylation of tyrosine on receptors, which attracts STAT proteins. Tyrosine-phosphorylated STATs combine into dimers which are then transported to the cell nucleus to regulate specific genes. These dimers exhibit both unique and overlapping effects [1].

The developing understanding of the JAK/STAT pathways has changed perspectives on several complex and difficult to treat human diseases. JAK inhibitors are producing encouraging results in a wide range of diseases, but with wide variability in both patient outcomes and side effects, some of which are serious [2].

The JAK family are receptor-associated tyrosine protein kinases, activated when cytokines bind to their associated receptors, to onward transmit regulatory signals. They consist of four main sub-types; JAK1, JAK2, JAK3, and TYK2. JAK1,2 and TYK2 are found in almost all tissues, whilst JAK3 is predominantly expressed in the lymphatic system, the bone marrow, vascular smooth muscle, and endothelial cells. The therapeutic use of kinase inhibition began with the use of imatinib for the treatment of chronic myelogenous leukemia [3]. By 2014, the USA Food and Drug Administration (FDA) had approved 31 kinase inhibitors for a range of oncology indications [4, 5].

Schwartz describes the inter-relationship between cytokine receptors, where the JAK enzymes are associated with each type of those receptors, which overlap between more than one receptor [2]. Schwartz concluded that gaining a better understanding of the mechanisms, will facilitate better patient therapeutic outcomes. A range of molecules have been developed, many designed *in silico*, aiming to achieve better selectivity for particular JAKs. However, Virtanen describes the complexity of this process, and how in some early trials,

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medications designed for greater selectivity show only similar effects and side effects to those seen with less selective agents [6].

As the use of the JAK inhibitors has progressively moved toward long-term therapy in chronic inflammatory conditions, a further important aspect that emerges relates to the routes of metabolism and elimination. These medications are often used in the treatment of complex patients who are taking multiple medications, so the effect upon medication clearance mechanisms such as the cytochrome P450 enzymes, leading to interactions with other medications becomes problematic with some of these agents. Here, molecules such as baricitinib and filgotinib that have CYP independent elimination pathways may be shown to offer some advantages.

In dermatology, JAK inhibition has been investigated in a range of conditions known to have auto-immune involvement such as psoriasis and atopic dermatitis (AD). These conditions, have been reported to be ameliorated through inhibition of a range of cytokines including combinations of TNF, IL-17,12, and 23 and also IL-23 in isolation [2]. In AD, overexpression of IL-4, 5, and 13 have been noted [2, 7]. With the known association of the JAK signaling system with these cytokines, the inhibitor tofacitinib was investigated in several trials for dermatological conditions. In this review, each of the JAK inhibitors trialled in the treatment of these skin conditions is reviewed.

Materials and Methods

The review was conducted based upon a manual search for emerging evidence on all JAK and TYK2 medications currently used or under research to investigate their future use in auto-immune dermatological conditions, searching particularly for the words AD and psoriasis, as a narrative review.

Narrative Review

Topical Ruxolitinib

Both JAK1 and JAK2 are selectively inhibited by ruxolitinib. The US Food and Drug Administration recently approved its usage in a cream formulation for the topical treatment of mild-to-moderate atopic dermatitis in non-immunocompromised individuals aged 12 and up who are not effectively controlled by conventional topical medications. In the ruxolitinib evaluation in AD studies of topical preparations, 2,631 (study 1) and 618 (study 2) patients were randomized. Using the Investigators Global Assessment (IGA), more patients achieved treatment success with 0.75% ruxolitinib cream and 1.5% ruxolitinib cream compared to placebo assessed at week 8 ($p < 0.0001$). A noticeable decrease in itching was reported after 12 hours of first application versus placebo and infrequent and lower severity of reactions at the application site (<1%) [8].

Ruxolitinib cream 1.5%, applied twice daily, provided the greatest improvement in Eczema Area and Severity Index (EASI) as compared to a medium potency topical corticosteroid, however, in this study it was not compared with a more potent topical corticosteroid [8]. Adverse effects included pruritis and burning sensations at the application site, but their incidence was reduced in the treatment group compared to placebo. A pharmacokinetics study recently reported plasma ruxolitinib concentrations after topical application. Applied over 20% of body surface area it was not found to produce systemic plasma concentrations [8].

Topical Delgocitinib

Delgocitinib exhibits inhibitory effects on all the receptor types in the JAK–linked family plus TYK2 [8]. In Japan, 0.5 percent ointment has been licensed for the treatment of Alzheimer's disease [8-10]. Phase 1 and 2 studies demonstrated the effectiveness of topical delgocitinib in decreasing pruritus on day 1, through the possible down-regulation of the IL-31 pathway. The number of patients with mEASI-50 and mEASI-75 was observed to increase with delgocitinib therapy and continued to increase for the duration of treatment. The efficacy and safety of delgocitinib 0.5% ointment were explored in patients aged ≥16 years (n=158) with moderate to severe AD in Japan. The study showed that after the 4th week of therapy, the change of mean percentage of EASI was 44.3% with delgocitinib compared to 1.7% in the placebo group. The improvement was maintained through to the 24th week [8].

Mild adverse effects were reported in 4.7% of the patients in the treatment group and 1.9% of those in the placebo group. The most commonly reported side effects were; nasopharyngitis, acne, and Kaposi varicelliform eruption. Delgocitinib 0.5% ointment produced improvement in pediatric patients [8]. Japanese patients (2-15 years of age) with AD, randomized as a 1:1:1 ratio, received 0.25% or 0.5% delgocitinib ointment or placebo ointment twice daily for a period of 4 weeks, followed by assessment, then treatment continued for up to 56 weeks. There was a significant change in the EASI score from baseline, in the delgocitinib ointment groups compared to the placebo group. The most reported adverse events were mild and were considered not related to delgocitinib.

Topical Tofacitinib

Patients treated for AD with topical tofacitinib 2% showed significant improvement in EASI, Physician's Global Assessment (PGA), and % Body Surface Affected (BSA) by week 1, and improvements in pruritus were noted by day 2 [11]. The mean percentage of change in EASI score from baseline at week 4 was significantly more ($p < 0{\cdot}001$) using tofacitinib (81·7%) versus control (-29·9%). Significant ($p<0{\cdot}001$) improvements vs. placebo were demonstrated in all outcome measures at week 4 in the tofacitinib group. Improvement in pruritus was also seen. Both treatments and placebo showed similar safety and were well tolerated at the

site of application, with more adverse events documented for placebo vs. tofacitinib [11]. Further analysis has predicted that in a treated patient with BSA ≤50%, 2% tofacitinib ointment systemic concentrations were measured during the treatment of mild-moderate AD and did not exceed the 10% of observed levels during oral tofacitinib therapy patients with plaque psoriasis using 5mg twice daily [12].

Oral Tofacitinib

Tofacitinib is a potent inhibitor of JAK1, JAK2, JAK3, and TYK2 [11]. Oral tofacitinib was administered in a dose of 5 mg once or twice daily in 6 patients, in an open-label study. Their SCORAD decreased significantly by 66.6% from 36.5 to 12.2 across 8 to 29 weeks of treatment, with no significant side effects, but the number of patients was limited, and the study had no control group [11]. Tofacitinib is metabolized by CYP3A4 and CYP2C19, so has the potential for a wide range of drug interactions [2].

Oral Gusacitinib

Gusacitinib inhibits both the JAK and SYK pathways that are under research as an oral medication. In a phase1b trial involving 36 patients, the doses of 20, 40, or 80 mg all achieved EASI-50 in 20% at 20mg, 100% at 40mg and 83% at 80mg. The higher doses were significantly better than the placebo (EASI-50, 22%). Pruritis was reported to be reduced by week 4 of therapy in most patients. The EASI-75 response was 63% and 50% in the 40 mg group and 80 mg/d respectively as compared with 22% in the placebo group [13]. This clinical response was associated with a decline in the levels of the inflammatory cutaneous biomarkers TH2, TH17, and TH22 as well as barrier-related measures (filaggrin [FLG] and CLDN23) [14].

Oral Baricitinib

Baricitinib was designed to selectively inhibit JAK1 and JAK2 with a lesser affinity for JAK3. It was the first approved oral JAK inhibitor licensed for the treatment of adults with moderate to severe AD [15]. Efficacy was demonstrated in a phase II study in which patients also applied topical glucocorticosteroid. After 16 weeks, based on the primary outcome specified; EASI-50, there were significantly better results with a daily dose of 4 mg baricitinib (61%) compared to the placebo group (37%) [16].

The BREEZE-AD1 and BREEZE-AD2 trials randomized adult patients with moderate to severe AD, to receive baricitinib at 1 mg, 2 mg, 4 mg, or placebo over 16 weeks. The primary endpoint studied was the Investigator's Global Assessment (IGA). (In BREEZE-AD1, at 4mg dose 16.8% responded compared to 4.8% for placebo. In BREEZE-AD2 at 2mg, improvement was seen in 13.8%, versus 4.5% for placebo: At 16 weeks, the 4mg dose was also reported to significantly improve the secondary endpoints; quality of life, pain, pruritis, sleep quality and EASI-75/90 [17]. A 2021 meta-analysis combining eight studies concluded a good safety profile and efficacy using a single dose of oral baricitinib 4 mg, as monotherapy or in combination with a topical corticosteroid, starting from the first week of treatment at 4 mg dosage. The most frequently reported side effects were nasopharyngitis, upper respiratory tract infections, the elevation of creatine phosphokinase (CPK), and headache [18]. Baricitinib provided oral availability, the prompt onset of action, and significant improvement, with rapid relief of pruritis, having CYP independent clearance, and fewer medication interactions. This may provide an advantageous approach for the treatment of AD.

Oral Abrocitinib

Abrocitinib is JAK1 selective [19]. In phase 3, a double-blind, randomized trial, abrocitinib at doses of 200 mg or 100 mg once daily in adults with moderate-to-severe AD was evaluated and compared to the monoclonal antibody dupilumab and placebo for both efficacy and safety. Signs and symptoms of AD at both doses of abrocitinib and dupilumab were significantly reduced, compared to placebo at week 12. The improved IGA response at week 12 was observed in 48.4%, 36.6%, and 36.5% of patients on abrocitinib doses of 200-mg, and 100 mg and those receiving dupilumab respectively, compared to 14.0% in the placebo group. An EASI-75 response at week 12 was observed in 70.3%, 58.7%, 58.1%, and 27.1%, respectively. On the assessment of pruritis at week 2, it was found that the 200-mg dose of abrocitinib was superior to all other groups. In terms of side effects, nausea and acne were most frequent. Patients in this study were receiving background therapy with other topical medications [20]. A recent systematic review concluded that both 100 mg and 200 mg were associated with a greater IGA response, more responders at EASI-50%, EASI-75%, and EASI 90%, with the 200mg dose being superior to 100mg. More participants in the aprocitinib group showed improvement in a numeric rating scale (NRS), dermatology life quality index (DLQI), or the Children's Dermatology Life Quality Index (CDLQI) compared to placebo, with no difference between the two abrocitinib doses. Both doses were associated with lower SCORAD index, % BSA, pruritus and symptoms assessment for atopic dermatitis index (PSAAD), and patients oriented eczema measure (POEM) than placebo [21].

The prevalence of side effects, specifically nausea and headache, was higher with a 200 mg dose than with 100 mg. In the 200-mg group, the adverse effects reported were thrombocytopaenia (n=5), herpes zoster (n=2) and decreased platelet count (n=2), whilst in the 100-mg group, eczema herpeticum (n=2), herpangina (n=1) and pneumonia (n=1).

A double-blind, randomized placebo-controlled trial in parallel groups involved the administration of once-daily treatment with 200 mg or 100 mg of oral abrocitinib for 12 weeks. It was found that the signs and symptoms of AD significantly improved. The percentage of improvement on the IGA scale was 44.5%, and 27.8% for those receiving 200 mg and 100 mg of abrocitinib respectively this is significantly

more than the IGA scale of which 6.3% for those receiving placebo. Moreover, reductions in the EASI were 82.6% using abrocitinib 200mg, 59.0% using abrocitinib 100mg, and 35.2% for those receiving placebo [19].

Oral Upadacitinib

The JAK1 inhibitor upadacitinib is licensed for the treatment of rheumatoid arthritis [22]. In the safety and efficacy phase 2b study (n=167), patients were randomized to receive upadacitinib 7.5 mg, 15 mg, and 30 mg daily, or a placebo. The basis of comparison was the change in EASI score between baseline and 16 weeks. All evaluated doses of upadacitinib demonstrated improvement compared to placebo; (39% for 7.5 mg, 62% for 15 mg, 74% for 30 mg, 62% for 15mg and 39% for 7.5mg compared to. 23% for placebo). In 24% of the patients treated with 30 mg/d, there was an EASI-100 response, which was not seen in any of those treated with a placebo [23]. The upadacitinib Measure Up 1 and 2 studies were designed to assess safety and efficacy in patients with moderate to severe AD. At 16 weeks, using a dose of 15mg daily, in Measure Up 1, 281 patients (70%) and in Measure Up, 2 276 patients (60%) had achieved EASI-75. In those receiving 30mg, EASI-75 was achieved by 285 patients (80%) in Measure Up 1 and by 282 (73%) in Measure Up 2. In the placebo groups, it was achieved by 16% and 13% Comparing IGA0/1, as an outcome, at 15mg the figures were 48% (1) and 39% (2), and at 30mg 62% (1) and 52% (2) whilst in the placebo group the figures were 8% (1) and 5% (2) All recipients of upadacitinib reported a rapid reduction in pruritis, which was still maintained at 16 weeks. Side effects reported included upper respiratory tract infection, headache, nasopharyngitis, and acne. Monotherapy with upadacitinib, therefore, appears to offer a well-tolerated and effective treatment option in moderate-to-severe AD [24].

Combined with topical corticosteroids, upadacitinib dosed at 15mg and 30mg proved superior to control (topical corticosteroids alone) with a favorable side effect profile [25]. In a randomized, double-blinded, trial of upadacitinib vs dupilumab in 692 patients with moderate-to-severe AD, at week 16, the patients receiving upadacitinib who achieved EASI-75 were 71.0 % which was superior to dupilumab (61.1%). Secondary endpoints were also achieved significantly more with upadacitinib than dupilumab, including improvement in the worst pruritus NRS as early as week 1 ($p < .001$), EASI-75 as early as week 2 ($p < .001$), and EASI-100 at week 16 ($p < .001$) [26]. However, the upadacitinib group demonstrated higher rates of herpes zoster eruptions, eczema herpeticum, and severe bacterial infections, compared to higher rates of injection site reactions and conjunctivitis in the dupilumab group.

In Other Conditions

For tofacitinib, using the Psoriasis Area and Severity Index (PASI) significant improvement at oral doses of 5mg and 10 mg twice daily were reported [27, 28], but only 10mg twice daily was shown non-inferior to etanercept, the standard of care at the time of the trial [29]. Baricitinib has also been evaluated and was also found effective at 8mg and 10mg daily, the higher end of the dosage range [30]. The range of side effects reported, and the drug interactions, particularly for tofacitinib which like many other medications is metabolized by both CYP3A4 and CYP2C19, have focussed attention on the possibility of using topical formulations. Conversely, baricitinib has CYP independent metabolism and is predominantly renally excreted [2].

In dermatological conditions, the topical application offers the potential to avoid systemic side effects and interactions. In trials, both tofacitinib and ruxolitinib applied topically improved psoriasis to a greater extent than other approved therapies but the improvement was not sustained on discontinuation. There was minimal absorption and no reported systemic effects [31, 32].

Tofacitinib ointment was effective, showing after 4 weeks of treatment, 80% improvement in EASI [11]. It has been suggested that JAK inhibition might be particularly effective in reducing pruritis and scratching [33]. JAK inhibition has also been investigated in alopecia areata, another immune-medicated condition where overexpression of inflammatory cytokines has been demonstrated. One mechanism involved in the condition is an expression of genes regulated through IFNγ. This signals through JAK1 and JAK2 [34]. Studies indicate that baricitinib, ruxolitinib, and tofacitinib are effective in autoimmune alopecia, but that the efficacy of tofacitinib may decrease with time, and in all cases, the condition returns on therapy withdrawal [34-38]. Craiglow demonstrated the efficacy of topical application of ruxolitinib in alopecia universalis [39]. That JAK inhibition appears to lead to hair re-growth is of particular interest [40]. Tofacitinib has also been reported to improve vitiligo [41], palmoplantar pustulosis [42], and idiopathic erythema multiforme [43].

Conclusion

This review summarises current published evidence for JAK inhibitors used in AD and other dermatological conditions. All the agents administered orally; abrocitinib, baricitinib, gusacitinib, and upadacitinib and topical delgocitinib, ruxolitinib, and tofacitinib, improved skin outcomes when compared to placebo, with reported improvement of itch, sleep, and quality of life. JAK inhibitors are showing acceptable efficacy for some patients in the treatment of AD with a mostly tolerable side effect profile. Although most adverse events (AEs) observed in the trials were of mild to moderate severity, trials evaluating JAK inhibitors over longer durations of therapy in other indications like arthritis suggest an increased risk of serious AEs, such as reactivation of herpes zoster, malignancy, thromboembolic events, and cardiovascular events [44-46]. Further prospective studies, particularly including the use in pediatric patients and with long-term follow-up and detailed evaluation of cost-effectiveness are required to inform clinical decisions and future guidelines.

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