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EFFICACY AND SAFETY OF ORAL JANUS KINASE INHIBITORS FOR ATOPIC DERMATITIS: A NARRATIVE REVIEW

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by eczematous lesions and intense pruritus, which severely impacts patients' quality of life. While recent advances such as biologic therapies (e.g., dupilumab) have improved AD management, many patients still experience inadequate disease control, persistent itch, or treatment side effects. The Janus kinase/ signal transducer and activator of transcription (JAK-STAT) signaling pathway has emerged as a key driver of AD's inflammatory process, making it a promising therapeutic target for new treatments.
Purpose: The aim of this paper was to evaluate the efficacy and safety of oral JAK inhibitor therapies in moderate-to-severe AD. The review synthesizes clinical trial findings for three agents - upadacitinib, abrocitinib, and baricitinib - with a focus on disease-severity endpoints, itch reduction, speed of therapeutic response, long-term disease control, and adverse-event profiles. It also examines how these therapies address previously unmet needs in AD care, including rapid relief of pruritus and treatment options for patients who do not achieve satisfactory outcomes with existing systemic therapies.
Methodology: A narrative literature review was conducted using Google Scholar and PubMed, focusing on clinical trials, extension studies, and meta-analyses published up to 2025 that examined oral JAK inhibitors for AD. Key sources include Phase III randomized controlled trials (RCTs) and their long-term extensions, head-to-head studies comparing JAK inhibitors with biologic therapy, and relevant guidelines. Data on efficacy endpoints (EASI, vIGA-AD, pruritus scores), onset of action, durability of response, and adverse events were extracted and synthesized to present an integrated overview of each drug's performance and safety.
Conclusions: Oral JAK inhibitors offer rapid and substantial control of skin lesions and pruritus in moderate-to-severe atopic dermatitis. Their distinct efficacy and safety profiles support personalized systemic therapy. Evidence to date indicates that JAK inhibitors are suitable for long-term management with standard monitoring. Future research should clarify their optimal place in the therapeutic algorithm, including direct comparisons and real-world outcomes.

KEYWORDS

Atopic Dermatitis, JAK Inhibitors, Upadacitinib, Abrocitinib, Baricitinib, Eczema, Pruritus, Targeted Therapy, Cytokine, Review

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1. Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by intense pruritus, typical lesion morphology and distribution, and frequently the coexistence of other atopic disorders in the personal or family medical history (Jeskey et al., 2024; Weidinger et al., 2018). Over the last three decades, the prevalence of atopic dermatitis in industrialized countries has increased two- to threefold and currently affects 15–30% of children and 2–10% of adults, making it one of the most common chronic inflammatory skin diseases (Barbarot et al., 2018; Nutten, 2015; Odhiambo et al., 2009). The rising incidence and chronic, recurrent course of AD make the disease a growing public health concern (Silverberg, 2017).

The etiopathogenesis of AD is multifactorial and involves genetic predisposition, environmental triggers, disturbances in innate and adaptive immunity, and impairment of the epidermal barrier (Weidinger et al., 2018). Filaggrin deficiency leading to reduced epidermal integrity promotes increased transepidermal water loss (TEWL) and the penetration of allergens, microorganisms and environmental irritants (Sroka-Tomaszewska & Trzeciak, 2021). This process activates multiple cytokine axes that induce chronic cutaneous inflammation, intense pruritus and dysregulated immune responses (Boguniewicz & Leung, 2011). Suppression of the innate cutaneous immune system by a pro-inflammatory microenvironment facilitates colonization of the skin by Staphylococcus aureus, further sustaining chronic inflammatory activity (Sivori et al., 2024).

The impact of AD extends beyond the visible skin lesions. Persistent pruritus, pain and skin hypersensitivity lead to a marked reduction in quality of life, sleep disturbances, and result in absences from work or school (Murota et al., 2025; Bawany et al., 2021). Inadequate disease control may result in social withdrawal and occupational exclusion, while the psychological burden associated with AD can predispose patients to anxiety, depression and, in severe cases, even suicidal ideation (Dalgard et al., 2015; Rønnstad et al., 2018). In the pediatric population, AD is additionally associated with an increased risk of visceral obesity and arterial hypertension (De Simoni et al., 2022).

Disease activity is assessed using standardized scoring systems such as SCORAD (Scoring Atopic Dermatitis), EASI (Eczema Area and Severity Index) and vIGA-AD (validated Investigator's Global Assessment for Atopic Dermatitis) (Schmitt et al., 2007; Hanifin et al., 2001). Each of these tools measures a distinct construct: SCORAD accounts for both lesion extent and morphology along with subjective symptoms such as pruritus and sleep disturbance; EASI focuses on the objective severity and distribution of skin lesions, whereas vIGA-AD is a simplified five-point instrument reflecting the clinician's global assessment of disease severity. The Peak Pruritus Numeric Rating Scale (PP-NRS) is one of the key tools for assessing itch intensity in clinical trials on atopic dermatitis and is currently considered a standard measure of antipruritic efficacy (Yosipovitch et al., 2019).

These scoring systems are used to stratify patients into mild, moderate, or severe AD. This

stratification directly informs the therapeutic approach. Objective assessment of disease severity enables not only the selection of appropriate initial therapy but also longitudinal monitoring of treatment response and timely identification of patients requiring escalation to systemic therapy (Wollenberg et al., 2025).

2. Current Pharmacologic Strategies in Atopic Dermatitis

The treatment of atopic dermatitis involves a multifaceted therapeutic approach aimed at controlling inflammatory symptoms, reducing pruritus, preventing disease flares, and improving patients' quality of life (Wollenberg et al., 2025). The foundation of therapy consists of avoiding triggering allergens and irritants, daily use of emollients and appropriate skin care, all of which play a key role in restoring the epidermal barrier and reducing transepidermal water loss (TEWL) (Maden, 2024). During disease flares, anti-inflammatory treatment is necessary - most commonly with topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI), adjusted to lesion severity, anatomical location and patient age. These therapies remain the mainstay of treatment for mild AD; however, in many patients their effectiveness is insufficient, particularly in cases of extensive skin involvement, predominant pruritus, and chronic relapsing disease (Wollenberg et al., 2025; Eichenfield et al., 2014).

In patients requiring systemic treatment, immunomodulatory and immunosuppressive agents, such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil, are used, although their utility is limited by adverse effects, the need for laboratory monitoring and, in some cases, the lack of long-term safety data (Wollenberg et al., 2025).

A breakthrough in AD therapy has been achieved with biologic agents targeting key cytokines of the type 2 inflammatory pathway, most notably dupilumab and tralokinumab. Although numerous studies have confirmed their efficacy and safety, a proportion of patients fail to achieve an adequate clinical response,

experience only partial improvement, or continue to suffer from persistent pruritus despite improvement of inflammatory lesions (Blauvelt et al., 2017; Silverberg et al., 2021). Additionally, certain adverse effects - such as conjunctivitis with dupilumab therapy - may limit treatment continuation in selected patients (Akinlade et al., 2019).

One of the most pressing clinical challenges remains pruritus control - patients consistently identify itch as the symptom with the most profound impact on quality of life (Vakharia et al., 2018). Even in the presence of effective control of cutaneous inflammation, pruritus may persist. In clinical practice, it is frequently observed that despite improvement in visible skin lesions, patients continue to report an unacceptable level of itch, which significantly limits the overall benefits of therapy. Another key therapeutic aspect is the speed of onset - both patients and clinicians emphasize the need for treatments providing rapid improvement, as a slowly developing response does not meet expectations and fails to ensure satisfactory comfort (Silverberg et al., 2023; Yosipovitch et al., 2020).

Despite the breakthrough represented by biologic therapies, multiple unmet needs remain in routine clinical practice: some available systemic therapies are limited by efficacy, long-term safety or accessibility, while a substantial proportion of patients either do not respond to biologics or experience only partial improvement. There also remains a clear need for oral therapies - whether as alternatives or complementary options to biologics - that provide ease of administration, high antipruritic efficacy, a predictable safety profile and feasibility for long-term use (Wollenberg et al., 2025). These unmet needs directly led to the development of therapies targeting the JAK–STAT pathway.

3. The JAK–STAT Pathway as a Therapeutic Target in Atopic Dermatitis

The JAK–STAT pathway has become one of the key therapeutic targets in atopic dermatitis due to its central role in regulating pro-inflammatory cytokine signaling (Huang et al., 2022; Schwartz et al., 2017). Janus kinases (JAKs) and STAT proteins form an interconnected molecular system attached to the intracellular domains of cytokine and growth factor receptors, mediating the transduction of extracellular signals to the cell nucleus and initiating transcription of genes responsible for immune responses (O'Shea & Plenge, 2012). This system consists of four kinases (JAK1, JAK2, JAK3 and TYK2) and seven STAT proteins, which form various dimer combinations depending on the cell type and the activated receptor. As a result, inhibition of different JAK enzymes translates into modulation of distinct cytokine groups, allowing selective interference with specific inflammatory pathways (Miot et al., 2023).

Unlike conventional immunosuppressive agents such as cyclosporine and corticosteroids, which broadly suppress multiple inflammatory mediators, JAK inhibitors enable a more targeted immunologic intervention (Damsky & King, 2017). Their therapeutic activity is also broader than that of biologic agents that target a single cytokine, as JAK inhibition blocks the signaling of multiple cytokines simultaneously via the JAK–STAT pathway. This mechanism is particularly relevant in AD, where the predominant Th2 immune signature does not fully account for the disease's complexity. Sustained hyperactivation of numerous cytokines - including IL-4, IL-5, IL-10, IL-13, IL-31, IFN-γ, IL-22, IL-17 and IL-33 - creates a microenvironment of chronic cutaneous inflammation, contributing both to inflammatory lesion formation and to neuronal transmission of pruritus (Guttman-Yassky et al., 2018; Fania et al., 2022). Therefore, intervening at this shared signaling hub - the JAK-STAT pathway -provides a clinical advantage by modulating multiple inflammatory axes simultaneously. This results not only in effective reduction of skin lesions but also in rapid relief of pruritus, the symptom that most strongly affects patients' quality of life (Oetjen et al., 2017).

This combined effect, stemming from the inhibition of multiple cytokines at once, underpins the growing interest in therapies targeting the JAK–STAT pathway. Against this background, oral JAK1 inhibitors such as upadacitinib and abrocitinib, and the JAK1/JAK2 inhibitor baricitinib, have emerged as key candidates for the treatment of moderate-to-severe AD (Wollenberg et al., 2025).

4. Efficacy of Oral JAK Inhibitors

4.1 Upadacitinib

The efficacy of upadacitinib, a selective JAK1 inhibitor, has been clearly demonstrated in large clinical trials Measure Up 1 and Measure Up 2, which included a combined cohort of 1,609 patients aged 12–75 years with moderate-to-severe AD (Guttman-Yassky et al., 2021). Both analyses showed a pronounced, dose-dependent superiority of once-daily upadacitinib over placebo across all key endpoints. EASI-75 responses were achieved by 60% and 70% of patients receiving 15 mg upadacitinib and by 73% and 80% of those receiving 30 mg, compared with only 13–16% in the placebo groups. vIGA-AD 0/1 response rates followed a similarly robust trend, highlighting a clear therapeutic advantage. Importantly, upadacitinib demonstrated not only high rates of primary responses, but also deep clinical improvement, with EASI-90 and EASI-100 achieved significantly more often than in placebo groups, indicating the drug's capacity to induce near-complete remission of skin inflammation. Upadacitinib also led to clinically meaningful reductions in pruritus, with PP-NRS ≥4 improvement occurring several-fold more frequently than in placebo groups. For patients, this translates into rapid improvements in daily functioning and sleep quality, as well as relief from their most distressing symptoms (Yosipovitch et al., 2020; Vakharia et al., 2018).

Upadacitinib also demonstrated robust efficacy when used in combination with topical corticosteroids (TCS). In the AD Up trial, EASI-75 and EASI-90 responses at week 16 were significantly more frequent than in placebo, and long-term observations up to week 52 reproduced these effects (Reich et al., 2021). These findings support the use of TCS during the initial phase of systemic therapy for patients with a more severe AD phenotype, without reducing the effectiveness of the oral agent.

Long-term data provide additional clinically relevant insights. In an extension analysis including patients completing Measure Up 1, Measure Up 2 and AD Up, sustained upadacitinib efficacy was observed up to week 140 of treatment (Irvine et al., 2025). Rates of EASI-75, EASI-90, and vIGA-AD 0/1 remained consistently high, demonstrating that continuous long-term therapy maintains therapeutic benefit without loss of efficacy or need for cyclic withdrawal. Notably, 76% of patients who did not reach EASI-75 at week 16 achieved this response with continued therapy, indicating progressive improvement over time. Durable symptom control also applied to pruritus - PP-NRS ≥4 was maintained in 65% of patients receiving 15 mg and 71% receiving 30 mg, and approximately half achieved PP-NRS 0/1.

The clinical significance of upadacitinib is further underscored by head-to-head evidence. In the HEADS UP study, the 30 mg upadacitinib group achieved EASI-75 more frequently and demonstrated a faster reduction in pruritus compared with the dupilumab group (Blauvelt et al., 2021). Patients receiving upadacitinib showed greater improvement across all anatomical regions as early as week 1, with therapeutic effects sustained throughout the trial. Complete remission (EASI-100) was also more common in the upadacitinib group.

In the extension phase of HEADS UP, spanning up to 52 weeks, patients who initially received dupilumab were switched to upadacitinib (Blauvelt et al., 2023). A clear further improvement in disease control was observed upon switching. Among patients who did not reach EASI-75 after 24 weeks of dupilumab therapy, 88.5% achieved EASI-75 within 16 weeks following the switch, while 65% achieved EASI-90 and 30% reached full remission (EASI-100). Additionally, switching resulted in a rapid and clinically meaningful reduction in pruritus, irrespective of the prior response to dupilumab. The persistence of efficacy through week 52 indicates that transitioning to upadacitinib is a valuable strategy for patients with suboptimal biologic response - improving control of skin inflammation and enabling rapid relief of pruritus.

These findings were further confirmed in the LEVEL UP trial, in which patients treated with upadacitinib achieved EASI-90 significantly more often and experienced faster and greater reductions in pruritus than patients receiving dupilumab (Silverberg et al., 2024). This advantage applied to both quantitative outcomes (response rates) and qualitative outcomes (rate of improvement and impact on subjective symptoms).

4.2 Abrocitinib

In the JADE MONO-1 (Simpson et al., 2020) and JADE MONO-2 (Silverberg et al., 2020) trials, which included patients aged ≥12 years with moderate-to-severe AD treated with abrocitinib monotherapy, a clear superiority of abrocitinib over placebo was demonstrated across all major endpoints. EASI-75 and vIGA-AD 0/1 responses occurred significantly more frequently in the groups receiving 100 mg and 200 mg once daily, with a distinct dose-dependent effect - the highest clinical efficacy was observed with the 200 mg dose. Clinical improvement also extended to reductions in pruritus. Early and significant differences in PP-NRS scores were observed as soon as day 2 of treatment, and the median time to achieving a clinically meaningful reduction in pruritus (≥4-point PP-NRS improvement) was 14 days for the 200 mg dose versus 92 days for placebo (Silverberg et al., 2020).

The JADE TEEN trial (Eichenfield et al., 2021) supported these observations in adolescents aged 12–<18 years treated with abrocitinib in combination with topical corticosteroids (TCS). Both 100 mg and 200 mg doses led to significantly higher rates of clinical response compared with placebo. The findings of JADE TEEN suggest that abrocitinib is an effective oral option for adolescents with moderate-to-severe AD - particularly in patients requiring enhanced disease control despite topical therapy. The results of this study confirm that the drug's therapeutic profile is consistent across age groups, reinforcing its applicability in both adolescents and adults.

The head-to-head JADE COMPARE study (Bieber et al., 2021), which directly compared abrocitinib with dupilumab, generated key evidence distinguishing the clinical profiles of the two therapies. After 12–16 weeks of treatment, abrocitinib 200 mg provided comparable overall control of skin inflammation but demonstrated the clearest superiority in reducing pruritus. Improvement of ≥4 points in PP-NRS occurred as early as day 2 with abrocitinib, whereas patients treated with dupilumab required an average of approximately 4 weeks to achieve a comparable reduction. This difference in the speed of action highlights the uniquely rapid antipruritic effect of abrocitinib, which is particularly valuable in patients with severe and persistent itch.

Long-term effectiveness was further supported by the JADE EXTEND open-label extension study (Reich et al., 2023), which included 1116 adults and adolescents who completed prior phase 3 JADE trials - JADE MONO-1, JADE MONO-2, JADE COMPARE and JADE TEEN. Treatment with abrocitinib 100 mg or 200 mg once daily resulted in sustained clinical efficacy throughout 48 weeks of observation. EASI-75 and vIGA-AD 0/1 responses remained stable, while control of pruritus and improvements in quality of life were maintained without attenuation over time.

The JADE REGIMEN trial further demonstrated the importance of continuous therapy by evaluating the impact of maintaining versus withdrawing abrocitinib treatment after initial induction (Blauvelt et al., 2022). Clinically good responders were randomized to continue therapy or transition to placebo. The findings showed that treatment discontinuation led to a pronounced and relatively rapid relapse - affecting both skin inflammation and pruritus - whereas patients continuing therapy, particularly at the 200 mg dose, maintained stable remission with high rates of EASI-75 and EASI-90 responses and durable improvements in quality of life.

4.3 Baricitinib

In the BREEZE-AD1 and BREEZE-AD2 trials (Simpson et al., 2020), baricitinib administered as monotherapy demonstrated significantly greater clinical efficacy than placebo. At week 16, baricitinib significantly increased the rates of vIGA-AD 0/1 and EASI-75 responses in a dose-dependent manner, with the highest efficacy observed with the 4 mg dose. Improvements in skin signs were accompanied by enhanced quality of life, as reflected by DLQI and POEM outcomes.

Long-term efficacy of baricitinib was confirmed in the BREEZE-AD3 extension study (Silverberg et al., 2021). Clinical responses were maintained through week 68 of treatment, indicating durable therapeutic benefit with prolonged use. Although modest fluctuations in the proportion of patients achieving EASI-75 were observed in the 4 mg group, this variability did not apply to the more stringent endpoint of vIGA-AD 0/1, which remained stable over time. These findings suggest that minor variability in EASI measurements did not compromise the maintenance of the deepest clinical endpoint, with clear or almost clear skin remaining stable throughout follow-up. Long-term reductions in pruritus and improvements in quality of life were likewise maintained.

Combination therapy with baricitinib and topical corticosteroids (TCS) provided additional clinical benefit. In the BREEZE-AD7 trial (Reich et al., 2020), adding baricitinib to standard TCS treatment resulted in significantly higher rates of improvement in skin inflammation and pruritus, with the greatest benefit - both

in magnitude and speed of action - observed at the 4 mg dose. These effects remained stable through week 68 of treatment (Silverberg et al., 2023).

The clinical relevance of combination therapy was emphasized in the BREEZE-AD4 trial (Bieber et al., 2022), which enrolled patients with moderate-to-severe AD whose prior treatment with cyclosporine had been ineffective or poorly tolerated. In this therapeutically challenging population, baricitinib 4 mg combined with TCS enabled clinically meaningful improvement in skin inflammation and pruritus, with responses maintained through week 52. These results indicate that baricitinib may be a particularly valuable option for patients with severe AD requiring second-line systemic therapy after cyclosporine failure, offering effective and durable disease control.

The efficacy of baricitinib has also been demonstrated in pediatric patients in the BREEZE-AD PEDS trial (Torrelo et al., 2023), which included children and adolescents aged 2–<18 years with moderate-to-severe AD. The highest dose (equivalent to 4 mg in older patients) demonstrated a clear advantage over placebo in both primary endpoints (vIGA-AD 0/1) and deeper responses such as EASI-75 and EASI-90. Benefits were not limited to skin lesions; patients treated with baricitinib experienced significant reductions in pruritus, improved sleep, and reduced need for topical corticosteroids. These findings suggest that baricitinib may represent a valuable systemic oral treatment option for younger patients with AD, particularly when therapeutic goals include simultaneous control of skin inflammation, reduction of pruritus, and improved daily functioning.

5. Safety of Oral JAK Inhibitors

The safety of JAK inhibitors in atopic dermatitis is a clinically relevant topic, determined both by their mechanism of action and by the specific characteristics of patients with chronic immune-mediated disease (Huang et al., 2022). Inhibition of the JAK–STAT pathway affects a broad spectrum of cytokines involved in inflammatory and immune responses, which on one hand underlies the high clinical efficacy of these agents, but on the other introduces a characteristic class-wide adverse event profile (Fania et al., 2022; Schwartz et al., 2017). It is important to note that patients with moderate-to-severe AD already demonstrate an increased susceptibility to both cutaneous and systemic infections prior to treatment initiation. This is attributable to immune dysregulation, impaired epidermal barrier function, Staphylococcus aureus colonization, and chronic pruritus causing repetitive microtrauma (Yosipovitch et al., 2019; Boguniewicz & Leung, 2011).

Across placebo-controlled trials, the safety profile of JAK inhibitors in AD is characterized by a predictable and reproducible pattern of adverse events. The most frequently reported events include upper respiratory tract infections, nasopharyngitis, headache, acne and transient elevations in creatine kinase (Tsai et al., 2024). Most of these events were mild or moderate in severity, resolved spontaneously or with continued therapy, and infrequently led to permanent treatment discontinuation (Guttman-Yassky et al., 2021; Simpson et al., 2020; Bieber et al., 2021).

Certain adverse events require particular clinical vigilance, including herpesvirus infections - herpes simplex, herpes zoster, and eczema herpeticum. Although most episodes are mild to moderate in severity and respond well to antiviral therapy, their potential for recurrence and the possibility of more severe presentation in patients with poorly controlled disease justify increased clinical attention. (Guttman-Yassky et al., 2021).

Characteristic and predictable laboratory abnormalities include transient hematologic deviations (especially thrombocytopenia), elevations in creatine kinase, and lipid abnormalities (Tsai et al., 2024). Dyslipidemia - involving increases in total cholesterol and LDL and HDL fractions - occurs relatively frequently but typically without deterioration in the LDL/HDL ratio, permitting continuation of therapy with appropriate lipid monitoring (Wollenberg et al., 2025). Major adverse cardiovascular events (MACE) and venous thromboembolism (VTE) represent potential but rare risks. Their incidence in the AD population remains very low (Yoon et al., 2024). Long-term AD studies do not show increasing rates of MACE or VTE over time (Irvine et al., 2025).

Current evidence suggests that the safety profile of JAK inhibitors in atopic dermatitis may be more favorable than in rheumatologic or gastroenterologic conditions, in which the risk signal for VTE and major cardiovascular events has been more pronounced (Ytterberg et al., 2022). These differences may be explained by the younger and metabolically less burdened AD population, the dominance of a Th2 immune signature, and the absence of chronic systemic inflammation with a pro-thrombotic profile observed in conditions such as rheumatoid arthritis or inflammatory bowel disease (Howell et al., 2019). A network meta-analysis including more than 10,000 patients with moderate-to-severe AD demonstrated that selective JAK1 inhibitors (such as upadacitinib and abrocitinib) were not associated with a significantly increased incidence of malignancy compared with placebo (Manzar et al., 2024).

Long-term data in AD do not indicate a gradual increase in adverse event frequency with prolonged exposure to JAK inhibitors. In multiyear analyses, no progressive rise in opportunistic infections, cardiovascular complications or thromboembolic events was observed, and laboratory abnormalities remained stable and predictable (Irvine et al., 2025; Reich et al., 2023; Bieber et al., 2021). This long-term safety stability is particularly relevant given the chronic and relapsing nature of AD and the frequent need for continuous therapy. Based on these observations, class-specific safety recommendations have been established, including routine monitoring of complete blood count with differential and ALT/AST levels - particularly during the early months of treatment - periodic evaluation of lipid profile, and heightened clinical vigilance for herpesvirus infections, especially herpes zoster and herpes simplex (Wollenberg et al., 2025).

5.1 Safety Profile of Upadacitinib

The safety profile of upadacitinib exhibits the typical characteristics of the JAK inhibitor class, while also presenting some features specific to this molecule. The most common adverse event was acne, reported significantly more frequently than in placebo and dupilumab groups. Lesions were generally mild to moderate in severity, primarily located on the face and trunk, showed no tendency toward scarring, and rarely led to treatment discontinuation - suggesting a limited clinical impact despite the relatively high incidence. Other frequently reported adverse events included upper respiratory tract infections, nasopharyngitis, headache, and elevated creatine kinase - events that were predominantly mild to moderate and typically resolved spontaneously or during continued therapy (Guttman-Yassky et al., 2021; Reich et al., 2021; Silverberg et al., 2024). Among infectious complications, a slightly increased risk of herpes zoster has been observed compared with dupilumab; most cases involved a single dermatome, were mild to moderate in severity, and resolved without requiring permanent treatment interruption. No cases of central nervous system involvement, disseminated infection, or severe herpesvirus disease were reported (Silverberg et al., 2024).

Laboratory abnormalities including transient elevations in ALT/AST, increased creatine kinase activity, and less frequently mild anemia and neutropenia were predominantly mild, transient and asymptomatic. These changes typically resolved spontaneously or during continued treatment and only occasionally required temporary treatment interruption (Guttman-Yassky et al., 2021; Reich et al., 2021; Silverberg et al., 2024). The preserved laboratory profile, along with the low incidence of clinically meaningful events, indicates that observed deviations in laboratory parameters rarely translate into clinical consequences.

A key aspect of risk assessment is the stability of safety over time. Long-term analyses up to 140 weeks showed few serious adverse events, low rates of treatment discontinuation due to safety concerns, and no evidence of increasing risk with cumulative exposure (Irvine et al., 2025). The safety profile has remained predictable and consistent across Measure Up 1/2, AD Up and the head-to-head HEADS UP study. Collectively, the data indicate that upadacitinib is well tolerated, with a predictable adverse event profile in which class-specific JAK inhibitor risks are typically mild and rarely require therapeutic intervention. Therefore, when patients are adequately selected and laboratory parameters appropriately monitored, the long-term safety of upadacitinib is considered favorable in the context of treating moderate-to-severe AD.

5.2 Safety Profile of Abrocitinib

Abrocitinib, while sharing the class-wide adverse event spectrum of JAK inhibition, displays a distinct clinical signature dominated by nausea, particularly at the 200 mg dose. Nausea typically appears early in the course of treatment, is mild to moderate in severity, and has a median duration of 13 days. Other frequently reported adverse events include nasopharyngitis, headache, and upper respiratory tract infections (Simpson et al., 2020; Silverberg et al., 2020).

In both adult and adolescent populations, a clinically relevant but predictable laboratory change was transient, dose-dependent thrombocytopenia, peaking at approximately week 4 of treatment, after which platelet counts gradually returned toward baseline regardless of treatment continuation (Silverberg et al., 2020; Eichenfield et al., 2021).

Herpesvirus infections, including herpes simplex and herpes zoster, occurred more frequently in patients receiving abrocitinib than in placebo groups; however, the vast majority of cases were mild, localized, and responded well to antiviral therapy (Silverberg et al., 2020).

In the head-to-head comparison of abrocitinib and dupilumab (Bieber et al., 2021), the overall incidence of adverse events was higher in the abrocitinib 200 mg group than in the dupilumab group; however, most adverse events were mild or moderate in severity. The most characteristic adverse event associated with abrocitinib was nausea (11.1%), whereas conjunctivitis was most typical for dupilumab. Herpesvirus infections,

including herpes zoster, were observed exclusively in the abrocitinib group, but did not require treatment discontinuation or dose modification, and no cases were multidermatomal. Thrombocytopenia also occurred only in the abrocitinib group but was rare (0.9%) and did not lead to serious clinical consequences. The rates of serious adverse events and treatment discontinuation due to adverse events were comparable between groups, indicating that both therapies are well tolerated.

Long-term data (through 48 weeks) indicate stability of the safety profile over time, with no evidence of increasing rates of serious infections, laboratory abnormalities or thromboembolic complications with prolonged exposure (Reich et al., 2023; Blauvelt et al., 2022). In clinical practice, the key measures remain monitoring of complete blood count (particularly platelet count) during the early weeks of treatment and patient education regarding typical mild gastrointestinal symptoms, which usually resolve despite continued therapy (Wollenberg et al., 2025). Overall, the adverse-event profile of abrocitinib is predictable, clinically manageable, and responds well to routine monitoring, making it a mature and safe therapeutic option for appropriately selected patients with AD.

5.3 Safety Profile of Baricitinib

The safety profile of baricitinib in atopic dermatitis has been well characterized across placebo-controlled trials and long-term extension studies. The most frequently reported adverse events were upper respiratory tract infections, nasopharyngitis, headache, diarrhea, and asymptomatic elevations in creatine kinase (CPK). These events were generally mild to moderate in severity, resolved spontaneously or while treatment was continued, and rarely resulted in permanent treatment discontinuation. Herpes simplex and herpes zoster infections occurred more frequently in baricitinib-treated groups than in placebo, although most episodes were mild, localized, and self-limited (Bieber et al., 2021; Simpson et al., 2020; Silverberg et al., 2021).

Safety in the pediatric population (2–<18 years) was confirmed in the BREEZE-AD PEDS trial, where the incidence of adverse events was comparable across all doses of baricitinib and placebo (50.0–53.5% vs 50.0%), indicating good tolerability in this patient group (Torrelo et al., 2023). The adverse-event profile in children and adolescents closely mirrored that observed in adults - most events were mild or moderate, severe adverse events were rare and similar to placebo, and the most frequently reported AEs included abdominal pain, acne, headache, diarrhea, nasopharyngitis and upper respiratory tract infections, with comparable frequencies between baricitinib and placebo. No increased risk of cardiovascular complications or serious infections was observed; notably, there were no cases of venous thromboembolism, major adverse cardiovascular events, gastrointestinal perforation or malignancies. Collectively, BREEZE-AD PEDS confirms a favorable and predictable safety profile for baricitinib in pediatric patients, without signals suggesting age-specific safety concerns.

A distinctive safety feature of baricitinib relative to other oral JAK inhibitors used in AD is its minimal effect on hematologic parameters, without the platelet count reductions or other hematologic deviations observed more frequently with abrocitinib (Bieber et al., 2021; Silverberg et al., 2020). This characteristic supports the potential clinical usefulness of baricitinib in patients with pre-existing hematologic abnormalities or increased risk of anemia, neutropenia or thrombocytopenia.

Long-term observational data have not shown increases in the incidence of systemic complications over time. No signals of increased risk for major adverse cardiovascular events (MACE), venous thromboembolism (VTE) or malignancy were identified, and cumulative safety indicators remained stable throughout follow-up (Bieber et al., 2021; Silverberg et al., 2023). Overall, available evidence indicates that baricitinib has a favorable and predictable safety profile, representing a particularly valuable option for long-term treatment of moderate-to-severe AD.

6. Discussion

The results of the studies reviewed demonstrate that oral JAK inhibitors represent an important expansion of therapeutic options for moderate-to-severe atopic dermatitis, addressing a range of clinical needs that have remained unmet for years despite the availability of topical and biologic therapies (Wollenberg et al., 2025). These treatments align with four key domains of clinical expectations: speed of onset, depth of response, durability of effect, and convenience of administration (Guttman-Yassky et al., 2021; Simpson et al., 2020; Silverberg et al., 2020; Bieber et al., 2022). From a practical perspective, oral administration enables treatment for patients who do not wish to receive injectable agents, are unable to do so, or have not achieved satisfactory outcomes with biologic therapy. Consequently, JAK inhibitors are positioned not as competitors but as

complementary to biologics - expanding the possibilities for individualized systemic therapy (Blauvelt et al., 2021; Silverberg et al., 2024; Bieber et al., 2021).

Although all JAK inhibitors share a common mechanism of action, they are not interchangeable, and each presents a distinct clinical profile. This differentiation supports therapeutic individualization based on disease phenotype, dominant symptoms and treatment goals.

Upadacitinib demonstrates the highest overall efficacy among available systemic therapies for AD, with exceptionally high rates of EASI-90 and EASI-100 responses sustained over time (Guttman-Yassky et al., 2021; Irvine et al., 2025; Reich et al., 2021). These characteristics suggest particular suitability for patients with high disease activity, where the therapeutic objective extends beyond improving skin inflammation to achieving near-complete remission. Head-to-head findings reinforce this view - upadacitinib outperforms dupilumab in speed of clinical response, pruritus reduction and deep response rates, highlighting its value for patients with partial or inadequate response to biologic therapy (Blauvelt et al., 2021; Blauvelt et al., 2023; Silverberg et al., 2024).

Abrocitinib is characterized by the most rapid and pronounced antipruritic effect, with PP-NRS improvement achieved within 48 hours of initiation (Silverberg et al., 2020). Its superiority in itch reduction has also been demonstrated in direct comparison with dupilumab (Bieber et al., 2021). This property may be of particular clinical relevance in patients in whom pruritus predominates and where rapid onset of action is a therapeutic priority. Findings from JADE EXTEND and JADE REGIMEN collectively underline two essential clinical aspects of abrocitinib: (1) high levels of response can be sustained long-term during continuous treatment, and (2) maintenance of remission depends on continuation of therapy (Reich et al., 2023; Blauvelt et al., 2022). These observations support the role of abrocitinib as an effective long-term systemic therapy, especially when durable control of pruritus and reduction of flare-associated rescue therapy are prioritized.

Baricitinib demonstrates lower rates of deep responses than upadacitinib and abrocitinib; however, its efficacy profile remains clinically relevant - particularly in therapeutically challenging populations such as patients with prior cyclosporine failure and pediatric patients (Bieber et al., 2022; Torrelo et al., 2023). Its minimal effect on hematologic parameters may be of special significance in individuals with preexisting anemia, neutropenia or thrombocytopenia - situations where treatment with selective JAK1 inhibitors may require increased caution (Bieber et al., 2021; Wollenberg et al., 2025). Another clinically relevant feature of baricitinib is its low risk of ocular adverse events, particularly conjunctivitis, which has limited tolerability in some patients receiving dupilumab (Bieber et al., 2021; Akinlade et al., 2019). Accordingly, baricitinib may be the most suitable option for patients requiring systemic therapy who (1) do not tolerate cyclosporine, (2) have hematologic contraindications to JAK1 inhibitors, or (3) present ocular adverse events during biologic treatment. Baricitinib offers high clinical utility through its balance of moderate efficacy and a highly predictable, well-tolerated safety profile.

The diversity of therapeutic profiles among JAK inhibitors corresponds directly with the evolving paradigm of treatment personalization in AD, in which therapy selection is guided not only by disease severity but also by dominant symptoms, prior treatment history, patient preference and comorbidities. Another important dimension of JAK inhibitor use is patient-centred decision-making. Clinical experience and surveys consistently demonstrate that patients with AD value rapid improvement and convenience of use as highly as objective skin clearance. For many individuals, the ability to take an oral therapy rather than an injectable biologic plays a key role in treatment acceptance and adherence. Incorporating these preferences into therapeutic planning may therefore improve long-term disease control and treatment satisfaction (Silverberg et al., 2024; Wollenberg et al., 2025).

JAK inhibitors are used not only in AD but also in a range of other inflammatory conditions, for which several agents hold regulatory approval. In clinical practice, this means that patients with AD and coexisting immune-mediated diseases may derive additional therapeutic benefit from JAK inhibition. This applies particularly to individuals with coexisting alopecia areata, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis or inflammatory bowel disease. Given the overlap in immunopathogenic pathways - most notably cytokine signaling through the JAK–STAT pathway - JAK inhibitors offer the potential for therapeutic benefit not only in AD but also in coexisting immune-mediated disorders. (Konzett et al., 2025; Wollenberg et al., 2025; Howell et al., 2019).

Safety findings are consistent across studies - adverse events are most often mild to moderate, predictable and manageable (Bieber et al., 2021; Tsai et al., 2024). Notably, long-term therapy has not been associated with increased risk of serious adverse events, including MACE, VTE or malignancy (Manzar et al.,

2024). This supports the feasibility of prolonged therapy in appropriately selected patients, a key point in managing a chronic and relapsing disease such as AD.

Despite a growing volume of clinical evidence, current knowledge remains subject to important limitations. There are still no direct head-to-head comparisons of all three available JAK inhibitors, limiting the ability to determine optimal therapeutic selection for specific patient subgroups. Although long-term data are encouraging, real-world evidence is only beginning to emerge - particularly regarding multi-year treatment. Furthermore, optimal long-term treatment strategies and the potential role of gradual dose reduction or therapy withdrawal following stable remission remain insufficiently evaluated. Knowledge gaps also persist regarding special clinical populations, including pregnant or breastfeeding women, patients >65 years, and individuals with metabolic, cardiovascular or thromboembolic risk. These gaps highlight the need for continued research to refine benefit-risk assessment and update clinical recommendations accordingly.

Future evidence should additionally expand real-world data, encompassing long-term effectiveness and safety, patient-reported outcomes, adherence and the impact of treatment on social functioning. Finally, in the context of expanding systemic treatment options, pharmacoeconomic analyses - incorporating direct and indirect costs as well as quality-of-life metrics - will likely play an important role in shaping future clinical guidelines and reimbursement decisions.

7. Conclusions

The clinical evidence reviewed indicates that the oral JAK inhibitors - upadacitinib, abrocitinib and baricitinib - are becoming increasingly important in the management of moderate-to-severe atopic dermatitis, addressing therapeutic needs that have remained only partially met to date. The presented findings confirm their ability to achieve rapid and effective control of both skin inflammation and pruritus - the latter being a key determinant of quality of life for patients with AD. Differences among the agents in terms of onset of action, response profile and safety offer a meaningful opportunity for therapeutic personalization. Available safety data point to a predictable and stable adverse-event profile, with no indication of increasing risk of serious systemic complications during long-term therapy. At the same time, further research is needed - particularly head-to-head comparisons between JAK inhibitors, long-term treatment strategies and real-world evidence to fully define the optimal positioning of JAK inhibitors within the therapeutic algorithm for atopic dermatitis.

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