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Pharmacodynamics of Janus kinase inhibitors for the treatment of atopic dermatitis

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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 time from 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, translocating 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

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3 Baricitinib is an orally administered small molecule, representing a selective inhibitor of JAK1
4 and JAK2. The drug received its first approval for the treatment of moderate to severe
5 rheumatoid arthritis in 2017 [30]. Recently, the drug was approved in Europe and Japan, but
6 not in US, for moderate-to-severe AD in adulthood, at both 4 and 2 mg oral daily dosage
7 [31,32].
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10
11 Baricitinib selectively inhibits both JAK1 and JAK2 tyrosine kinases, with an [half-maximal
12 inhibitory concentration (IC₅₀) of 5.9 and 5.7 nmol/L, respectively. Albeit to a lesser extent,
13 it also exerts inhibitory activity on TYK2 and JAK3, (IC₅₀ of 53 and ≈560 nmol/L,
14 respectively) [33].
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18 Through JAK1 and JAK2 inhibition, baricitinib suppresses Th2 cytokines, such as IL-4, IL-5,
19 and IL-13, and IL-31, which are key cytokines in the pathophysiology of AD, but it also
20 interferes with the signal transduction of IL-6, IL-12, IL-20, IL-22, IL-23, and interferon (IFN)-
21 γ.
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26 In *in vitro* assays, baricitinib has proven to modulate both the innate and the adaptive
27 immune system by inhibiting both Th1 and Th17 differentiation, as well as IL-6-induced
28 phosphorylation of STAT1 and STAT3 [34].
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32 In a human skin equivalent model stimulated with Th2-signature cytokines (IL-4, IL-13, IL-
33 31), baricitinib reduced pathological changes associated with AD (including keratinocyte
34 STAT3 expression), and increased the expression of FLG [35].
35

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37 Furthermore, in lesional AD skin, baricitinib reduced phosphorylated STAT3 (pSTAT3)
38 expression in epidermal keratinocytes at different time points, which reflected a clinical
39 improvement of AD lesions [36].
40

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42 Two phase I studies were conducted to assess pharmacokinetics and pharmacodynamics
43 properties of baricitinib at single or multiple ascending doses in healthy volunteers.
44

45
46 Baricitinib oral administration was associated with an inhibition of IL-6-induced STAT3
47 phosphorylation in whole blood in a dose- and time-dependent manner, with maximal
48 inhibition occurring 1-2 hours after dosing, and restoration of baseline STAT3
49 phosphorylation by 16–24 hours from baricitinib administration. Additionally, a decrease in
50 the absolute neutrophilic count (ANC) in a dose-related manner was reported, with a peak
51 effect in 8 hours and a restoration of baseline values, 12–24 hours post-dose, potentially
52 explained by a neutrophil margination effect. Conversely, absolute lymphocytic count (ALC)
53 increased, with a peak effect in 6 hours after dosing, and reduced to normal values by 24
54 hours after dosing [37].
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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 $\mu\text{mol/L}$) [39,40]. In vitro, the drug potently inhibited cytokine signaling associated with JAK1 inflammatory cascades, such as IL-6 and IFN γ . 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 IFN γ . 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 phosphorylation, 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 Fc ϵ R1 $^{+}$) 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-specific 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 IFN γ -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

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3 treatment period, was associated with an expected incidence rate of grade ≥ 2
4 thrombocytopenia ($\leq 75,000$ platelets/uL), of 0% and 2.7%, respectively [49] .
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8 **4.2 Topical JAK inhibitors**

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10 **4.2.1 Ruxolitinib**

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12 Ruxolitinib is a first-generation inhibitor of JAK1/2, FDA-approved at different oral dosages
13 for the treatment of myelofibrosis, polycythaemia vera and acute graft-versus-host disease
14 [50].
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16 Recently, 1.5% ruxolitinib cream, applied twice daily, received FDA indication for the short-
17 term (8 weeks) and non-continuous treatment of mild to moderate AD in non-
18 immunocompromised patients (>12 years of age) who resulted not adequately treated with
19 other topical therapies [51].
20

21 Ruxolitinib potently inhibits JAK1 and JAK2 inhibitor with a IC_{50} for JAK1/2 < 5 nM,
22 and modest selectivity against TYK2 and JAK3 [IC_{50} for JAK3 resulted > 400 nM], and the
23 consequent suppression of proinflammatory activity regulated by several cytokines, such as
24 IL-23 and interferon (IFN)- γ [52,53].
25

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

34 In another AD murine model, topical administration of ruxolitinib cream decreased STAT3
35 phosphorylation and subsequently oedema, lymphocyte infiltration and keratinocytes
36 proliferation, as well as suppressed tissue inflammation induced by intradermal IL-23 and
37 TSLP stimulation [55].
38

39 Furthermore, in a 28-day toxicology study performed in Gottingen minipigs, topical ruxolitinib
40 was well tolerated and did not cause any clinical or histopathological alteration. Noteworthy,
41 no epidermal atrophy was reported (more likely associated with topical application of
42 steroids) [55]. These results were confirmed by another experiment in which ruxolitinib
43 cream (up to 1.5%) applied twice daily for up to 9 months in Gottingen minipigs was not
44 found to be associated with any adverse effect [52].
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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 IC₅₀ 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 restoration 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].

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3 Subsequently, the drug was approved for the treatment of psoriatic arthritis, ulcerative colitis,
4 and juvenile idiopathic arthritis, thereafter.
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7 In vitro cellular assays showed potent inhibitory effects on both JAK1 and JAK3
8 signaling, with 5-100-fold selectivity over JAK2 [65]. A preclinical study revealed a significant
9 reduction of dendritic cell migration obtained in a mice model of allergic dermatitis using
10 topical application of tofacitinib 0.1% [66]. In addition, significantly lower levels of IL-1 β , IL-
11 4, IL-6, TARC, IL-31, TNF α , and TSLP were detected in the tofacitinib-treated mice,
12 compared to mice treated with vehicle [66]. Overall, both scratching behavior and ear
13 thickness in the topically tofacitinib-treated mice were significantly reduced. Conversely, the
14 efficacy of oral tofacitinib was limited to a significant reduction of mice scratching behavior
15 [66].
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22 23 **5. Conclusion**

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25 Several key inflammatory cytokines, involved in the pathogenesis of AD, signal through the
26 JAK-STAT pathway, supporting the use of JAK inhibitors for the treatment of AD. This class
27 of drugs comprises several agents that differ from each other. This heterogeneity mainly
28 consists of a different target selectivity, a different ability to inhibit the various JAKs isoforms,
29 affecting pharmacodynamics, efficacy and safety. As these drugs are able to block
30 numerous mediators involved in many aspects of host defense, hematopoiesis, metabolism,
31 cell growth, and cell differentiation, they might interfere with the activity of multiple cell lines,
32 and thus various biological processes. Therefore, second generation JAK inhibitors with
33 putative increased selectivity against JAK1, such as upadacitinib and abrocitinib, might
34 potentially maintain elevated efficacy and limiting warning signals.
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44 45 **6. Expert opinion**

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47 The large pharmacological class of JAK inhibitors is constantly expanding, and a consistent
48 proportion of them has been developed and tested for the treatment of AD, in topical and
49 oral formulations.
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52 Among topical JAK inhibitors, tofacitinib, ruxolitinib and delgocitinib are in the most
53 advanced phases of development for the treatment of mild-to-moderate AD while oral JAK
54 inhibitors resulted effective in treating moderate-to-severe AD [67-73]. Nevertheless, it is
55 important to highlight the different selectivity of various JAK inhibitors, which influences
56 pharmacodynamics, efficacy, and safety [74]. In addition, efficacy as well as safety might be
57 also affected by patient genetics [75]. In another inflammatory skin disorder, such as
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3 psoriasis, pharmacogenetic studies provided insights about treatment response and/or
4 toxicity to TNF- α , p40IL12/IL23, and IL-17 inhibitors, cyclosporine and methotrexate [76-83].
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6 Pharmacogenetics has not been investigated for JAK inhibitors, but it might represent a valid
7
8 tool contributing to the most appropriate drug selection for a patient-tailored pharmacological
9
10 approach.

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12 This evidence could be even more relevant considering that findings derived from clinical
13 trials and evaluating the use of oral JAK inhibitors in immune-mediated disorders, such as
14 RA or psoriasis, have arisen safety concerns, suggesting a potentially increased risk of
15 infections, venous thromboembolism (VTE), and malignancies, which could be theoretically
16 associated with the mode of action of this class of drugs [84].
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18

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20 For example, JAK2 homodimers are implicated in signaling via erythropoietin,
21 thrombopoietin (TPO), and GM-CSF, therefore JAK2 inhibition might theoretically contribute
22 to neutropenia, anemia, and alterations in platelet count, which indeed have been reported
23 during administration of baricitinib [85-88]. The JAK2 role in myelopoiesis and platelet
24 production could represent the biological basis for the link between JAK inhibitor and VTE.
25 Changes in platelet counts, in particular their increase, are thought to be determined by the
26 JAK2 inhibition, interfering with TPO uptake and degradation [89].
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30 On the contrary, the use of JAK1 inhibitors were associated with early, dose-dependent, but
31 transient decrease in platelet count [90].
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35 Among other hematologic abnormalities, neutrophil reduction was reported during
36 upadacitinib administration in AD clinical trials, likely dependent on JAK 1/2
37 transphosphorylation [91,92].
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41 Furthermore, acne, viral reactivation and opportunistic infections are AEs associated with
42 JAK inhibitors [73,91,92]. Most of the infections are related to herpes viruses that are
43 favored by JAK1 inhibition blocking type 1 and type 2 IFN-mediated signals, together with
44 cytokines binding to the gamma chain of the IL-2R, which is important in lymphocyte
45 development and activation [93-95]. On the other hand, the signaling of certain cytokines
46 (i.e., IL-12 and IL-23) protecting against opportunistic infections, is expected to be preserved
47 by JAK1-selective inhibitors as it is dependent on JAK2/TYK2 [96,97].
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51 The potential marketization of a new class of topical agents could be of great interest for
52 physicians because current topical therapies are limited to corticosteroids and calcineurin
53 inhibitors, albeit the majority of patients suffers from mild or mild-to-moderate forms of AD
54 [98]. Although corticosteroids are highly effective and widely used in the clinical setting, their
55 long-term side-effects (i.e., skin atrophy) might discourage their continuous, long-term use.
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3 In addition, the so-called "corticosteroid-phobia" is very common among patients and
4 especially among caregivers of pediatric patients, negatively affecting drug adherence and
5 efficacy [99]. Calcineurin inhibitors, on the other hand, show limited efficacy and low
6 tolerability that could hamper their prescription. Because of this narrow array of therapeutics
7 for the treatment of mild-to-moderate AD, topical JAK inhibitors might represent a valid
8 option, though their market price will be fundamental to define the place-in-therapy for this
9 class of compounds.
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15 In conclusion, since many key cytokines in AD require JAK1 for signal transmission
16 (IL-4, IL-13, IL-31, TSLP) [8], selective JAK1 inhibition can provide high efficacy for AD
17 treatment, whereas a reduced affinity for JAK1 associated with the concomitant inhibitory
18 activity on JAK2-dependent and JAK3-dependent pathways may lessen efficacy and raise
19 safety concerns. This could suggest that selective JAK1 inhibitors, such as upadacitinib and
20 abrocitinib, rather than JAK inhibitors with broader spectrum-of-action, may represent a
21 highly promising therapeutic option for AD treatment, as they might be able to prevent off-
22 target effects of JAK inhibitors, especially related to the hematologic aspects.
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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 responses.

EPO: erythropoietin; G-CSF: granulocyte-colony stimulating factor; GH: growth hormone; GM-CSF: granulocyte macrophage- colony stimulating factor; IFN: interferon; LIF: leukemia inhibitory factor; OSM: oncostatin M ; TPO: thrombopoietin.

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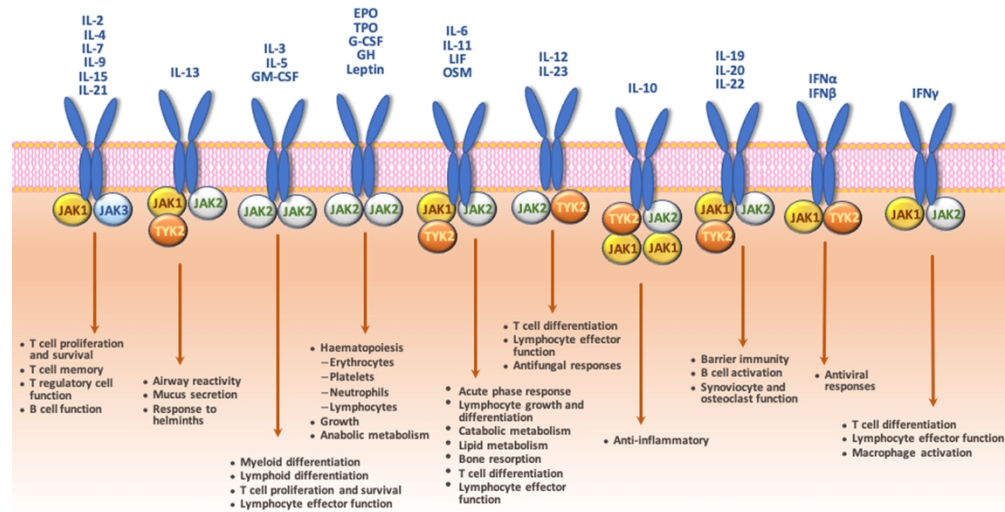


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Table 1. List of novel JAK inhibitors investigated for the treatment of atopic dermatitis, describing their main targets and formulations.

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

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