Pharmacodynamics of Janus kinase inhibitors for the treatment of atopic dermatitis

Pharmacodynamics of Janus kinase inhibitors for the treatment of atopic dermatitis

Journal:	*Expert Opinion On Drug Metabolism and Toxicology*
Manuscript ID	EOMT-2022--0027.R1
Manuscript Type:	Review (Invited)
Keywords:	abrocitinib, atopic dermatitis, baricitinib, delgocitinib, pharmacodynamics, ruxolitinib, upadacitinib

Pharmacodynamics of Janus kinase inhibitors for the treatment of atopic dermatitis

Laura Calabrese[1,2], Andrea Chiricozzi[1,2,*], Clara De Simone[1,2], Barbara Fossati[1], Alessandra D'Amore[1] and Ketty Peris[1,2]

[1] UOC di Dermatologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy

[2] Dermatologia, Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy

***Corresponding author:**

Andrea Chiricozzi

Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome

Tel.: +39-339.5668320

Fax: +39-0761-571321

E-mail: chiricozziandrea@gmail.com

Abstract

Introduction: Atopic dermatitis (AD) is the most common inflammatory skin disorder. Despite the high disease burden, the therapeutic options are limited and their efficacy in controlling AD might be partially satisfactory.

Areas Covered: Most of the key mediators in AD pathogenesis act through the JAK/STAT signaling pathway, which represents a valid therapeutic target. The first generation of JAK inhibitors, namely tofacitinib and ruxolitinib, inhibit multiple JAKs, whereas newer JAK inhibitors show more selective inhibitory effects for specific JAKs. The aim of this review was to discuss the role of the JAK/STAT pathway in AD and its inhibition, with a special focus on pharmacodynamic properties. We checked the English-language literature, published in the last 15 years using PubMed, Google Scholar, and Scopus.

Expert opinion: JAK inhibitors have different selectivity for various JAK molecules, which influences their pharmacodynamics, efficacy and safety profile. Since many key cytokines in AD signal through JAK1, and as the selective JAK1 inhibition may be effective, avoiding the concomitant inhibition of JAK2- and JAK3-dependent pathways could be associated with additional safety issues. Therefore, selective JAK1 inhibitors may represent promising therapeutic agents for AD, as they might prevent off-target effects of JAK inhibitors, especially related to the hematologic profile.

Keywords: abrocitinib, atopic dermatitis, baricitinib, delgocitinib, pharmacodynamics, ruxolitinib, upadacitinib

Article highlights:

- JAK inhibitors are small molecules targeting one or more members of the JAK family. Blocking these intracellular transcription factors, JAK inhibitors can exert multiple anti-inflammatory, immunosuppressive and antiproliferative properties.
- JAK inhibitors are traditionally classified into two classes: the first-generation JAK inhibitors (pan-JAKs), which inhibit multiple JAKs and newer JAK inhibitors, with a more selective mode-of-action.
- The different pharmacodynamic properties of JAK inhibitors and, particularly, their different selectivity for JAK isoforms have important implications in terms of efficacy and safety profile of each pharmaceutical agent.
- Several JAK inhibitors have already proven efficacy for the treatment of atopic dermatitis. Some of these agents, such as ruxolitinib and delgocitinib, are applied topically, whereas others are administered orally, namely baricitinib, upadacitinib and abrocitinib, or both (i.e., tofacitinib).
- As many key cytokines in atopic dermatitis signal through JAK1 for signal transmission, selective JAK1 inhibitors, rather than pan-JAKs or JAK1/2 inhibitors, avoid useless inhibition of other signaling pathways, obtaining high efficacy for AD treatment and a more favorable safety profile.
- Selective JAK1 inhibitors, such as upadacitinib and abrocitinib, may represent promising therapeutic agents for the treatment of atopic dermatitis in the near future.

1. Introduction

Atopic dermatitis (AD) is a common immune-mediated skin disease with a long-lasting course and a multifactorial pathogenesis. It affects an increasing number of patients, with a worldwide prevalence ranging from 3% to 10% in adults and up to 25% in childhood [1].

The disease is clinically characterized by itchy eczematous lesions primarily involving flexural areas, face, neck and distal extremities.

The pathophysiology of AD is yet to be fully elucidated, although an integrated interplay between genetic and environmental factors contributing to epidermal barrier disruption, commensal skin microbiota dysbiosis, alterations in immune responses, causing the disease occurrence and/or exacerbation, is known [2]. Extra-cutaneous manifestations of atopy may include food allergies, asthma, conjunctivitis, and rhinitis that, similarly to AD, are immunologically characterized by an aberrant activation of type 2 inflammation. Family history of atopy conditions represents one of the strongest risk factors for AD, confirming the pathogenic relevance of the genetic predisposition [3]. In particular, the genetic susceptibility consists of mutations of genes encoding for keratinocyte differentiation proteins, such as filaggrin (*FLG*) or loricrin (*LOR*) [4], and type 2 inflammatory mediators, including IL-4 and IL-13 [5].

Furthermore, the role of environmental factors in AD onset has long been discussed. The main risk factors encompass the urban setting, as well as low ultraviolet light exposure or dry climatic conditions. In addition, low exposure to infectious agents in childhood is thought to increase susceptibility to atopic diseases (hygiene hypothesis) [6].

Skin manifestations may be commonly associated with persistent and severe pruritus, as well as sleep disturbances causing detrimental impact on patients' quality of life, influencing both social and emotional functioning, and frequently impairing work activity and social isolation [7]. The localization in sensitive areas such as face, neck, hands and genitals can represent an additional aggravating factor for stigmatization and social isolation. Despite the high burden of the disease, the available therapeutic options for AD are limited and their efficacy in controlling the disease is partially satisfactory. Thereby, therapeutic needs for a consistent proportion of AD patients are still unmet.

Better knowledge of the immune pathways involved in AD pathogenesis led to the identification of new targets and the development of therapeutic agents blocking either soluble cytokines, their receptors, or intracellular signal transducers.

2. Literature search

We checked PubMed, Google Scholar, and Scopus for the following key words: “Atopic Dermatitis” “JAK inhibitors,” “JAK”, “baricitinib”, “upadacitinib”, “abrocitinib”, “ruxolitinib,”, “delgocitinib”, “tofacitinib”, “Janus kinase”, “JAK-STAT”, “pharmacodynamics”, within a timefrom ranging from March 2007 to February 2022. Details on ongoing trials and preliminary results from trials testing oral and topical JAK inhibitors in AD were searched on Clinicaltrial.gov.

3. Immune pathogenesis of AD

AD has been traditionally considered a T helper (Th) 2-mediated disorder, however the immune profile of the disease is far more complex and has been recently expanded to type 2 inflammation and other inflammatory pathways, including Th22, Th17, Th9, and Th1. that contribute to AD pathogenesis, albeit at different strength [8]. Type 2 inflammation includes both innate (i.e., innate lymphoid cells [ILC]2, mast cells, eosinophils) and adaptive (i.e., Th2, T cytotoxic 2) immune cells producing IL-13, IL-4, IL-5, and/or IL-31. These immune cells can be recruited and activated by chemokines deriving from keratinocytes and other tissue cells [9-11].

The result of the immune cell infiltration is an overall increase of type 2 cytokines that result pathogenically relevant because *(i)* they induce and maintain skin inflammation; *(ii)* they stimulate IgE class switching in plasma cells [12]; *(iii)* they impair keratinocyte differentiation and epidermal barrier functionality; *(iv)* they mediate itch sensation [13,14].

While the acute stages of the disease are featured by a predominant Th2 microenvironment, the progression to the chronic phases is accompanied by a gradual up-regulation of Th1, Th17 and Th22-mediated responses, which also have been described as relevant in certain sub-populations of AD patients, particularly in children and in Asian subjects [15,16].

Most of the soluble mediators involved in the pathogenesis of AD exert their effects upon binding to specific transmembrane receptor with subsequent initiation of the intracellular signaling through the Janus kinases (JAK)/signal transducer and activator of transcription (STAT) pathway.

3.1 JAK/STAT signaling pathway in AD

The JAK/STAT pathway is a paradigm of receptor-mediated signal transduction, involved in several key biological processes, including cell proliferation, differentiation, apoptosis, and immune regulation (Figure 1)

JAK family consists of four cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) [17], while STAT members (STATs) are represented by seven isoforms: STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6 [18].

More than 50 soluble mediators signal through JAK-STAT pathway [19]. Cytokine binding to receptor subunits and their consequent dimerization, activate JAKs with the phosphorylation of the intracellular receptor domain, creating a docking site for STATs [20]. STATs contain a specific SH2 (src-homology 2), phosphotyrosine-binding domain, which can regulate multiple signaling pathways, traslocating into the nucleus and acting as transcription factors [21,22]. Because of its role in the regulation of a wide number of immune functions [23], the JAK/STAT pathway has been investigated in many chronic inflammatory skin diseases and its therapeutic inhibition resulted therapeutically successful in some of these, such as AD, psoriasis, vitiligo, and alopecia areata [24]. Many of the key cytokines involved in AD pathogenesis, such as IL-4, IL-13, IL-31 and TSLP, exert their functions through activation of the JAK/STAT pathway [25-29].

4. JAK inhibitors in AD

JAK inhibitors are small molecules targeting one or more members of the JAK family. Blocking these intracellular transcription factors, JAK inhibitors can exert multiple anti-inflammatory, immunosuppressive and antiproliferative properties.

Tofacitinib and ruxolitinib, inhibits multiple JAKs, whereas newer JAK inhibitors show a more selective spectrum of action blocking a narrower range of cytokine-mediated signals.

Several JAK inhibitors have been recently developed and are currently under investigation for the treatment of AD. Some of these agents are applied topically, others are administered orally, or both (Table 1).

4.1 Oral JAK inhibitors

4.1.1 Baricitinib

Baricitinib is an orally administered small molecule, representing a selective inhibitor of JAK1 and JAK2. The drug received its first approval for the treatment of moderate to severe rheumatoid arthritis in 2017 [30]. Recently, the drug was approved in Europe and Japan, but not in US, for moderate-to-severe AD in adulthood, at both 4 and 2 mg oral daily dosage [31,32].

Baricitinib selectively inhibits both JAK1 and JAK2 tyrosine kinases, with an [half-maximal inhibitory concentration (IC_{50}) of 5.9 and 5.7 nmol/L, respectively. Albeit to a lesser extent, it also exerts inhibitory activity on TYK2 and JAK3, (IC_{50} of 53 and ≃560 nmol/L, respectively) [33].

Through JAK1 and JAK2 inhibition, baricitinib suppresses Th2 cytokines, such as IL-4, IL-5, and IL-13, and IL-31, which are key cytokines in the pathophysiology of AD, but it also interferes with the signal transduction of IL-6, IL-12, IL-20, IL-22, IL-23, and interferon (IFN)-γ.

In *in vitro* assays, baricitinib has proven to modulate both the innate and the adaptive immune system by inhibiting both Th1 and Th17 differentiation, as well as IL-6-induced phosphorylation of STAT1 and STAT3 [34].

In a human skin equivalent model stimulated with Th2-signature cytokines (IL-4, IL-13, IL-31), baricitinib reduced pathological changes associated with AD (including keratinocyte STAT3 expression), and increased the expression of FLG [35].

Furthermore, in lesional AD skin, baricitinib reduced phosphorylated STAT3 (pSTAT3) expression in epidermal keratinocytes at different time points, which reflected a clinical improvement of AD lesions [36].

Two phase I studies were conducted to assess pharmacokinetics and pharmacodynamics properties of baricitinib at single or multiple ascending doses in healthy volunteers.

Baricitinib oral administration was associated with an inhibition of IL-6-induced STAT3 phosphorylation in whole blood in a dose- and time-dependent manner, with maximal inhibition occurring 1-2 hours after dosing, and restoration of baseline STAT3 phosphorylation by 16–24 hours from baricitinib administration. Additionally, a decrease in the absolute neutrophilic count (ANC) in a dose-related manner was reported, with a peak effect in 8 hours and a restoration of baseline values, 12–24 hours post-dose, potentially explained by a neutrophil margination effect. Conversely, absolute lymphocytic count (ALC) increased, with a peak effect in 6 hours after dosing, and reduced to normal values by 24 hours after dosing [37].

4.1.2 Upadacitinib

Upadacitinib (ABT-494) is an orally administered selective JAK1 inhibitor, approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and AD [38].

Upadacitinib is a reversible ATP competitive inhibitor with a much higher selectivity for JAK1 compared to JAK2, JAK3 or TYK2 (IC_{50} 0.045, 0.109, 2.1 and 4.7 μmol/L) [39,40]. In vitro, the drug potently inhibited cytokine signaling associated with JAK1 inflammatory cascades, such as IL-6 and IFNγ. Conversely, upadacitinib exerted minimal effects on cytokine signaling involving JAK2, such as erythropoietin receptor signaling, essential for hematopoiesis, and JAK3, such as IL-15 signaling, important for NK cell homeostasis.

Assessing the suppression of STAT phosphorylation, upadacitinib showed potent inhibitory activity on the signal mediated by four JAK1-dependent cytokines, namely IL-6, oncostatin M, IL-2, and IFNγ. The inhibition of these cytokine-mediated signals was about 60-fold stronger than the effects on erythropoietin signaling, which is solely dependent on JAK2 [40]. This strong suppression was also confirmed by measuring IL-6 signal inhibition in human blood cells: the IC_{50} values for upadacitinib were 0.207 μM in the CD3+ T-cell population, and 0.078 μM in the CD14+ monocytic population [40].

In a study conducted on healthy volunteers, upadacitinib suppressed STAT3 and STAT5 phosporylation, induced by IL-6 and IL-7, respectively, in a dose- and concentration-dependent manner [41] . In RA patients, a transient reduction of ALC was reported during treatment with upadacitinib.

Further, an exposure-response study on healthy individuals demonstrated a lack of effect of upadacitinib on the QT interval [42].

Pharmacodynamic properties of upadacitinib were also assessed in a phase IIb study on patients with AD. The drug was administered orally at the dosage of 15 or 30 mg daily and it was responsible of a significant dose-dependent amelioration of epidermal hyperplasia and cutaneous inflammation. A reduction of epidermal thickness, K16 immunoreactivity and Ki67 cell counts was reported, as well as the decrease in the number of dendritic cells (CD11c+ and FcεR1+) and CD3+ T cells compared to placebo. These histological changes together with a significant reduction of absolute eosinophil counts (AEC) were related to clinical improvement [43-44]. Notably, no statistically significant difference in antigen-specifc IgE levels was detected in the upadacitinib group compared to placebo [44].

4.1.3 Abrocitinib

Abrocitinib (PF-04965842) is an orally administered, selective JAK1 inhibitor which has recently received EMA and FDA approval for the treatment of adults with moderate-to-severe AD [45].

It demonstrated a strong selectivity for JAK1 over the other three JAK isoforms in biochemical assays: JAK2 (28-fold), JAK3 (> 340-fold) and tyrosine kinase 2 (TYK2, 43-fold). In cellular assays, it preferentially inhibits cytokine-induced STAT phosphorylation dependent on JAK1, sparing signaling induced by JAK2/JAK2, or JAK2/TYK2 pairs [46].

A phase I, first-in-human, dose-escalation study was conducted to evaluate pharmacokinetics and pharmacodynamics properties of abrocitinib in healthy subjects. Decreases from baseline in neutrophil counts from day 4 through day 10 were reported with abrocitinib 100 mg and 200 mg twice daily, which quickly recovered to the baseline levels following treatment interruption. Decrease in reticulocyte cell count was also described, as well as the decrease in mean platelet volume and the increase in lymphocyte counts, none of which were considered clinically relevant [47].

In patients with AD, treatment with abrocitinib was associated with dose-dependent reduction in serum biomarkers of inflammation (IL-31, IL-22, eosinophil count, thymus and activation-regulated chemokine [TARC]). The suppression of JAK1 signalling was demonstrated by reduction of NK cell count and IFNγ-induced protein 10 (IP-10). These changes were reversible after treatment discontinuation. Mean ALC increased by 2 weeks after starting treatment with abrocitinib and returned to baseline levels after 9 months of treatment. However, most patients maintained an ALC within the reference range. In addition, treatment with abrocitinib was associated with a dose-related increase in B cell count and a dose-related decrease in NK cell count [46].

A reduced platelet count was detected in patients treated with both 200mg and 100mg abrocitinib, although not clinically relevant, with the exception of one patient in the 200 mg abrocitinib group. The maximum reduction was seen at week 4, with a gradual return to normal levels, thereafter [48]. .

Based on these results, a kinetic-pharmacodynamic model of platelet time course was elaborated, to quantify and to predict the relationship between drug dose and its effect on platelet counts. Based on this model, the risk of a higher-grade thrombocytopenia decreased by almost 50% after the first 4 weeks of abrocitinib treatment and remained steady until the end of treatment. Furthermore, treatment with abrocitinib 100 and 200 mg, over a 12-week

treatment period, was associated with an expected incidence rate of grade ≥ 2 thrombocytopenia (≤ 75,000 platelets/uL), of 0% and 2.7%, respectively [49] .

4.2 Topical JAK inhibitors

4.2.1 Ruxolitinib

Ruxolitinib is a first-generation inhibitor of JAK1/2, FDA-approved at different oral dosages for the treatment of myelofibrosis, polycythaemia vera and acute graft-versus-host disease [50].

Recently, 1.5% ruxolitinib cream, applied twice daily, received FDA indication for the short-term (8 weeks) and non-continuous treatment of mild to moderate AD in non-immunocompromised patients (>12 years of age) who resulted not adequately treated with other topical therapies [51].

Ruxolitinib potently inhibits JAK1 and JAK2 inhibitor with a IC_{50} for JAK1/2 < 5 nM, and modest selectivity against TYK2 and JAK3 [IC_{50} for JAK3 resulted > 400 nM], and the consequent suppression of proinflammatory activity regulated by several cytokines, such as IL-23 and interferon (IFN)-γ [52,53].

The efficacy of ruxolitinib cream was demonstrated in experimental models of dermatitis. For instance, in murine models of TSLP-induced dermatitis, ruxolitinib cream has proven efficacy in ameliorating symptoms by modulating the expression of genes involved in JAK-STAT signaling pathway, including IL-33, IL-4Rα, IL-7R, JAK1, JAK3, STAT1, STAT3, STAT5A/B, and STAT6 [54]. Administration of ruxolitinib cream dose-dependently reduced ear swelling and lessened immune cell infiltrates, namely Th2 and Th1 cells, at the draining auricular lymph nodes [54].

In another AD murine model, topical administration of ruxolitinib cream decreased STAT3 phosphorylation and subsequently oedema, lymphocyte infiltration and keratinocytes proliferation, as well as suppressed tissue inflammation induced by intradermal IL-23 and TSLP stimulation [55].

Furthermore, in a 28-day toxicology study performed in Gottingen minipigs, topical ruxolitinib was well tolerated and did not cause any clinical or histopathological alteration. Noteworthy, no epidermal atrophy was reported (more likely associated with topical application of steroids) [55]. These results were confirmed by another experiment in which ruxolitinib cream (up to 1.5%) applied twice daily for up to 9 months in Gottingen minipigs was not found to be associated with any adverse effect [52].

4.2.2 Delgocitinib

Delgocitinib (JTE-052) is a first-generation topical pan-JAKs inhibitor (JAK1/2/3 and Tyk2 inhibitor), that is approved by the Japanese authorities at the formulation of 0.5% and 0.25% ointment for the treatment of AD [56,57].

Delgocitinib pharmacodynamics was assessed in several studies. In vitro enzymatic assays showed marked inhibitory activity on all JAK isoforms, in an ATP-competitive manner, with IC_{50} values of 2.8, 2.6, 13, and 58 nM for JAK1, JAK2, JAK3, and Tyk2, respectively [58].

In vitro, delgocitinib reduced the activation of T cells, B cells, monocytes and mast cells [38], inhibiting the expression of IL-2, IL-6, IL-23, granulocyte-macrophage colony-stimulating factor (GM-CSF) and IFN-α signalling, as well as the production of Th1-, Th2- and Th17-derived cytokines [59]. Delgocitinib effects on keratinocyte differentiation and skin barrier function were investigated in a human skin equivalent model, showing restauration of FLG and LOR mRNA expression levels. in a dose-dependent manner and the inhibition IL-4/-13-induced STAT3 phosphorylation [60].

Furthermore, topical administration of the JAK inhibitor improved skin barrier function through an increased production of FLG and Natural Moisturizing Factor (NMF) in murine models of AD as well as in immunocompromised mice grafted with human skin [60].

In another study, topical application of 0.3% or 3% delgocitinib ointment ameliorated hapten-induced chronic dermatitis in AD mice models and reduced the severity of the histopathological changes in a dose-dependent manner, more effectively than tacrolimus ointment. Of note, delgocitinib ointment did not cause skin atrophy [59].

Finally, a phase I study (QBX1-1) on healthy volunteers evaluated safety and tolerability of delgocitinib, through photo-testing and patch-testing. AEs were all mild in severity and high tolerability of both 0.3% and 3% delgocitinib ointment was reported [61].

4.2.3 Tofacitinib

Tofacitinib is a first-generation JAK inhibitor interfering with all JAKs but preferentially with JAK1 and JAK3 [62,63]. Its oral formulation at 5 mg twice daily, was first approved for the treatment of moderate-to-severe rheumatoid arthritis (RA), in November 2012 [64].

Subsequently, the drug was approved for the treatment of psoriatic arthritis, ulcerative colitis, and juvenile idiopathic arthritis, thereafter.

In vitro cellular assays showed potent inhibitory effects on both JAK1 and JAK3 signaling, with 5-100-fold selectivity over JAK2 [65]. A preclinical study revealed a significant reduction of dendritic cell migration obtained in a mice model of allergic dermatitis using topical application of tofacitinib 0.1% [66]. In addition, significantly lower levels of IL-1β, IL-4, IL-6, TARC, IL-31, TNFα, and TSLP were detected in the tofacitinib-treated mice, compared to mice treated with vehicle [66]. Overall, both scratching behavior and ear thickness in the topically tofacitinib-treated mice were significantly reduced. Conversely, the efficacy of oral tofacitinib was limited to a significant reduction of mice scratching behavior [66].

5. Conclusion

Several key inflammatory cytokines, involved in the pathogenesis of AD, signal through the JAK-STAT pathway, supporting the use of JAK inhibitors for the treatment of AD. This class of drugs comprises several agents that differ from each other. This heterogeneity mainly consists of a different target selectivity, a different ability to inhibit the various JAKs isoforms, affecting pharmacodynamics, efficacy and safety. As these drugs are able to block numerous mediators involved in many aspects of host defense, hematopoiesis, metabolism, cell growth, and cell differentiation, they might interfere with the activity of multiple cell lines, and thus various biological processes. Therefore, second generation JAK inhibitors with putative increased selectivity against JAK1, such as upadacitinib and abrocitinib, might potentially maintain elevated efficacy and limiting warning signals.

6. Expert opinion

The large pharmacological class of JAK inhibitors is constantly expanding, and a consistent proportion of them has been developed and tested for the treatment of AD, in topical and oral formulations.

Among topical JAK inhibitors, tofacitinib, ruxolitinib and delgocitinib are in the most advanced phases of development for the treatment of mild-to-moderate AD while oral JAK inhibitors resulted effective in treating moderate-to-severe AD [67-73]. Nevertheless, it is important to highlight the different selectivity of various JAK inhibitors, which influences pharmacodynamics, efficacy, and safety [74]. In addition, efficacy as well as safety might be also affected by patient genetics [75]. In another inflammatory skin disorder, such as

psoriasis, pharmacogenetic studies provided insights about treatment response and/or toxicity to TNF-α, p40IL12/IL23, and IL-17 inhibitors, cyclosporine and methotrexate [76-83]. Pharmacogenetics has not been investigated for JAK inhibitors, but it might represent a valid tool contributing to the most appropriate drug selection for a patient-tailored pharmacological approach.

This evidence could be even more relevant considering that findings derived from clinical trials and evaluating the use of oral JAK inhibitors in immune-mediated disorders, such as RA or psoriasis, have arisen safety concerns, suggesting a potentially increased risk of infections, venous thromboembolism (VTE), and malignancies, which could be theoretically associated with the mode of action of this class of drugs [84].

For example, JAK2 homodimers are implicated in signaling via erythropoietin, thrombopoietin (TPO), and GM-CSF, therefore JAK2 inhibition might theoretically contribute to neutropenia, anemia, and alterations in platelet count, which indeed have been reported during administration of baricitinib [85-88]. The JAK2 role in myelopoiesis and platelet production could represent the biological basis for the link between JAK inhibitor and VTE. Changes in platelet counts, in particular their increase, are thought to be determined by the JAK2 inhibition, interfering with TPO uptake and degradation [89].

On the contrary, the use of JAK1 inhibitors were associated with early, dose-dependent, but transient decrease in platelet count [90].

Among other hematologic abnormalities, neutrophil reduction was reported during upadacitinib administration in AD clinical trials, likely dependent on JAK 1/2 transphosphorylation [91,92].

Furthermore, acne, viral reactivation and opportunistic infections are AEs associated with JAK inhibitors [73,91,92]. Most of the infections are related to herpes viruses that are favored by JAK1 inhibition blocking type 1 and type 2 IFN-mediated signals, together with cytokines binding to the gamma chain of the IL-2R, which is important in lymphocyte development and activation [93-95]. On the other hand, the signaling of certain cytokines (i.e., IL-12 and IL-23) protecting against opportunistic infections, is expected to be preserved by JAK1-selective inhibitors as it is dependent on JAK2/TYK2 [96,97].

The potential marketization of a new class of topical agents could be of great interest for physicians because current topical therapies are limited to corticosteroids and calcineurin inhibitors, albeit the majority of patients suffers from mild or mild-to-moderate forms of AD [98]. Although corticosteroids are highly effective and widely used in the clinical setting, their long-term side-effects (i.e., skin atrophy) might discourage their continuous, long-term use.

In addition, the so-called “corticosteroid-phobia" is very common among patients and especially among caregivers of pediatric patients, negatively affecting drug adherence and efficacy [99]. Calcineurin inhibitors, on the other hand, show limited efficacy and low tolerability that could hamper their prescription. Because of this narrow array of therapeutics for the treatment of mild-to-moderate AD, topical JAK inhibitors might represent a valid option, though their market price will be fundamental to define the place-in-therapy for this class of compounds.

In conclusion, since many key cytokines in AD require JAK1 for signal transmission (IL-4, IL-13, IL-31, TSLP) [8], selective JAK1 inhibition can provide high efficacy for AD treatment, whereas a reduced affinity for JAK1 associated with the concomitant inhibitory activity on JAK2-dependent and JAK3-dependent pathways may lessen efficacy and raise safety concerns. This could suggest that selective JAK1 inhibitors, such as upadacitinib and abrocitinib, rather than JAK inhibitors with broader spectrum-of-action, may represent a highly promising therapeutic option for AD treatment, as they might be able to prevent off-target effects of JAK inhibitors, especially related to the hematologic aspects.

Funding

This paper was not funded.

Declaration of interest

A Chiricozzi served as an advisory board member and consultant and has received fees and speakers honoraria or has participated in clinical trials for AbbVie, Almirall, Leo Pharma, Lilly, Janssen, Novartis, Sanofi Genzyme, Pfizer and Incyte. C De Simone has received consulting fees or honorarium from AbbVie, Amgen, Novartis, Celegene, Sanofi, UCB Pharma, Janssen, and Lilly and payment for lectures from AbbVie, Lilly, Novartis, UCB Pharma and Celgene. K Peris has served as advisory board, received honoraria for lectures and/or research grants from AbbVie, Almirall, Lilly, Galderma, Leo Pharma, Pierre Fabre, Novartis, Sanofi, Sun Pharma and Janssen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

A reviewer on this manuscript has disclosed receiving research, speaking and/or consulting support from Eli Lilly and Company, GlaxoSmithKline/Stiefel, AbbVie, Janssen, Alovtech, vTv Therapeutics, Bristol-Myers Squibb, Samsung, Pfizer, Boehringer Ingelheim, Amgen Inc, Dermavant, Arcutis, Novartis, Novan, UCB, Helsinn, Sun Pharma, Almirall, Galderma, Leo Pharma, Mylan, Celgene, Valeant, Menlo, Merck & Co, Qurient Forte, Arena, Biocon, Accordant, Argenx, Sanofi, Regeneron, the National Biological Corporation, Caremark, Advance Medical, Suncare Research, Informa, UptoDate and the National Psoriasis Foundation; this reviewer is also the founder and majority owner of www.DrScore.com [drscore.com] and founder and part owner of Causa Research. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

References

Papers of special note have been highlighted as: * of interest or ** of considerable interest

[1] Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. *Dermatol Clin*. 2017; **35**(3):283-289.

[2] David Boothe W, Tarbox JA, Tarbox MB. Atopic Dermatitis: Pathophysiology. *Adv Exp Med Biol.* 2017; **1027**:21-37.

[3] Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab.* 2015; **66**:S8–16.

[4] Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N. Engl J Med* 2011; **365**:1315–1327.

[5] Paternoster L, Standl M, Chen CM, et al. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. *Nat Genet* 2011; **44**: 187–192.

[6] Weidinger S, Beck LA, Bieber T, et al. *Nat Rev Dis Primers* 2018; **21**:4(1):1.

[7] Drucker AM, Wang AR, Li WQ et al. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol* 2017; **137**(1):26-30.

[8] Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol* 2017;**139**(4S): S65-S76.

**** This article provides a comprehensive description of AD immunopathogenesis with a focus on current and future therapies.***

[9] Onoue A, Kabashima K, Kobayashi M, et al. Induction of eosinophil- and Th2-attracting epidermal chemokines and cutaneous late-phase reaction in tape-stripped skin. *Exp Dermatol* 2009; **18**: 1036–1043.

[10] Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* 2002; **3**:673–680.

[11] Ito T, Wang YH, Duramad O, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med* 2005; **202**: 1213–1223.

[12] Salimi M, Barlow GL, Saunders SP, et al. A role for IL-25 and IL-33-driven type2 innate lymphoid cells in atopic dermatitis. *J Exp Med* 2013; **210**, 2939–2950.

[13] Bautista DM, Wilson SR, Hoon MA. Why we scratch an itch: the molecules, cells and circuits of itch. Nat. *Neurosci* 2014; **17**: 175–182.

[14] Feld M, Garcia R, Buddenkotte J, et al. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves. *J Allergy Clin Immunol* 2016; **138**: 500–508.

[15] Gittler JK, Shemer A, Suárez-Fariñas M et al. Progressive activation of T(H)2/ T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol* 2012; **130**: 1344–1354.

[16] Noda S, Suárez-Fariñas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. *J Allergy Clin Immunol* 2015; **136**: 1254–1264.

[17] Shreberk-Hassidim R, Ramot Y, Zlotogorski A. Janus kinase inhibitors in dermatology: A systematic review. *J Am Acad Dermatol.* 2017; **76**(4):745-753.e19

[18] Szalus K, Trzeciak M, Nowicki RJ. JAK-STAT Inhibitors in Atopic Dermatitis from Pathogenesis to Clinical Trials Results. *Microorganisms.* 2020; **8**(11):1743.

[19] Nakashima C, Yanagihara S, Otsuka A. Innovation in the treatment of atopic dermatitis: Emerging topical and oral Janus kinase inhibitors. *Allergol Int* 2022; **71**(1):40-46.

[20] Schwartz DM, Bonelli M, Gadina M et al. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol* 2016; **12**(1):25-36.

[21] Ihle JN. The Stat family in cytokine signaling. *Curr Opin Cell Biol.* 2001; **13**(2):211-7.

[22] Chapman S, Kwa M, Gold LS, et al. JAK inhibitors in dermatology: a comprehensive review, Part 1. *J Am Acad Dermatol* 2021; **86**(2):406-413.

[23] Xin P, Xu X, Deng C, et al. The role of JAK/STAT signaling pathway and its inhibitors in diseases. Int *Immunopharmacol* 2020; **80**:106210.

[24] Montilla AM, Gómez-García F, Gómez-Arias PJ, et al. Scoping Review on the Use of Drugs Targeting JAK/STAT Pathway in Atopic Dermatitis, Vitiligo, and Alopecia Areata. *Dermatol Ther (Heidelb)* 2019; **9**(4):655-683.

[25] Nelms K, Keegan AD, Zamorano J, et al. The IL-4 receptor: signaling mechanisms and biologic functions. *Annu Rev Immunol.* 1999; **17**:701-38.

[26] Junttila IS. Tuning the Cytokine Responses: An Update on Interleukin (IL)-4 and IL-13 Receptor Complexes. *Front Immunol* 2018; **7**;9:888.

[27] He H, Guttman-Yassky E. JAK Inhibitors for Atopic Dermatitis: An Update. *Am J Clin Dermatol.* 2019; **20**(2):181-192.

* ***This systematic review offers a comprehensive overview regarding the use of JAK inhibitors in atopic dermatitis***

[28] Rochman Y, Kashyap M, Robinson GW, et al. Thymic stromal lymphopoietin-mediated STAT5 phosphorylation via kinases JAK1 and JAK2 reveals a key difference from IL-7-induced signaling. *Proc Natl Acad Sci U S A.* 2010; **107**(45):19455-60.

[29] Ferretti E, Corcione A, Pistoia V. The IL-31/IL-31 receptor axis: general features and role in tumor microenvironment. *J Leukoc Biol* 2017; **102**(3):711-717.

[30] US Food and Drug Administration. OLUMIANT® (baricitinib). Highlights of Prescribing Information. May 2018. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf.

[31] European Medicines Agency. Baricitinib (Olumiant): summary of product characteristics; 2017.
Available from: http://ec.europa.eu/health/documents/communityregister/2017/20170213136870/anx_136870_en.pdf. Last Accessed Jan 27, 2022.

[32] Calabrese L, Malvaso D, Chiricozzi A, et al. Baricitinib: therapeutic potential for moderate to severe atopic dermatitis. *Expert Opin Investig Drugs* 2020; **29**(10):1089-1098.

[33] Markham A. Baricitinib: First Global Approval. Drugs. 2017 Apr;77(6):697-704.

[34] Kubo S, Nakayamada S, Sakata K, et al. Janus Kinase Inhibitor Baricitinib Modulates Human Innate and Adaptive Immune System. *Front Immunol* 2018; **28**;9:1510.

[35] Liu X, Michael S, Bharti K, et al. A biofabricated vascularized skin model of atopic dermatitis for preclinical studies. *Biofabrication* 2020; **9**:12(3):035002.

[36] Australian Product Information OLUMIANT® (baricitinib). Highlights of Prescribing Information. Apr 2021. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01225-1&d=20220127172310101. Last accessed Jan 27, 2022

[37] Shi JG, Chen X, Lee F et al. The Pharmacokinetics, Pharmacodynamics, and Safety of Baricitinib, an Oral JAK 1/2 Inhibitor, in Healthy Volunteers. *J ClinPharmacol* 2014; **54**(12):1354-61.

***** This article provides an extensive overview of the pharmacokinetic, pharmacodynamic properties and safety of baricitinib, orally administered in healthy volunteers***

[38] European Medicines Agency. Upadacitinib (Rinvoq): summary of product characteristics; 2021
Available from:

https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_it.pdf. Last Accessed Jan 27, 2022.

[39] Duggan S, Keam SJ. Upadacitinib: First Approval. *Drugs* 2019; **79**(16):1819-1828.

[40] Parmentier JM, Voss J, Graf C, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). *BMC Rheumatol* 2018; **2**:23.

***** This article shows the structural basis for the JAK1 selectivity of upadacitinib, demonstrating that upadacitinib is ~ 60 fold selective for JAK1 over JAK2 and > 100 fold selective over JAK3 in cellular assays.***

[41] US Food and Drug Administration. RINVOQ® (upadacitinib). Highlights of Prescribing Information. 2019. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211675s000lbl.pdf. Last accessed Jan 27, 2022

[42] Mohamed MF, Zeng J, Jiang P, et al. Use of early clinical trial data to support thorough QT study waiver for upadacitinib and utility of food efect to demonstrate ECG assay sensitivity. *Clin Pharmacol Ther* 2018; **103**(5):836–42.

[43] Song T, Pavel AB, Peng X, et al. Upadacitinib treatment of atopic dermatitis patients leads to reductions in epidermal hyperplasia and cellular infltrates [abstract no. 1024]. *J Investig Dermatol* 2019; **139(**5 Suppl.):S177.

[44] Beck LA, Silverberg JI, Grebe K, et al. Eosinophil count and serum immunoglobulin E levels in atopic dermatitis: analysis of upadacitinib phase 2 study fndings [abstract no. 376]. *J Allergy Clin Immunol* 2019; **143**(2 Suppl.):AB125.

[45] European Medicines Agency. Abrocitinib (Cibinqo): summary of product characteristics; 2021. Available from: https://www.ema.europa.eu/en/documents/overview/cibinqo-epar-medicine-overview_it.pdf. Last Accessed Jan 27, 2022.

[46] European Medicines Agency. Abrocitinib (Cibinqo): product information; 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/cibinqo-epar-product-information_en.pdf. Last Accessed Jan 27, 2022.

[47] Peeva E, Hodge MR, Kieras E, et al. Evaluation of a Janus kinase 1 inhibitor, PF-04965842, in healthy subjects: A phase 1, randomized, placebo-controlled, dose-escalation study. *Br J Clin Pharmacol* 2018; **84**(8):1776-1788.

[48] Gooderham MJ, Forman SB, Bissonnette R, et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial. *JAMA Dermatol* 2019; **155**(12):1371-1379.

[49] Soto E, Banfield C, Gupta P, et al. Kinetic-Pharmacodynamic Model of Platelet Time Course in Patients With Moderate-to-Severe Atopic Dermatitis Treated With Oral Janus Kinase 1 Inhibitor Abrocitinib. *CPT Pharmacometrics Syst Pharmacol* 2020; **9**(10):553-560.

[50] US Food and Drug Administration. JAKAFI® (ruxolitinib). Highlights of Prescribing Information. May 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202192s017lbl.pdf. Last accessed Jan 26, 2022.

[51] US Food and Drug Administration. OPZELURA® (ruxolitinib). Highlights of Prescribing Information. Sep 2021. Available from: https://www.opzelura.com/prescribing-information.pdf. Last accessed Jan 26, 2022.

[52] Ruxolitinib Cream Investigator's Brochure. Wilmington, DE: Incyte Corporation. Last accessed Jan 26, 2022.

[53] Quintás-Cardama A, Vaddi K, Liu P et al. Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms. *Blood* 2010; **15**:115(15):3109-17.

[54] Scuron MD, Fay BL, Connell AJ, et al. Ruxolitinib Cream Has Dual Efficacy on Pruritus and Inflammation in Experimental Dermatitis. *Front Immunol* 2021; **11**:620098.

**** This article provides evidence on the efficacy of topical ruxolitinib in a murine model of acute and chronic dermatitis***

[55] Fridman JS, Scherle PA, Collins R, et al. Preclinical evaluation of local JAK1 and JAK2 inhibition in cutaneous inflammation. *J Invest Dermatol.* 2011; **131**(9):1838-44.

[56] Japan Tobacco. JT Receives manufacturing and marketing approval of CORECTIM® ointment 0.5% for the treatment of atopic dermatitis in Japan. January 23, 2020. Available from: https://www.jt.com/media/news/2020/pdf/20200123_E01.pdf. Last accessed Jan 26, 2022.

[57] Japan Tobacco. JT receives approvals of CORECTIM® ointment 0.25% and CORECTIM® ointment 0.5% for the treatment of pediatric atopic dermatitis in Japan. March 23, 2021. Available from: https://www.jt.com/media/news/2021/pdf/20210323_E1.pdf. Last accessed Jan 26, 2022.

[58] Tanimoto A, Ogawa Y, Oki C, et al. Pharmacological properties of JTE-052: a novel potent JAK inhibitor that suppresses various infammatory responses in vitro and in vivo. *Infamm Res* 2015; **64**(1):41–51.

***** This article thoroughly investigates the pharmacodynamic properties of topical delgocitinib in vitro and in vivo***

[59] Tanimoto A, Shinozaki Y, Yamamoto Y, et al. A novel JAK inhibitor JTE-052 reduces skin infammation and ameliorates chronic dermatitis in rodent models: comparison with conventional therapeutic agents. *Exp Dermatol* 2018; **27**(1):22–9

[60] Amano W, Nakajima S, Yamamoto Y et al. JAK inhibitor JTE-052 regulates contact hypersensitivity by downmodulating T cell activation and differentiation. *J Dermatol Sci* 2016; **84**:258–65.

[61] Nakagawa H, Nemoto O, Yamada H, et al. Phase 1 studies to assess the safety, tolerability and pharmacokinetics of JTE-052 (a novel Janus kinase inhibitor) ointment in Japanese healthy volunteers and patients with atopic dermatitis. *J Dermatol* 2018; **45**(6):701-709.

[62] Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2017; **376**(18):1723-1736.

[63] Chiricozzi A, Faleri S, Saraceno R et al. Tofacitinib for the treatment of moderate-to-severe psoriasis. *Expert Rev Clin Immunol* 2015; **11**(4):443-55.

[64] US Food and Drug Administration. XELJANZ® (tofacitinib). Highlights of Prescribing Information. September 2020. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203214s026lbl.pdf. Last Accessed, Jan 26, 2022.

[65] Meyer DM, Jesson MI, Li X, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. *J Inflamm (Lond)* 2010; **11**:7:41.

[66] Fukuyama T, Ehling S, Cook E, et al. Topically Administered Janus-Kinase Inhibitors Tofacitinib and Oclacitinib Display Impressive Antipruritic and Anti-Inflammatory Responses in a Model of Allergic Dermatitis. *J Pharmacol Exp Ther.* 2015; **354**(3):394-405.

[67] Kim BS, Howell MD, Sun K, et al. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *J Allergy Clin Immunol* 2020; **145**:572-82.

[68] Kim BS, Sun K, Papp K, et al. Effects of ruxolitinib cream on pruritus and quality of life in atopic dermatitis: Results from a phase 2, randomized, dose-ranging, vehicle- and active-controlled study. *J Am Acad Dermatol* 2020; **82**(6):1305-1313.

[69] Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol* 2021; **85**(4):863-872.

[70] Nakagawa H, Nemoto O, Igarashi A, et al. Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study. *Br J Dermatol* 2018; **178**(2):424-432.

[71] Nakagawa H, Nemoto O, Igarashi A, et al. Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: A phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study. *J Am Acad Dermatol* 2020; **82**(4):823-831.

[72] Bissonnette R, Papp KA, Poulin Y, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol* 2016; **175**(5):902-911.

[73] Nogueira M, Torres T. Janus Kinase Inhibitors for the Treatment of Atopic Dermatitis: Focus on Abrocitinib, Baricitinib, and Upadacitinib. *Dermatol Pract Concept* 2021; **11(4):**e2021145.

[74] Chovatiya R, Paller AS. JAK inhibitors in the treatment of atopic dermatitis. *J Allergy Clin Immunol* 2021; **148**(4):927-940.

[75] Caputo V, Strafella C, Cosio T, et al. Pharmacogenomics: An Update on Biologics and Small-Molecule Drugs in the Treatment of Psoriasis. *Genes (Basel)* 2021; **12**(9):1398.

[76] Murdaca G, Spanò F, Contatore M, et al. Pharmacogenetics of etanercept: role of TNF-α gene polymorphisms in improving its efficacy. *Expert Opin Drug Metab Toxicol* 2014; **10**(12):1703-10.

[77] Guis S, Balandraud N, Bouvenot J, et al. Influence of -308 A/G polymorphism in the tumor necrosis factor alpha gene on etanercept treatment in rheumatoid- arthritis. *Arthritis Rheum* 2007; **57**(8):1426-30

[78] Maxwell JR, Potter C, Hyrich KL, et al. Association of the tumour necrosis factor-308 variant with differential response to anti-TNF agents in the treatment of rheumatoid arthritis. *Hum Mol Genet* 2008; **17**(22):3532-8

[79] Costanzo A, Bianchi L, Flori ML, et al. Secukinumab shows high efficacy irrespective of HLA-Cw6 status in patients with moderate-to-severe plaque-type psoriasis: SUPREME study. *Br J Dermatol* 2018; **179**(5):1072-1080.

[80] Talamonti M, Botti E, Galluzzo M, et al. Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab. *Br J Dermatol* 2013; **169**(2):458-63.

[81] Talamonti M, Galluzzo M, van den Reek JM, et al. Role of the HLA-C*06 allele in clinical response to ustekinumab: evidence from real life in a large cohort of European patients. *Br J Dermatol* 2017; **177**(2):489-496.

[82] Vasilopoulos Y, Sarri C, Zafiriou E, et al. A pharmacogenetic study of ABCB1 polymorphisms and cyclosporine treatment response in patients with psoriasis in the Greek population. *Pharmacogenomics* J 2014; **14**(6):523-5.

[83] Grželj J, Mlinarič-Raščan I, Marko PB, et al. Polymorphisms in GNMT and DNMT3b are associated with methotrexate treatment outcome in plaque psoriasis. *Biomed Pharmacother* 2021; **138**:111456.

[84] Harrington R, Al Nokhatha SA, Conway R. JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the Emerging Clinical Data. *J Inflamm Res* 2020; **13**:519-531.

[85] Guttman-Yassky E, Silverberg JI, Nemoto O et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol* 2019; **80**(4):913-921.e9.

[86] Kay J, Harigai M, Rancourt J, et al. Changes in selected haematological parameters associated with JAK1/JAK2 inhibition observed in patients with rheumatoid arthritis treated with baricitinib. *RMD Open* 2020; **6**(3):e001370.

[87] Papp KA, Menter MA, Raman M, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. *Br J Dermatol* 2016; **174(**6):1266-76.

[88] O'Shea JJ, Kontzias A, Yamaoka K, et al. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis* 2013; **72**(suppl 2):ii111-ii115.

[89] Koride S, Nayak S, Banfield C, et al. Evaluating the role of Janus kinase pathways in platelet homeostasis using a systems modeling approach. *CPT Pharmacometr Syst Pharmacol* 2019; **8**(7):478–88.

[90] Kaser A, Brandacher G, Steurer W, et al. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. *Blood* 2001; **98**(9):2720–5.

[91] Guttman-Yassky E, Thaçi D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020; **145**(3):877-884.

[92] Sunzini F, McInnes I, Siebert S. JAK inhibitors and infections risk: focus on herpes zoster. *Ther Adv musculoskelet Dis* 2020; **12**:1759720X20936059.

[93] Lee AJ, Ashkar AA. The dual nature of type I and type II interferons. *Front Immunol* 2018; **9**:2061.

[94] Waickman AT, Park JY, Park JH. The common gamma-chain cytokine receptor: tricks-and-treats for T cells. *Cell Mol Life Sci* 2016; **73**(2):253–69.

[95] Gadina M, Hilton D, Johnston JA, et al. Signaling by type I and II cytokine receptors: ten years after. *Curr Opin Immunol* 2001; **13**(3):363–73.

[96] Boisson-Dupuis S. The monogenic basis of human tuberculosis. *Hum Genet* 2020; **139**(6–7):1001–9.

[97] Jindal AK, Suri D, Guleria S, et al. Recurrent salmonella typhi infection and autoimmunity in a young boy with complete IL-12 receptor β1 deficiency. *J Clin Immunol* 2019; **39**(4):358–62.

[98] Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018; **32**(5):657-682.

[99] Li AW, Yin ES, Antaya RJ. Topical Corticosteroid Phobia in Atopic Dermatitis: A Systematic Review. *JAMA Dermatol*. 2017; **153**(10):1036-1042.

Figure legend

Figure 1. The JAK/STAT pathway is a paradigm of receptor-mediated signal transduction, and it is involved in a myriad of key biological processes, including cell proliferation, differentiation, apoptosis, immune regulation, anti-microbial rensponses.
EPO: erythropoietin; G-CSF: granulocite-colony stimulating factor; GH: growth hormone; GM-CSF: granulocite macrophage- colony stimulating factor; IFN: interferon; LIF: leukemia inhibitory factor; OSM: oncostatin M ; TPO: thrombopoietin.

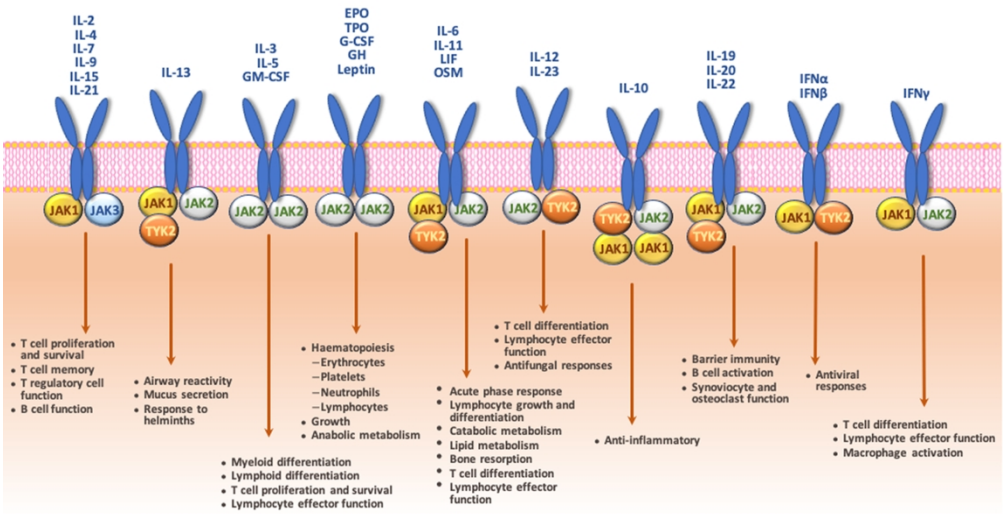

Figure 1. The JAK/STAT pathway is a paradigm of receptor-mediated signal transduction, and it is involved in a myriad of key biological processes, including cell proliferation, differentiation, apoptosis, immune regulation, anti-microbial rensponses.
EPO: erythropoietin; G-CSF: granulocite-colony stimulating factor; GH: growth hormone; GM-CSF: granulocite macrophage- colony stimulating factor; IFN: interferon; LIF: leukemia inhibitory factor; OSM: oncostatin M ; TPO: thrombopoietin.

339x176mm (330 x 330 DPI)

Table 1. List of novel JAK inhibitors investigated for the treatment of atopic dermatitis, describing their main targets and formulations.

Drug	Main target	Formulation
Ruxolitinib	JAK1, JAK2	Topical
Delgocitinib	Pan-JAK	Topical
Tofacitinib	Pan-JAK	Topical/Oral
Baricitinib	JAK1, JAK2	Oral
Upadacitinib	JAK1	Oral
Abrocitinib	JAK1	Oral