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Topical Janus Kinase Inhibitors for Atopic Dermatitis in Children Under 12 Years: A Systematic Review

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Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease with childhood onset. However, children with moderate-to-severe AD often do not achieve adequate disease control with current broad immunotherapies, leaving them with limited treatment options. The Janus kinase (JAK)-signal transducer and activator of transcription pathway is central to AD pathogenesis and an emerging therapeutic target. Ruxolitinib and delgocitinib are two topical JAK inhibitors that have been studied in pediatric populations. This structured literature review, utilizing a systematic search strategy, aimed to evaluate the efficacy and safety of topical JAK inhibitors in children under 12 years of age with AD. A systematic search of PubMed/MEDLINE and Cochrane CENTRAL was performed in accordance with PRISMA guidelines. Eligible studies included randomized controlled trials, open-label extension studies, and pharmacokinetic and safety studies of topical JAK inhibitors in patients under 12 years of age with AD. Systemic JAK inhibitor studies, adult-only trials, non-AD eczematous conditions, and non-peer-reviewed sources were excluded. Four eligible trials were identified. In children aged 2-11 years, ruxolitinib cream (0.75% and 1.5%) significantly improved investigator's global assessment 0/1 response, Eczema Area and Severity Index-75/90, pruritus, and quality of life compared with the control cream, and efficacy was maintained in long-term studies. Treatment was well tolerated, with mainly mild application-site reactions and minimal systemic exposure. Delgocitinib ointment (0.25% and 0.5%) demonstrated consistent efficacy and a favorable safety profile in Japanese pediatric populations, including infants as young as 6 months, and long-term follow-up studies showed sustained tolerability and undetectable plasma levels in most patients. Limitations included small sample sizes, short, blinded treatment periods, geographic restrictions, and a lack of head-to-head comparisons with standard therapies. Although limited, current evidence suggests that topical JAK inhibitors are effective and well-tolerated in children <12 years of age with AD, offering itch relief and potential as steroid-sparing options. Multinational, long-term pediatric trials are needed to define their comparative effectiveness and role in treatment.

Keywords: Atopic dermatitis, pediatric, JAK inhibitors

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Introduction

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases of childhood, affecting approximately 20% of United States (US) children and tens of millions worldwide. It imposes a significant burden on patients and families in terms of economic costs and reduced quality of life[1].

AD pathogenesis is multifactorial. Epidermal barrier defects permit allergen entry, while microbial dysbiosis and immune activation amplify disease. T helper type 2 cells (Th2) cytokines, along with Th17, Th22, and innate lymphoid cells, further sustain the inflammatory response[2]. First-line therapies such as emollients, topical corticosteroids, and calcineurin inhibitors are effective for many patients. However, children with widespread disease are often managed with off-label systemic immunosuppressants. These include cyclosporine or methotrexate, each of which carries a less favorable safety profile[3]. Dupilumab is currently the only systemic biologic approved for use in patients as young as 6 months of age; however, some patients remain uncontrolled or are intolerant[4,5].

Highlights

- Topical the Janus kinase (JAK) inhibitors show efficacy in children under 12 with atopic dermatitis.
- Ruxolitinib improves investigator's global assessment, Eczema Area and Severity Index, itch, and quality of life with minimal systemic exposure.
- Delgocitinib demonstrates sustained benefit and favorable safety in infants and children.
- Trials report mainly mild, localized adverse effects without systemic JAK-related signals.
- Larger, multinational pediatric studies are needed to define long-term safety and use.

These limitations highlight the need for additional, targeted approaches beyond broad immunosuppression. One such focus is the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway, which is central to AD pathogenesis. It integrates signals from cytokines such as interleukin 4 (IL-4), IL-13, IL-31, thymic stromal lymphopoietin, and IL-22[6]. Activation of this pathway compromises the epidermal barrier and promotes inflammation and pruritus[6,7]. Thus, JAK inhibition can simultaneously block multiple pathogenic drivers. In adults, treatment options have expanded to include JAK inhibitors, ranging from topical formulations to systemic agents such as abrocitinib, upadacitinib, and baricitinib for more extensive disease[8].

However, targeted treatment options for children under 12 remain limited, despite the onset usually occurring in childhood[9]. Ruxolitinib cream, a selective JAK1/2 inhibitor that blocks signaling by IL-4, IL-13, and IL-31, has recently been approved for children as young as 2 years of age, though its use is restricted to non-immunocompromised patients with limited body-surface-area involvement[10]. Delgocitinib ointment, a pan-JAK inhibitor targeting JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), is approved in Japan for pediatric AD but remains investigational in the US and Europe[11,12]. Safety, however, remains uncertain. Most data derive from adults, and pediatric use raises additional concerns about effects on immune maturation[13].

Extending JAK inhibitor therapy to this population would address a critical unmet need and could reduce the disease burden associated with uncontrolled AD[14]. This review summarizes current and emerging JAK-STAT-directed therapies for AD, emphasizing children under 12 years, for whom data remain sparse despite the high prevalence and early onset of AD.

Materials and Methods

Data Sources

We performed a systematic search in accordance with the PRISMA guidelines to identify clinical studies of topical JAK inhibitors in children under 12 years of age with AD. The search strategy and the study selection process are illustrated in **Figure 1**. PubMed/MEDLINE, PubMed Central, and Cochrane CENTRAL (including Embase, ClinicalTrials.gov, ICTRP, and CINAHL) were searched from inception to September 2025 without language restrictions. Ethical approval was not required as this study is a structured literature review of previously published data. Full electronic search strategies for all databases are provided in **Supplementary Table 1**.

Database searches yielded 185 records in total, of which 9 duplicates were removed. After screening and full-text review, 4 studies met the inclusion criteria. Of these, 3 were randomized, cream-controlled trials that formed the basis for the comparative efficacy evaluation, while 1 open-label study contributed safety and pharmacokinetic evidence. 3 additional ongoing trials were identified and reported separately (**Figure 1**).

Study Selection

Eligible studies included randomized controlled trials, open-label extensions, and pharmacokinetic or safety studies that (1) evaluated a topical JAK inhibitor, (2) enrolled patients with a clinical diagnosis of AD, and (3) reported outcomes for children under 12 years of age, either exclusively or as a subgroup. Exclusion criteria were (1) systemic JAK inhibitor studies, (2) adult-only populations (≥12 years), (3) non-AD eczematous conditions, (4) conference abstracts or registry records without peer-reviewed publication, and (5) reviews or commentaries. Duplicate records were manually consolidated, and reasons for exclusion were documented. When multiple publications reported the same study (e.g., primary trial reports and subgroup analyses), these were treated as a single study for study selection and PRISMA flowcharting. However, all relevant publications were included in the reference list.

Data Extraction

Key data were extracted from each eligible study, including study design, population characteristics, intervention details, efficacy outcomes [e.g., investigator's global assessment (IGA) response, Eczema Area and Severity

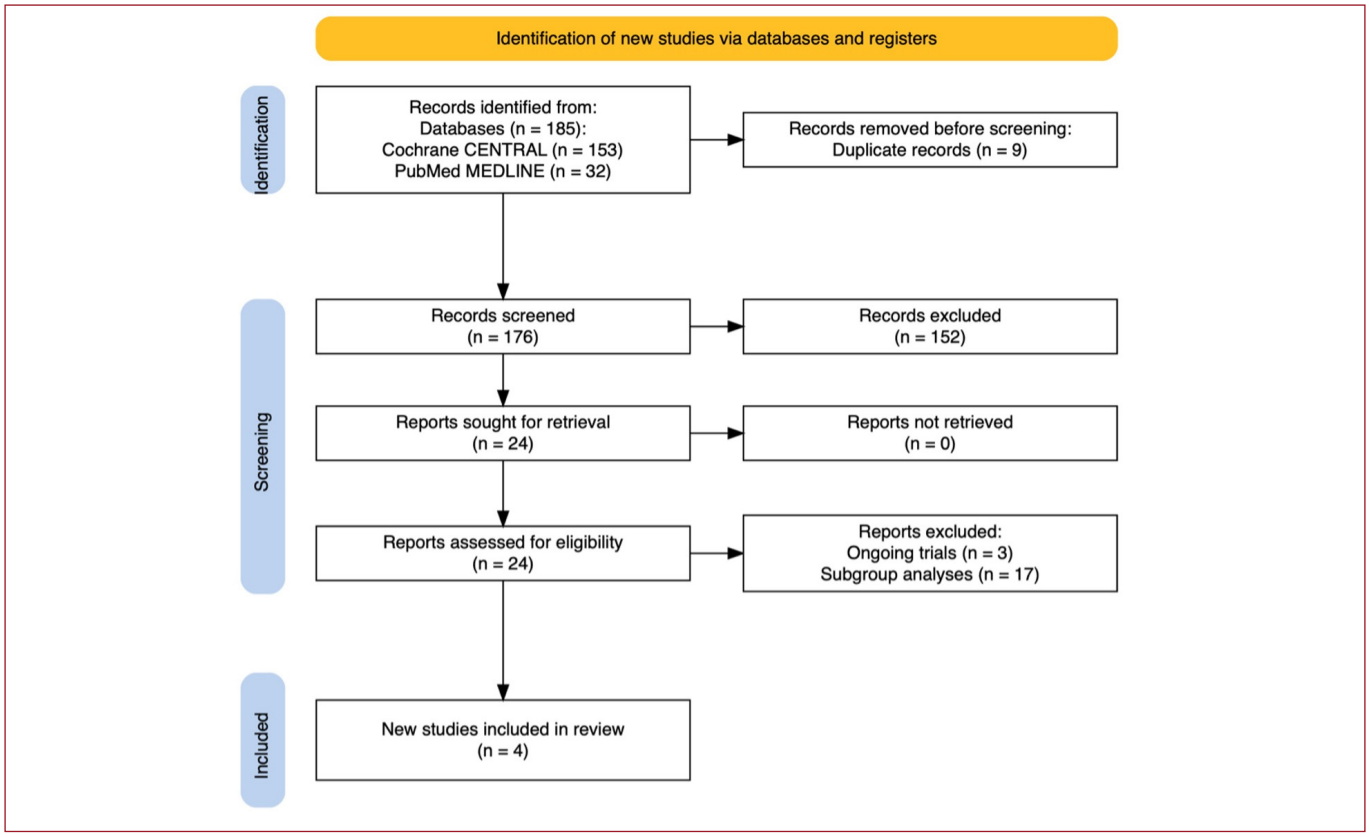

Figure 1. Identification of new studies via databases and registers

Index (EASI)-75/90, pruritus], and safety findings (including systemic exposure and adverse events). Given the small number of eligible studies and the heterogeneity of study designs, a qualitative synthesis was performed to summarize the efficacy and safety findings. No meta-analysis was performed due to the limited number of eligible studies and heterogeneity in study design and outcome reporting.

Results

Ruxolitinib

Clinical studies have demonstrated the efficacy and safety of ruxolitinib cream in children with AD. In the phase 3 TRuE-AD3 trial, 330 children aged 2-11 years were randomized to receive ruxolitinib 0.75% cream, ruxolitinib 1.5% cream, or control cream, twice daily for 8 weeks. At week 8, IGA treatment success was achieved by 36.6% and 56.5% of children in the ruxolitinib groups, respectively, versus 10.8% with the control cream, with parallel improvements in EASI-75/90, itch, and quality of life. The safety profile was favorable, with mostly mild application-site reactions and no systemic JAK-related adverse events[15]. Subgroup and pooled analyses confirmed efficacy across age groups, including adolescents and adults. A maximum-use study in children with extensive disease (≥35% body surface area) showed rapid disease control by week 4, maintained with as-needed use through 52 weeks, with reassuring safety and low systemic exposure[15]. In a larger cohort study of n=1,075 children over the age of 6 months, ruxolitinib also increased the rate of achieving an itch-free state compared with a control cream, with faster itch resolution observed in children than in adults[16].

Adverse

Across TRuE-AD3 (phase 3, n=330; ages 2-11), ruxolitinib 0.75/1.5% bis in die for 8 weeks was well tolerated; the safety profile in children matched that seen in adolescents and adults, with mostly mild application-site reactions and no systemic JAK-class safety signals reported during the 8-week blinded period[15]. In the pediatric maximum-use study, 31% of participants experienced treatment-emergent adverse events (AEs); no AEs of special interest were reported, including no serious infections, malignancies, major adverse cardiovascular events, or thromboses. Mean steady-state plasma levels also remained below the adult inhibitory concentration 50 for JAK-mediated myelosuppression[16]. A pooled phase-3 analysis focusing on the “itch-free state” further supports symptomatic benefit of topical ruxolitinib; safety findings in those trials were also favorable[17].

Delgocitinib

Delgocitinib ointment has been evaluated exclusively in Japan for the treatment of pediatric AD. In a phase 2 trial of children aged 2-15 years, both 0.25% and 0.5% ointment, applied twice daily, significantly improved modified EASI (mEASI) scores compared with control cream, with the higher dose providing greater benefit[12,18]. An important limitation of this trial is that children younger than 12 years were not included in the stratified analysis due to the limited cohort size. A subsequent phase 3 trial confirmed these findings, with a mean mEASI reduction of -39.3% versus +10.9% with control cream

at 4 weeks; extension data supported sustained efficacy and tolerability through 56 weeks. Based on changes in the mEASI, delgocitinib demonstrated a significantly greater improvement in disease severity compared with vehicle.

Post-hoc analyses showed that up to 71% of children with mild AD achieved IGA 0/1 with the 0.5% ointment, and that concomitant use with corticosteroids or tacrolimus did not raise safety concerns[19]. In a 52-week trial of 22 infants aged 6 to <24 months, both concentrations reduced mEASI scores; adverse events were mostly mild (e.g., viral infections, dermatitis exacerbations), and plasma levels were undetectable in most samples[20].

Adverse

Delgocitinib ointment inhibits JAK1, JAK2, JAK3, and TYK2, resulting in broad cytokine blockade. While this may confer additional anti-inflammatory benefit, it also raises theoretical concerns about safety with long-term use. However, in pediatric phase 2 and phase 3 trials with a 52-weeks extension, most AEs were mild and unrelated; no serious treatment-related AEs were reported, and efficacy gains were sustained through the extension[12,18]. A post-hoc analysis found no differences in safety signals between the 0.25% and 0.5% doses, including when co-administered with topical corticosteroids and/or tacrolimus[19]. Among infants aged 6 to <24 months (n=22; 52-weeks open-label), 95.5% experienced AEs (e.g., nasopharyngitis, dermatitis flares), but none were treatment-related. Plasma delgocitinib was undetectable in most samples, suggesting minimal systemic exposure[20].

Discussion

Topical JAK inhibitors represent an emerging therapeutic class for pediatric AD, offering rapid antipruritic effects and improvements in disease severity with generally favorable safety profiles[17,18]. Across randomized and supportive clinical studies, both ruxolitinib and delgocitinib have demonstrated robust short-term efficacy in children under 12 years of age, with sustained benefit observed in extension and maximum-use studies[16]. Importantly, adverse events have been largely limited to mild, localized reactions; systemic JAK-related safety signals have not been observed even with longer treatment durations or application to extensive body-surface areas[15,20]. Regulatory updates have further clarified pediatric indications for ruxolitinib cream[21]. These findings suggest that topical JAK inhibitors may serve as viable steroid-sparing options for this population. However, no head-to-head pediatric trials have directly compared JAK inhibitors with topical corticosteroids or calcineurin inhibitors. Therefore, inferences regarding comparative efficacy should be evaluated cautiously. A comparison of randomized controlled trials of topical JAK inhibitors in children under 12 years of age with AD is summarized in **Supplementary Table 2**.

Beyond trials, limited observational evidence also supports a growing clinical interest in topical JAK inhibitors in children. A retrospective study from India reported that topical JAK inhibitors led to greater improvements in EASI scores, pruritus, and quality of life than corticosteroids, without additional safety concerns[21]. Although the design and reporting limitations temper the interpretation, such findings highlight the need for well-designed real-world pediatric studies to complement trial evidence.

Taken together, the available data indicate that topical JAK inhibitors are effective and well tolerated in children with AD, with particular strength in pruritus control and quality-of-life improvement. Topical JAK inhibitors have also gained considerable traction among clinicians and patients as rapid, steroid-sparing options, reflecting their favorable short-term safety and efficacy profiles[19]. However, further research is needed to establish their long-term safety, comparative effectiveness, and role in treatment algorithms relative to that of existing topical therapies, particularly in children under 12 years of age.

Study Limitations

Several limitations of the available evidence should be considered. For ruxolitinib, TRuE-AD3 reports primary outcomes only through 8 weeks, limiting blinded inference regarding longer-term safety and efficacy. Its enrollment was restricted to North America, which may limit generalizability[15]. The maximum-use dataset included a small sample (n=29) and was open-label after week 4; concomitant therapy adjustments and pro re nata use may have introduced confounding[16]. Evidence to date is limited to cream-controlled trials, with no head-to-head pediatric trials versus topical corticosteroids or calcineurin inhibitors. Regulatory context has evolved (food and drug administration approval now extends to children ≥2 years), but these changes do not address underlying evidence limitations[10,20].

All pediatric trials of delgocitinib were conducted exclusively in Japan, limiting global generalizability. The blinded periods were short (4 weeks), and the extension phases were open-label and lacked control groups, thereby permitting rescue therapy and complicating long-term comparative inference[19]. Sample sizes were modest, and some supportive findings were derived from post-hoc analyses, which are hypothesis-generating rather than confirmatory.

Ongoing Clinical Trials

Our search identified several ongoing trials investigating topical JAK inhibitors in pediatric patients with AD. These include NCT06832618, a phase III randomized, double-blind trial evaluating ruxolitinib cream in children and adolescents aged 6 to <18 years with moderate disease, with an estimated primary completion in July 2026[22]. In addition, two trials of delgocitinib ointment are registered in Japan: Japan Primary Registries Network (JPRN)-jRCTs031240119[23], which is assessing delgocitinib in combination with topical corticosteroids for remission induction in pediatric patients, and JPRN-jRCTs031230314[24], a randomized controlled study evaluating delgocitinib ointment for maintenance of remission. Results from these studies will provide further evidence on the efficacy and safety of JAK inhibitors in younger populations. Characteristics of ongoing pediatric trials are summarized in **Supplementary Table 3**.

Conclusion

Topical JAK inhibitors, particularly ruxolitinib and delgocitinib, have demonstrated promising efficacy and a favorable safety profile in children under 12 years with AD. They offer fast-acting itch relief and potential for steroid-sparing disease control. Nonetheless, long-term safety, head-to-head comparisons with established therapies, and larger global pediatric trials remain essential to fully define their place in clinical practice.

Ethics

Ethics Committee Approval: Ethical approval was not required as this is a review of previously published data.

Footnotes

Author Contributions: Garg K: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Ozuzu U: Concept, Design, Writing; Khachemoune A: Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors declare no conflicts of interest.

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Supplementary Tables: https://jpediatricacademy.com/index.php/jpa/article/view/514/306

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