# An Update on JAK Inhibitors in Skin Disease

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Atopic dermatitis (AD) is a chronic inflammatory skin disorder affecting 7% of adults and 13% of children in the United States.[1,2] Atopic dermatitis is characterized by pruritus, dry skin, and pain, all of which can negatively impact quality of life and put patients at higher risk for psychiatric comorbidities such as anxiety and depression.[3] The pathogenesis of AD is multifactorial, involving genetics, epidermal barrier dysfunction, and immune dysregulation. Overactivation of helper T cell ($T_H2$) pathway cytokines, including IL-4, IL-13, and IL-31, is thought to propagate both inflammation and pruritus, which are central to AD. The JAK-STAT signaling pathway plays a pivotal role in the immune system dysregulation and exaggeration of $T_H2$ cell response, making JAK-STAT inhibitors (or JAK inhibitors) strong theoretical candidates for the treatment of AD.[4] In humans, the Janus kinases are composed of 4 different members—JAK1, JAK2, JAK3, and tyrosine kinase 2—all of which can be targeted by JAK inhibitors.[5]

JAK inhibitors such as tofacitinib have already been approved by the US Food and Drug Administration (FDA) to treat various inflammatory conditions, including rheumatoid arthritis, ulcerative colitis, and psoriatic arthritis; other JAK inhibitors such as baricitinib are only approved for patients with rheumatoid arthritis.[6,7] The success of these small molecule inhibitors in these immune-mediated conditions make them attractive candidates for the treatment of AD. Several JAK inhibitors are in phase 2 and phase 3 clinical trials as oral therapies (moderate to severe AD) or as topical treatments (mild to moderate AD). Currently, ruxolitinib (RUX) is the only topical JAK inhibitor that is FDA approved for the treatment of AD in the United States.[8] In this editorial, we focus on recent trials of JAK inhibitors tested in patients with AD, including topical RUX, as well as oral abrocitinib, upadacitinib, and baricitinib.

## Topical RUX in AD

Ruxolitinib is a topical JAK1/2 small molecule inhibitor approved by the FDA for the treatment of AD in 2021. In a randomized trial by Kim et al[9] in 2020, all tested regimens of RUX demonstrated significant improvement in eczema area and severity index (EASI) scores vs vehicle; notably, RUX cream 1.5% applied twice daily achieved the greatest mean percentage change in baseline EASI score vs vehicle at 4 weeks (76.1% vs 15.5%; $P<.0001$). Ruxolitinib cream was well tolerated through week 8 of the trial, and all adverse events (AEs) were mild to moderate in severity and comparable to those in the vehicle group.[9]

Topical JAK inhibitors appear to be effective for mild to moderate AD and have had an acceptable safety profile in clinical trials thus far. Although topical corticosteroids and calcineurin inhibitors can have great clinical benefit in AD, they are recommended for short-term use given side effects such as thinning of the skin, burning, or telangiectasia formation.[10,11] The hope is that topical JAK inhibitors may be an alternative to standard topical treatments for AD, as they can be used for longer periods due to a safer side-effect profile.

## Oral JAK Inhibitors in AD

Several oral JAK inhibitors are undergoing investigation for the systemic treatment of moderate to severe

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AD. Abrocitinib is an oral JAK1 inhibitor that has demonstrated efficacy in several phase 3 trials in patients with moderate to severe AD. In a 2021 trial, patients were randomized in a 2:2:2:1 ratio to receive abrocitinib 200 mg daily, abrocitinib 100 mg daily, subcutaneous dupilumab 300 mg every other week, or placebo, respectively.[12] Patients in both abrocitinib groups showed significant improvement in AD vs placebo, and EASI-75 response was achieved in 70.3%, 58.7%, 58.1%, and 27.1% of patients, respectively ($P<.001$ for both abrocitinib doses vs placebo). Adverse events occurred more frequently in the abrocitinib 200-mg group vs placebo. Nausea, acne, nasopharyngitis, and headache were the most frequently reported AEs with abrocitinib.[12] Another phase 3 trial by Silverberg et al[13] (N=391) had similar treatment results, with 38.1% of participants receiving abrocitinib 200 mg and 28.4% of participants receiving abrocitinib 100 mg achieving investigator global assessment scores of 0 (clear) or 1 (almost clear) vs 9.1% of participants receiving placebo ($P<.001$). Abrocitinib was well tolerated in this trial with few serious AEs (ie, herpangina [0.6%], pneumonia [0.6%]).[13] In both trials, there were rare instances of laboratory values indicating thrombocytopenia with the 200-mg dose (0.9%[12] and 3.2%[13]) without any clinical manifestations. Although a decrease in platelets was observed, no thrombocytopenia occurred in the abrocitinib 100-mg group in the latter trial.[13]

Baricitinib is another oral inhibitor of JAK1 and JAK2 with potential for the treatment of AD. One randomized trial (N=329) demonstrated its efficacy in combination with a topical corticosteroid (TCS). At 16 weeks, a higher number of participants treated with baricitinib and TCS achieved investigator global assessment scores of 0 (clear) or 1 (almost clear) compared to those who received placebo and TCS (31% with baricitinib 4 mg + TCS, 24% with baricitinib 2 mg + TCS, and 15% with placebo + TCS).[14] Similarly, in BREEZE-AD5, another phase 3 trial (N=440), baricitinib monotherapy demonstrated a higher rate of treatment success vs placebo.[15] Specifically, 13% of patients treated with baricitinib 1 mg and 30% of those treated with baricitinib 2 mg achieved 75% or greater reduction in EASI scores compared to 8% in the placebo group. The most common AEs associated with baricitinib were nasopharyngitis and headache. Adverse events occurred with similar frequency across both experimental and control groups.[15] Reich et al[14] demonstrated a higher overall rate of AEs—most commonly nasopharyngitis, upper respiratory tract infections, and folliculitis—in baricitinib-treated patients; however, serious AEs occurred with similar frequency across all groups, including the control group.

The selective JAK1 inhibitor upadacitinib also is undergoing testing in treating moderate to severe AD. In one trial, 167 patients were randomized to once daily oral upadacitinib 7.5 mg, 15 mg, or 30 mg or placebo.[16] All doses of upadacitinib demonstrated considerably higher percentage improvements from baseline in EASI scores compared to placebo at 16 weeks with a clear dose-response relationship (39%, 62%, and 74% vs 23%, respectively). In this trial, there were no dose-limiting safety events. Serious AEs were infrequent, occurring in 4.8%, 2.4%, and 0% of upadacitinib groups vs 2.5% for placebo. The serious AEs observed with upadacitinib were 1 case of appendicitis, lower jaw pericoronitis in a patient with a history of repeated tooth infections, and an exacerbation of AD.[16]

Tofacitinib, another JAK inhibitor, has been shown to increase the risk for blood clots and death in a large trial in the treatment of rheumatoid arthritis. Following this study, the FDA is requiring black box warnings for tofacitinib and also for the 2 JAK inhibitors baricitinib and upadacitinib regarding the risks for heart-related events, cancer, blood clots, and death. Given that these medications share a similar mechanism of action to tofacitinib, they may have similar risks, though they have not yet been fully evaluated in large safety trials.[17]

With more recent investigation into novel therapeutics for AD, oral JAK inhibitors may play an important role in the future to treat patients with moderate to severe AD with inadequate response or contraindications to other systemic therapies. In trials thus far, oral JAK inhibitors have exhibited acceptable safety profiles and have demonstrated treatment success in AD. More randomized, controlled, phase 3 studies with larger patient populations are required to confirm their potential as effective treatments and elucidate their long-term safety.

## Deucravacitinib in Psoriasis

Deucravacitinib is a first-in-class, oral, selective TYK2 inhibitor currently undergoing testing for the treatment of psoriasis. A randomized phase 2 trial (N=267) found that deucravacitinib was more effective than placebo in treating chronic plaque psoriasis at doses of 3 to 12 mg daily.[18] The percentage of participants with a 75% or greater reduction from baseline in the psoriasis area and severity index score was 7% with placebo, 9% with deucravacitinib 3 mg every other day ($P=.49$ vs placebo), 39% with 3 mg once daily ($P<.001$ vs placebo), 69% with 3 mg twice daily ($P<.001$ vs placebo), 67% with 6 mg twice daily ($P<.001$ vs placebo), and 75% with 12 mg once daily ($P<.001$ vs placebo). The most commonly reported AEs were nasopharyngitis, headache, diarrhea, nausea, and upper respiratory tract infection. Adverse events occurred in 51% of participants in the control group and in 55% to 80% of those in the experimental groups. Additionally, there was 1 reported case of melanoma (stage 0) 96 days after the start of treatment in a patient in the 3-mg once-daily group. Serious AEs occurred in only 0% to 2% of participants who received deucravacitinib.[18]

Two phase 3 trials—POETYK PSO-1 and POETYK PSO-2 (N=1686)—found deucravacitinib to be notably more effective than both placebo and apremilast in treating psoriasis.[19] Among participants receiving deucravacitinib 6 mg daily, 58.7% and 53.6% in the 2 respective trials achieved psoriasis area and severity index 75 response vs 12.7% and

9.4% receiving placebo and 35.1% and 40.2% receiving apremilast. Overall, the treatment was well tolerated, with a low rate of discontinuation of deucravacitinib due to AEs (2.4% of patients on deucravacitinib compared to 3.8% on placebo and 5.2% on apremilast). The most frequently observed AEs with deucravacitinib were nasopharyngitis and upper respiratory tract infection. The full results of these trials are expected to be published soon.[19,20]

## Final Thoughts

Overall, JAK inhibitors are a novel class of therapeutics that may have further success in the treatment of other dermatologic conditions that negatively affect patients' quality of life and productivity. We should look forward to additional successful trials with these promising medications.

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