



JANUS KINASE INHIBITORS VERSUS DUPILUMAB IN MODERATE-TO-SEVERE ATOPIC DERMATITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with skin barrier dysfunction and immune dysregulation. In moderate-to-severe cases, systemic therapy is often required. Dupilumab has been widely used as a biologic therapy targeting the IL-4 and IL-13 pathways, whereas Janus kinase inhibitors (JAK inhibitors, JAKi) exert broader effects through inhibition of the JAK–STAT signaling pathway. This systematic review aimed to evaluate the efficacy and safety profile of JAK inhibitors compared with dupilumab in patients with moderate-to-severe AD. A systematic literature search was conducted using PubMed, ScienceDirect, and the Cochrane Library in accordance with the PRISMA guidelines. English-language articles published between 2020 and 2026 were independently screened by two authors. Eligible studies included adult and/or adolescent patients with moderate-to-severe atopic dermatitis and evaluated oral Janus kinase inhibitors (JAK inhibitors) and/or compared them with dupilumab. The primary outcome was the achievement of EASI-75, while secondary outcomes included the safety profile of the therapies. Eight studies met the inclusion criteria. JAK inhibitors, particularly upadacitinib and abrocitinib, demonstrated rapid clinical improvement, especially in pruritus reduction and achievement of EASI-75 responses. However, JAK inhibitors were more frequently associated with infections, herpes zoster, eczema herpeticum, acne, nausea, and laboratory abnormalities. In contrast, dupilumab was more commonly associated with conjunctivitis, keratitis, and injection-site reactions. JAK inhibitors demonstrated a faster onset of symptom improvement in several studies, particularly with respect to pruritus relief and early EASI responses. Nevertheless, their use should be carefully balanced against the risks of infections, herpes zoster, acne, and laboratory parameter abnormalities. Dupilumab remains an important biologic treatment option with a relatively stable safety profile, although ocular adverse events, such as conjunctivitis and keratitis, should be anticipated.

Keywords: abrocitinib; atopic dermatitis; dupilumab; EASI-75; janus kinase inhibitors; safety; upadacitinib

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INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease characterized by eczematous lesions, pruritus, and various skin morphological changes that may significantly impair patients' quality of life. The disease is driven by dysregulation of immune signaling pathways mediated by inflammatory cytokines, including IL-4, IL-13, IL-31, IL-22, interferon- γ , and thymic stromal lymphopoietin, through the Janus kinase-signal transducer and activator of transcription (JAK–STAT) pathway (Cui et al., 2026).

Current management of AD follows a stepwise approach, including avoidance of triggering factors, maintenance of skin hydration, and the use of topical therapies such as corticosteroids, calcineurin inhibitors, and phosphodiesterase-4 inhibitors. However, patients with moderate-to-severe disease often require more comprehensive systemic treatment. Conventional systemic immunosuppressive agents, including azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil, have demonstrated effectiveness in reducing clinical symptoms but are generally not considered standard guideline-recommended therapies for AD. This is largely due to concerns regarding their long-term safety profiles and potential adverse effects (Sedeh et al., 2022).

Targeted therapy has increasingly been utilized in the management of immune-mediated diseases. Dupilumab is a monoclonal antibody that acts as an IL-4 receptor alpha (IL-4R α) antagonist, thereby inhibiting IL-4 and IL-13 signaling pathways. It was the first biologic agent approved for the treatment of moderate-to-severe atopic dermatitis. Nevertheless, clinical studies have shown that only a proportion of patients achieve clear or almost clear skin after 16 weeks of treatment (Schuler et al., 2023). Janus kinase inhibitor (JAKi), including upadacitinib, abrocitinib, and baricitinib, have demonstrated superior clinical improvement through their ability to modulate a broader range of inflammatory cytokines. However, a comprehensive systematic review is still needed to evaluate the efficacy and safety of JAK inhibitors in comparison with dupilumab in patients with moderate-to-severe atopic dermatitis (Nogueira & Torres, 2021). This systematic review aimed to qualitatively summarize the comparative evidence regarding the efficacy and safety of oral Janus kinase inhibitors compared with dupilumab in patients with moderate-to-severe atopic dermatitis.

METHOD

A systematic literature search was conducted to identify clinical studies evaluating systemic therapies for the treatment of atopic dermatitis (AD) using PubMed, ScienceDirect, and the Cochrane Library databases. This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). Two authors independently searched the databases using the following keywords: ("Dermatitis, Atopic"[MeSH] OR "atopic dermatitis" OR "atopic eczema") AND ("Janus Kinase Inhibitors"[MeSH] OR "JAK inhibitor" OR upadacitinib OR abrocitinib OR baricitinib) AND dupilumab. In addition, relevant studies were identified through manual screening of the reference lists of key articles and review papers.

The inclusion criteria comprised original research articles published in English that involved adult and/or adolescent patients aged ≥ 12 years with a diagnosis of moderate-to-severe atopic dermatitis. Eligible studies were required to evaluate systemic treatment with Janus kinase inhibitors (JAK inhibitors), including upadacitinib, abrocitinib, or baricitinib, and/or compare these agents with dupilumab as a biologic therapy. Study designs eligible for inclusion included randomized controlled trials, head-to-head studies, observational cohort studies, real-world studies, propensity score-matched studies, as well as extension and treatment-switching studies reporting relevant clinical outcomes.

Studies were required to report at least one efficacy outcome, such as EASI-75, EASI-90, pruritus scores, Atopic Dermatitis Control Tool (ADCT), Numerical Rating Scale (NRS), or Dermatology Life Quality Index (DLQI), and/or safety outcomes, including adverse events, infections, ocular complications, laboratory abnormalities, or treatment discontinuation due to adverse events.

Studies were excluded if they met any of the following criteria: (1) not original research articles, including narrative reviews, systematic reviews, meta-analyses, editorials, clinical guidelines, case reports, or case series; (2) involved populations other than patients with atopic dermatitis or mixed populations without extractable subgroup data for atopic dermatitis; (3) evaluated non-JAK inhibitor systemic therapies without comparison to dupilumab; (4) did not report efficacy or clinical safety outcomes; or (5) were duplicate publications or secondary/post hoc analyses of datasets that had already been included.

The primary outcome of this review was the proportion of patients achieving EASI-75. Secondary outcomes included safety profiles, encompassing adverse events, infections, ocular complications, laboratory abnormalities, and treatment discontinuation due to adverse events.

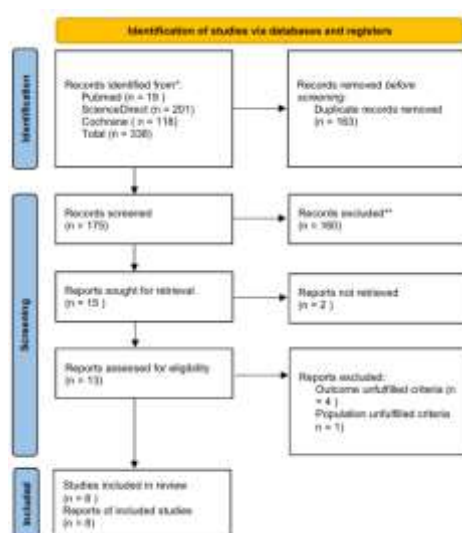


Figure 1. Flow Diagram of Study Selection According to the PRISMA Guidelines

Study selection was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The initial literature search of PubMed, ScienceDirect, and the Cochrane Library identified a total of 338 potentially relevant articles. After the removal of 163 duplicate records, 175 articles remained for title and abstract screening. Of these, 167 articles were excluded for not meeting the predefined inclusion criteria. Eight studies underwent full-text assessment, and all were deemed eligible for inclusion in the qualitative synthesis. Risk of bias was assessed using the revised Cochrane Risk of Bias tool (RoB 2) for randomized controlled trials and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for cohort studies (J. A. Sterne et al., 2016; J. A. C. Sterne et al., 2019).

RESULT

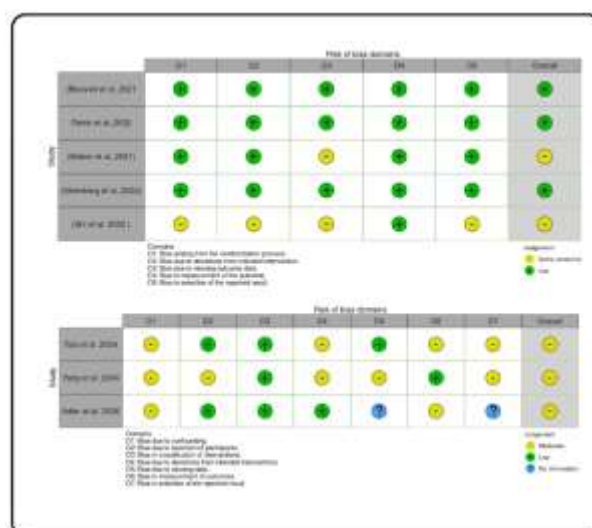


Figure 2. Risk of Bias Assessment Results for Individual Studies

The risk of bias assessment indicated that most randomized controlled trials (RCTs) were of good methodological quality. Studies by Blauvelt et al. (2021), Reich et al. (2022), and Silverberg et al. (2024) were assessed as having a low risk of bias across all domains of the RoB 2 tool. In contrast, Bieber et al. (2021) was rated as having some concerns, primarily related to the domain of missing outcome data. Similarly, Shi et al. (2022) demonstrated some concerns because of its extension and treatment-switching study design, which may be more susceptible to selection bias and incomplete outcome data. Among the observational studies assessed using the ROBINS-I tool, Tsai et al.

(2024), Yang et al. (2024), and Adler et al. (2026) were judged to have an overall moderate risk of bias. This was mainly attributable to potential confounding, limitations inherent to retrospective and real-world study designs, and incomplete information in certain assessment domains. Overall, the strongest evidence regarding treatment efficacy was derived from the RCTs, whereas the observational studies provided valuable supportive evidence, particularly for evaluating safety outcomes and the effectiveness of these therapies in routine clinical practice.

Table 1.

Systematic Review of the Baseline Characteristics of Included Studies

Authors / Studies	Comparison	Country	Study Type	Main Findings	Follow-up
Blauvelt et al., 2021 ⁷	Upadacitinib 30 mg vs dupilumab 300 mg	Multinational; 129 centers across 22 countries	RCT fase 3b, head-to-head, double-blind, double-dummy, active-controlled	EASI 75, EASI 90, EASI 100	24 weeks; primary outcome assessed at week 16. ⁷
Bieber et al., 2021 ⁸	Abrocitinib 200 mg or 100 mg versus Dupilumab 300 mg versus placebo, with background topical therapy	Multinational	RCT fase 3, double-blind, double-dummy	respons IGA and EASI-75	16 weeks; primary outcome assessed at week 12, with secondary outcomes evaluated at weeks 2 and 16.
Reich et al., 2022	Abrocitinib 200 mg versus Dupilumab 300 mg, with background topical therapy	Multinational	RCT fase 3, head-to-head, double-blind, double-dummy	early itch response, defined as PP-NRS4, and EASI-90 at week 4; EASI-90 outcomes at week 16.	26 weeks; primary outcomes assessed at weeks 2 and 4.
Silverberg et al., 2025 ⁹	Upadacitinib 15 mg with escalation to 30 mg in cases of inadequate response versus Dupilumab 300 mg administered according to the approved labeling.	Multinational	Phase 3b/4 randomized controlled trial (RCT), open-label with blinded efficacy assessors	EASI-90 dan WP-NRS 0/1	16 weeks for the initial treatment period.
Tsai et al., 2024 ¹⁰	Oral JAK inhibitors, namely Upadacitinib, Abrocitinib, or Baricitinib, versus Dupilumab	United States	Population-based, real-world, propensity score-matched cohort study	Comparative safety: oral JAK inhibitors versus Dupilumab	Up to 2 years following treatment initiation.
Shi et al., 2022	Abrocitinib 200 mg or 100 mg following prior use of Dupilumab	Multinational	Phase 3 extension study; analysis of patients switched from dupilumab to abrocitinib	EASI-75 response and treatment-related adverse events	12 weeks following the switch to abrocitinib.
Adler et al., 2026	Dupilumab vs JAK oral inhibitor	Real-world cohort	Real-world propensity score-matched analysis	This study evaluated ocular safety outcomes.	Not described in detail in the abbreviated abstract.
Yang et al., 2024	Upadacitinib vs dupilumab	China	Single-center, retrospective, real-world cohort study	EASI, ADCT, and NRS scores, as well as adverse events	12 weeks.

Table 2.
EASI-75 Effectiveness Outcomes

Study	Time point	EASI-75 JAKi	EASI-75 Dupilumab	Interpretation
Blauvelt et al., 2021	Week 16	248/342 or 72,4%	207/331 or 62,6%	Upadacitinib demonstrated higher efficacy than dupilumab.
Bieber et al., 2021	Week 16	157/221 or 71,0%	152/232 or 65,5%	Numerically higher outcomes were observed with upadacitinib compared with dupilumab; however, the difference was not statistically significant.
Reich et al., 2022	Week 26	254/348 or 73,0%	261/361 or 72,3%	Relatively similar
Silverberg et al., 2024	Week 2	26,7%	8,2%	A faster onset of response was observed; however, this was not the primary endpoint at Week 16.

A total of 4,752 patients were included in the analysis, comprising 2,372 patients in the JAK inhibitor group and 2,380 patients in the dupilumab group. Based on the five studies that reported age data for both treatment groups, the weighted mean age was approximately 35.5 years in the JAK inhibitor group and 35.2 years in the dupilumab group. Overall, the included studies demonstrated that oral JAK inhibitors were associated with a faster onset of symptom improvement than dupilumab, particularly with respect to pruritus relief and several early response outcomes. However, for some later endpoints, such as EASI-75 at Week 16 or Week 26, differences between abrocitinib and dupilumab were not consistently statistically significant. In the HEADS UP trial, upadacitinib 30 mg achieved higher rates of EASI-75 (71% vs. 61%) and EASI-100 (27.9% vs. 7.6%), as well as more rapid improvement in pruritus, compared with dupilumab at Week 16 (Blauvelt et al., 2021). In the study by Silverberg et al., upadacitinib demonstrated a faster onset of clinical improvement compared with dupilumab. The proportion of patients achieving an EASI-75 response at Week 2 was higher in the upadacitinib group than in the dupilumab group (26.7% vs. 8.2%) (Silverberg et al., 2024). In the JADE COMPARE and JADE DARE studies, abrocitinib 200 mg demonstrated more rapid improvement in pruritus than dupilumab, particularly with respect to early Peak Pruritus Numerical Rating Scale (PP-NRS4) responses. However, several skin-related outcomes at Week 16 were broadly comparable between the two treatment groups (Bieber et al., 2021; Reich et al., 2022). Several cohort studies consistently demonstrated that JAK inhibitors were associated with more rapid reductions in EASI and pruritus scores, greater improvements in quality of life, and a lower incidence of ocular adverse events compared with dupilumab (Adler et al., 2026; Tsai et al., 2024).

Table 3.
Systematic Review of Safety Profile Outcomes

Studies	Safety Outcomes of JAK Inhibitors versus Dupilumab	Duration of Follow-Up
Blauvelt et al., 2021	Upadacitinib was associated with higher rates of serious infections, eczema herpeticum, herpes zoster, and laboratory-related adverse events. In contrast, dupilumab was more frequently associated with conjunctivitis and injection-site reactions. No new safety signals were reported in either group.	16–24 weeks
Bieber et al., 2021	Abrocitinib was more frequently associated with nausea and acne, particularly at the 200 mg dose. Compared with dupilumab, abrocitinib 200 mg demonstrated superiority in early itch response; however, most key secondary outcomes at week 16 were not significantly different. Conjunctivitis tended to occur more frequently with dupilumab.	16 weeks
Reich et al., 2022	Abrocitinib 200 mg demonstrated an acceptable safety profile in head-to-head trials. In JADE DARE, adverse events requiring particular attention included nausea and acne with abrocitinib, whereas conjunctivitis was more prominent with dupilumab across the JADE trial analyses.	26 weeks
Silverberg et al., 2025	Upadacitinib was more frequently associated with acne, headache, common cold/nasopharyngitis, herpes zoster, and eczema herpeticum.	16 weeks

Studies	Safety Outcomes of JAK Inhibitors versus Dupilumab	Duration of Follow-Up
	Dupilumab was more commonly associated with ocular/eyelid inflammation and arthralgia. No new safety concerns were identified.	
Tsai et al., 2024	In real-world settings, oral JAK inhibitors did not demonstrate any new concerning safety signals; however, they were associated with an increased risk of infections and laboratory abnormalities. Dupilumab showed a higher risk of ophthalmic complications compared with oral JAK inhibitors.	Up to 2 years
Adler et al., 2026	Dupilumab was associated with an increased risk of conjunctivitis and keratitis compared with oral JAK inhibitors. This study is more appropriately used to discuss ocular adverse events rather than the effectiveness of cutaneous lesion improvement.	Not clearly specified in the brief abstract.
Shi et al., 2022	Following the switch from dupilumab to abrocitinib, serious adverse events were relatively uncommon. Conjunctivitis was more frequently observed while patients were receiving dupilumab, whereas nausea and acne occurred more commonly after switching to abrocitinib.	26 weeks of dupilumab treatment followed by 12 weeks of abrocitinib treatment.
Yang et al., 2024	The study reported effectiveness and safety outcomes in real-world clinical practice; however, detailed information regarding specific safety signals was not fully available from the open-access abstract.	12 weeks

Table 3 summarizes the safety profiles of Janus kinase inhibitors (JAK inhibitors) in the treatment of atopic dermatitis. Overall, JAK inhibitors were more frequently associated with systemic adverse events, including infections, herpes zoster, eczema herpeticum, acne, nausea, and laboratory abnormalities. In contrast, dupilumab was more commonly associated with ocular adverse events, particularly conjunctivitis and keratitis, as well as injection-site reactions. This pattern was observed in the study by Blauvelt et al. (2021), which reported higher rates of serious infections, herpes zoster, eczema herpeticum, and laboratory abnormalities in the upadacitinib group, whereas conjunctivitis and injection-site reactions were more frequently reported among patients receiving dupilumab. Similar findings were reported by Bieber et al. (2021) and Reich et al. (2022). Both studies found that abrocitinib was more commonly associated with nausea and acne, while ocular adverse events were more prominent in the dupilumab group. In the context of routine clinical practice, Tsai et al. (2024) highlighted the need for continued monitoring of patients receiving oral JAK inhibitors, as several studies reported a higher incidence of infections and laboratory abnormalities compared with dupilumab. Conversely, Adler et al. (2026) further supported the observation that dupilumab is associated with a higher risk of ocular inflammation than oral JAK inhibitors.

DISCUSSION

This systematic review demonstrated that oral JAK inhibitors, particularly upadacitinib and abrocitinib, tend to provide a faster onset of symptom improvement than dupilumab, especially with respect to pruritus relief and early clinical responses. However, this advantage in treatment onset should be considered alongside their safety profiles, as JAK inhibitors have been more frequently associated with infections, herpes zoster, acne, and laboratory abnormalities. In contrast, dupilumab has been more commonly associated with ocular adverse events.

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by skin barrier dysfunction and immune dysregulation. Genetic factors, particularly mutations in the filaggrin (FLG) gene, contribute to impaired epidermal integrity, rendering the skin more susceptible to allergens, irritants, and microbial colonization. From an immunopathophysiological perspective, AD is predominantly driven by type 2 inflammatory responses involving cytokines such as IL-4, IL-13, IL-31, IL-17, and IL-22 (G. Yang et al., 2020).

Advances in the understanding of the immunological pathways involved in AD have led to the development of targeted therapies, particularly dupilumab and Janus kinase (JAK) inhibitors. Dupilumab exerts its therapeutic effects by blocking IL-4 and IL-13 signaling through inhibition of

the IL-4 receptor alpha (IL-4R α), whereas JAK inhibitors, such as upadacitinib and abrocitinib, have a broader mechanism of action by inhibiting the JAK–STAT signaling pathway involved in multiple proinflammatory cytokine signaling cascades (Pappa et al., 2022).

The findings of this systematic review indicate that oral JAK inhibitors are effective treatment options for patients with moderate-to-severe atopic dermatitis, particularly in achieving rapid symptom improvement. EASI-75, defined as a reduction of at least 75% from baseline in the Eczema Area and Severity Index score, is commonly used as a measure of clinical efficacy in atopic dermatitis studies. In a head-to-head trial, Blauvelt et al. (2021) demonstrated that upadacitinib 30 mg achieved higher EASI-75 and EASI-100 response rates than dupilumab, accompanied by earlier improvement in pruritus. Among patients treated with abrocitinib, the JADE COMPARE study by Bieber et al. (2021) and the JADE DARE study by Reich et al. (2022) showed that abrocitinib 200 mg provided superior early pruritus relief compared with dupilumab, although several clinical outcomes assessed at later time points were broadly comparable between the treatment groups. Real-world evidence from Yang et al. (2024) further supported these findings, demonstrating greater early reductions in EASI, Atopic Dermatitis Control Tool (ADCT), and Numerical Rating Scale (NRS) scores with upadacitinib. Gargiulo et al. (2024) concluded that Janus kinase inhibitors represent effective therapeutic options for moderate-to-severe atopic dermatitis. However, their use in routine clinical practice should be individualized according to patient characteristics, treatment goals, comorbidities, and safety considerations (Gargiulo et al., 2024).

Nevertheless, the efficacy advantages of JAK inhibitors should be weighed against their safety profiles. Several studies have reported that JAK inhibitors are more frequently associated with infections, herpes zoster, eczema herpeticum, acne, nausea, and laboratory abnormalities. Supporting evidence from a pharmacovigilance study identified infection-related safety signals associated with oral JAK1 inhibitors, particularly upadacitinib and abrocitinib, based on data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) (Tang et al., 2025). The most prominent signal was herpes zoster, which represented the most frequently reported infectious adverse event associated with both agents. In addition, the study identified several established infection-related adverse events, including eczema herpeticum, herpes simplex infection, pneumonia, influenza, and urinary tract infections. Notably, the analysis also detected potential safety signals that have received limited attention in previous studies, including sepsis, appendicitis, and septic shock.

In contrast, dupilumab has been more commonly associated with conjunctivitis, keratitis, and injection-site reactions. Therefore, treatment selection for atopic dermatitis should be individualized, taking into account disease severity, the need for rapid symptom control, comorbidities, risk of infection, and the potential for ocular adverse events. The ocular complications associated with dupilumab are thought to result from inhibition of IL-13 signaling, which reduces conjunctival goblet cell density and mucin production. This may impair tear film stability and increase susceptibility of the ocular surface to inflammatory conditions, such as conjunctivitis and keratitis (Bakker et al., 2019)

Long-term safety analyses by Simpson et al. (2021) demonstrated that abrocitinib was generally well tolerated, although it remained associated with class-specific JAK inhibitor adverse events, including gastrointestinal symptoms, acne, and hematologic abnormalities. Similarly, a safety analysis by Guttman-Yassky et al. (2023) found that laboratory abnormalities associated with upadacitinib, including changes in hemoglobin levels, neutrophil and lymphocyte counts, creatine phosphokinase, and liver transaminases, were generally mild to moderate in severity. In contrast, the meta-analysis conducted by Ou et al. (2018) showed that dupilumab was more frequently associated with conjunctivitis and injection-site reactions, while demonstrating no substantial increase in the risk of systemic infections.

This review has several limitations. First, the included studies were heterogeneous in design, comprising randomized controlled trials, observational studies, propensity score–matched cohort studies, and treatment-switching studies. Second, follow-up durations and outcome assessment time points varied across studies, necessitating cautious interpretation when making direct comparisons between studies. Third, no quantitative meta-analysis was performed; therefore, conclusions regarding efficacy and safety are based on a qualitative narrative synthesis. Fourth, several real-world studies were subject to the potential influence of residual confounding and limitations in data completeness. Finally, long-term safety data remain limited for some treatment outcomes, highlighting the need for further research with extended follow-up periods.

CONCLUSION

Overall, oral JAK inhibitors demonstrated a faster onset of clinical improvement in patients with moderate-to-severe atopic dermatitis, particularly with respect to pruritus relief and early EASI responses. However, their use requires careful monitoring for potential adverse events, including infections, herpes zoster, acne, and laboratory abnormalities. Dupilumab remains an important biologic treatment option with a relatively stable safety profile, although ocular adverse events such as conjunctivitis and keratitis should be anticipated.

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