Efficacy and Safety of Janus Kinase Inhibitors for the Treatment of Atopic Dermatitis: A Systematic Review and Meta-Analysis

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\textbf{Abstract}

\textbf{Background:} Current therapeutic options for atopic dermatitis (AD) are limited. Janus kinase (JAK) inhibitors may be viable alternatives. \textbf{Objectives:} To assess the efficacy and safety of JAK inhibitors for AD treatment. \textbf{Methods:} We searched PubMed, Embase, the Cochrane Controlled Register of Trials, Web of Science, Global Resource of Eczema Trials database, and ClinicalTrials.gov from inception to September 1, 2020. Randomized clinical trials (RCTs) comparing JAK inhibitors with placebo/vehicle treatment for AD patients were included. The primary study outcomes included (1) the change (\%) from the Eczema Area and Severity Index (EASI) baseline expressed as weighted mean difference (WMD) and 95\% confidence interval (95\% CI), and (2) the Investigator’s Global Assessment (IGA) response and safety outcomes expressed as relative risk (RR) and 95\% CI. \textbf{Results:} We included 14 RCTs published in 13 studies (3,822 patients). Treatment with JAK inhibitors significantly improved IGA response (RR 2.83, 95\% CI 2.26–4.84, \(p < 0.001\)) and EASI score (WMD −28.82, 95\% CI −34.48 to −23.16, \(p < 0.001\)) by week 4 of treatment. Topical JAK inhibitors were significantly more efficacious than oral inhibitors. Upadacitinib treatment for 4 weeks was most effective in reducing EASI score (WMD −53.92, 95\% CI −69.26 to −38.58, \(p < 0.001\)), while abrocitinib for 4 weeks led to the most effective IGA response (RR 5.47, 95\% CI 2.74–10.93, \(p < 0.001\)).

\textbf{Conclusion:} Our results imply that JAK inhibitors are an effective and safe AD treatment. Nevertheless, further trials with longer duration and head-to-head comparisons of different JAK inhibitors are needed.

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\textbf{Introduction}

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is characterized by eczematous lesions and pruritus [1]. It is one of the most common skin disorders...
Topical anti-inflammatory agents and corticosteroids constitute primary treatment for AD. However, the prognosis is typically poor, mainly due to the low efficacy of the drugs used and marked adverse effects. Specifically, topical anti-inflammatory agents are ineffective in moderate-to-severe AD, and corticosteroids can have serious side effects [8, 9]. Biological therapies have advanced AD treatment by reducing the expression of pathogenic inflammatory factors [10]; however, such therapies are immunogenic and may lead to loss of efficacy. Some patients remain unresponsive [11, 12].

AD is characterized by multi-cytokine polarization, and a therapeutic approach capable of inhibiting more than one cytokine cascade from increasing efficacy is theoretically appealing [1, 13]. Cytokines that can contribute to the pathophysiology of AD include IL-4, IFN-γ, IL-31, IL-13, IL-23, and IL-22, as they interact with both type I and II cytokine receptors. The Janus kinase (JAK) family, comprising JAK1, JAK2, JAK3, and tyrosine kinase 2, are cytoplasmic tyrosine kinases. Both type I and II cytokine receptors lack intrinsic enzyme activity and depend on the JAKs for signal transduction [14]. Specifically, JAKs bind to intracellular chains of the cytokine receptor to generate functional signaling complexes and regulate the inflammatory process by activating intracytoplasmic transcription factors, i.e., the signal transducer and activator of transcription (STAT) molecules. Upon activation, STAT proteins dimerize, translocate into the nucleus, and either positively or negatively regulate downstream target gene expression, namely, inflammatory mediators [14, 15]. Thus, inhibiting JAK activity may be more effective than targeting a single cytokine. Further, JAK repression due to disruption of cytokine signaling attenuates a chronic itch propelled by type-2 cytokine and receptor interplay in sensory neurons [16]. JAK repression also improves skin barrier function by regulating the expression of filaggrin, a skin barrier protein [17]. These observations imply that JAK is an adaptable target for AD treatment, along with its neuronal mechanisms of action and its role in regulating epithelial barrier function and immune response.

There have been researches on the evidence of JAK inhibitors for the treatment of other immune-mediated skin disorder, including psoriasis and alopecia areata [18, 19]. Recently, several studies have also evaluated the use of various administration routes and multiple JAK inhibitors among different populations to treat AD. Here, this study evaluates available evidence on the efficacy and safety outcomes for treatment duration, administration route, and types of JAK inhibitors for treating AD.

### Materials and Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (online supplementary Appendix 1) [20, 21]. It is registered in PROSPERO (http://www.crd.york.ac.uk/prospero) with registration number CRD42020215945.

#### Search Strategy

We searched electronic databases (PubMed, Embase, the Cochrane Controlled Register of Trials, Web of Science, the Global Resource of Eczema Trials database, and ClinicalTrials.gov) without language restriction, from the inception to September 1, 2020. Full articles, systematic and literature reviews were retrieved and searched to identify additional eligible studies. The detailed search strategies were independently evaluated by a third investigator and are provided in online supplementary Table 1.

#### Study Selection

We included randomized clinical trials (RCTs) on AD treatment that compared JAK inhibitors with placebo/vehicle. We excluded duplicate publications, nonhuman studies, conference abstracts, and studies wherein data for outcomes of interest were not available. The eligibility of all articles was assessed by two investigators, and differences of opinion were settled by consensus or alternate consultation with a third investigator.

#### Data Extraction and Quality Assessment

Two reviewers independently extracted and cross-checked the data to avoid errors. Information extracted from the selected studies include:

- Country
- ClinicalTrials.gov Identifier
- Diagnosis criteria
- AD severity
- Baseline characteristics of patients, including sample size, age and gender percentage
- Treatment, including type and dosage of control and JAK inhibitors
- Outcomes of interest
- Timepoint of outcomes

Efficacy outcomes evaluated were (1) Investigator’s Global Assessment (IGA) response (clear [0] or almost clear [1] with an improvement of ≥2 grades from baseline); and (2) percent change from baseline in the Eczema Area and Severity Index (EASI). Safety outcomes were adverse events (AEs) leading to discontinuation and treatment-emergent AEs (TEAEs). When outcomes were presented in figures, WebPlotDigitizer (version 4.3, https://apps.au-
## Table 1. Characteristics of studies included in the meta-analysis

| Study | Country | Clinical trial identifier | Design | Diagnostic criteria | Severity of AD | Intervention group | Control group | Outcome | Measurement timepoint, weeks |
|-------|---------|--------------------------|--------|---------------------|----------------|-------------------|---------------|---------|------------------------------|
| Goodearlam et al. [23], 2019 | Multinational | NCT02780167 | Phase 3, double-blinded RCT, 3 arms | Hanifin and Rajka [36] | Moderate to severe | Abrocitinib 10 mg QD | Placebo | QD | 56 | 42.6 (35.1) | IGA, EASI, adverse event | 1, 2, 4, 8, 12, 24 |
| Silverberg et al. [24], 2019 | Multinational | NCT03753871 | Phase 2, double-blinded RCT, 3 arms | Hanifin and Rajka [36] | Moderate to severe | Abrocitinib 100 mg QD | Placebo | QD | 78 | 33.4 (13.8) | IGA, EASI, adverse event | 2, 4, 8, 12 |
| Simpson et al. [25], 2020 | Multinational | NCT03949060 | Phase 3, double-blinded RCT, 3 arms | Hanifin and Rajka [36] | Moderate to severe | Abrocitinib 200 mg QD | Placebo | QD | 77 | 31.5 (14.4) | IGA, EASI, adverse event | 2, 4, 8, 12 |
| Bussinette et al. [26], 2019 | Canada and USA | NCT0139981 | Phase 1, double-blinded RCT, 4 arms | NR | Moderate to severe | ASN002 20 mg QD | Placebo | QD | 9 | 29.9 (9.3) | IGA, EASI, adverse event | 2, 4 |
| Guttman-Yassky et al. [27], 2019 | US and Japan | NCT02759388 | Phase 2, double-blinded RCT, 3 arms | Hanifin and Rajka [36] | Moderate to severe | Baricitinib 2 mg QD plus TCS | Placebo | QD plus TCS | 49 | 38.0 (13.7) | IGA, EASI, adverse event | 4, 8, 12, 16 |
| NCT03733301 [28], 2019 | Multinational | NCT0373301 | Phase 3, double-blinded RCT, 3 arms | Eichenfeld et al. [37] | Moderate to severe | Baricitinib 2 mg QD plus TCS | Placebo | QD plus TCS | 109 | ≥18 | IGA, EASI, adverse event | 4, 16 |
| Simpson et al. BREEZE-AD1 [29], 2020 | Multinational | NCT03343396 | Phase 3, double-blinded RCT, 4 arms | Eichenfeld et al. [37] | Moderate to severe | Baricitinib 1 mg QD | Placebo | QD | 249 | 39.9 (17.5) | IGA, EASI, adverse event | 1, 2, 4, 16 |
| Simpson et al. BREEZE-AD2 [29], 2020 | Multinational | NCT0334422 | Phase 3, double-blinded RCT, 4 arms | Eichenfeld et al. [37] | Moderate to severe | Baricitinib 1 mg QD | Placebo | QD | 244 | 35 (12.4) | IGA, EASI, adverse event | 1, 2, 4, 16 |
| Nakagawa et al. [30], 2020 | Japan | JapicCTI-173554 | Phase 3, double-blinded RCT, 2 arms | Sakai et al. [38] | Moderate to severe | Delgocitinib 0.5% BID | Placebo | BID | 52 | 32.3 (11.2) | IGA, EASI, adverse event | 4 |
| Nakagawa et al. [31], 2019 | Japan | JapicCTI-173553 | Phase 2, double-blinded RCT, 3 arms | Sakai et al. [38] | Mild to severe | Delgocitinib 0.2% BID | Placebo | BID | 35 | 8.6 (4.0) | IGA, EASI, adverse event | 4 |
| Nakagawa et al. [32], 2018 | Japan | JapicCTI-152887 | Phase 2, double-blinded RCT, 6 arms | Sakai et al. [38] | Mild to moderate | Delgocitinib 0.2% BID | Placebo | BID | 31 | 31.6 (9.6) | IGA, EASI, adverse event | 12 |
| Kim et al. [33], 2020 | US and Canada | NCT03011892 | Phase 2, double-blinded RCT, 6 arms | Hanifin and Rajka [36] | Mild to moderate | Ruxolitinib 0.15% BID | Placebo | BID | 52 | 31.5 (18.0-69.0) | IGA, EASI, adverse event | 2, 4, 8 |
| Bissonnette et al. [34], 2016 | Canada | NCT0303181 | Phase 2, double-blinded RCT, 2 arms | Hanifin and Rajka [36] | Mild to moderate | Tofacitinib 2% BID | Placebo | BID | 34 | 30.4 (10.4) | PGA, EASI, adverse event | 1, 2, 4 |
| Guttman-Yassky et al. [35], 2020 | Multinational | NCT02932117 | Phase 2, double-blinded RCT, 4 arms | Hanifin and Rajka [36] | Moderate to severe | Upadacitinib 7.5 mg QD | Placebo | QD | 41 | 39.9 (17.3) | IGA, EASI, adverse event | 2, 4, 8, 12 |

AD, atopic dermatitis; BID, twice a day; EASI, Eczema Area and Severity Index; IGA, Investigator’s Global Assessment; NR, not reported; PGA, Physician’s Global Assessment; QD, once a day; RCT, randomized clinical trial; TCS, topical corticosteroid.
A meta-analysis of 12 studies including 3,537 patients using a fixed-effects model showed a significantly improved IGA response among patients treated with JAK inhibitors compared to those treated with placebo/vehicle (RR 2.83, 95% CI 2.25–3.56, \( p < 0.001 \)). No heterogeneity was detected (\( I^2 = 0% \)) (Fig. 1).

Percent Change from Baseline in EASI
A meta-analysis of 11 studies including 3,242 patients using a random-effects model showed a significant decrease in EASI score in JAK inhibitors group compared with the placebo/vehicle group (WMD –28.82, 95% CI –34.48 to –23.16, \( p < 0.001 \)). However, significant heterogeneity was detected among studies (\( I^2 = 50% \)) (Fig. 2).

Clinical Efficacy by Treatment Duration
A subgroup analysis was performed by pooling studies with the same treatment durations. A significant improvement in IGA response was found in the JAK inhibitor treatment group compared to placebo/vehicle at each time point with no heterogeneity (Table 2). The largest improvement occurred at week 4 in the JAK inhibitor treatment groups compared with the placebo/vehicle group (RR 3.59, 95% CI 2.66–4.84, \( p < 0.001 \)) (Table 2).

Similar efficacy was reported in EASI. JAK inhibitors showed a significant decrease in the EASI score at all time points compared to placebo/vehicle (Table 3). The largest reduction of EASI score occurred at week 4 in the JAK inhibitors treatment group compared to the placebo/vehicle group (WMD –42.00, 95% CI –48.64 to –35.36, \( p < 0.001 \)) (Table 3).

Clinical Efficacy by Administration Route
A subgroup analysis was performed by pooling studies using 1 of 2 available administration routes (oral and topical) with the same treatment durations. Both oral and topical administration of JAK inhibitors was associated with significantly improved IGA response compared with placebo/vehicle at each treatment time point, with no heterogeneity. The largest improvement in IGA re-
JAK Inhibitors for the Treatment of Atopic Dermatitis

sponse by oral administration occurred at week 4 (RR 3.65, 95% CI 2.53–5.27, p < 0.001), and the largest improvement by topical administration occurred at week 2 (RR 3.53, 95% CI 1.43–8.73, p = 0.006) (Table 2).

Both oral and topical administration of JAK inhibitors significantly reduced the EASI score compared with placebo/vehicle at each treatment time point. The largest reduction in EASI of both oral (WMD −37.66, 95% CI −49.06 to −26.27, p < 0.001) and topical administration (WMD −46.82, 95% CI −54.56 to −39.08, p < 0.001) occurred at week 4 (Table 3).

Clinical Efficacy by Baseline Severity
For a pooled subgroup analysis of studies with the same baseline severity of AD classified as mild-to-severe, mild-to-moderate, or moderate-to-severe, efficacy at week 4 was the time point for analysis due to insufficient data for other treatment durations. For EASI, topical administration demonstrated a greater effect compared to oral administration in the moderate-to-severe subgroup (topical: WMD −44.16, 95% CI −54.69 to −33.63, p < 0.001, oral: WMD −37.66, 95% CI −49.06 to −26.27, p < 0.001) (online supplementary Table 2).

Clinical Efficacy by Type of JAK Inhibitors
For a pooled subgroup analysis of studies using the same JAK inhibitors for the same treatment duration, efficacy at week 4 was the time point for this analysis based on prior results. We assessed six JAK inhibitors (abrocitinib, ASNO02, baricitinib, delgocitinib, rux-

![Fig. 1. Meta-analysis for overall efficacy of treatment with Janus kinase (JAK) inhibitors in patients achieving Investigator's Global Assessment response versus placebo/vehicle.](image-url)
ruxolitinib, upadacitinib, and tofacitinib, compared to placebo/vehicle (RR 5.47, 95% CI 2.74–10.93, p < 0.001). This result was confirmed at other measurement time points, with no heterogeneity (Table 2).

Regarding EASI scores, among the 6 JAK inhibitors assessed, namely, abrocitinib, baricitinib, delgocitinib, ruxolitinib, upadacitinib, and tofacitinib, upadacitinib provided the largest significant reduction compared to placebo/vehicle (WMD −53.92, 95% CI −69.26 to −38.58, p < 0.001). This result was confirmed at other measurement time points as well, and no significant heterogeneity (I² = 31%) was detected (Table 3).

Safety Outcomes
Adverse Effects Leading to Discontinuation
AEs were reported in 11 studies, which corresponded to 3,626 patients treated with 6 JAK inhibitors, viz. abrocitinib, baricitinib, delgocitinib, ruxolitinib, tofacitinib, and upadacitinib. The most frequently reported AEs leading to discontinuation were eczema, AD, headache, and abdominal pain (online supplementary Table 3a). There were no significant differences in the number of AEs between the JAK inhibitors and placebo/vehicle (RR 0.79, 95% CI 0.57–1.10, p = 0.16), with no significant heterogeneity (I² = 34%; online supplementary Table 4a).

Treatment-Emergent Adverse Effects
TEAEs were recorded in 11 studies that included 3,455 patients treated with 6 JAK inhibitors, i.e. abrocitinib,
baricitinib, delgocitinib, ruxolitinib, tofacitinib, and upadacitinib. The most frequently reported TEAEs were nasopharyngitis, headache, upper respiratory tract infection, and nausea (online supplementary Table 3b). A significant difference was found between JAK inhibitors and placebo/vehicle (RR 1.08, 95% CI 1.01–1.17, p = 0.03), with no significant heterogeneity ($I^2 = 37\%$). Additionally, abrocitinib was associated with a significantly higher rate of TEAEs than placebo/vehicle (RR 1.25, 95% CI 1.10–1.42, p = 0.001) (online supplementary Table 4b).

### Table 2. Subgroup analysis of JAK inhibitors for treatment of atopic dermatitis in patients achieving Investigator’s Global Assessment (IGA) response

| Subgroup | Comparison, treatment/control participants, n | RR [95% CI] | p value | $I^2$, % |
|----------|----------------------------------------------|-------------|---------|---------|
| At week 1 |                                             |             |         |         |
| Total    | 11/988/581                                  | 2.36 [1.05, 5.32] | 0.04 | 0       |
| Oral     | 10/953/547                                  | 1.59 [0.65, 3.90] | 0.32 | 0       |
| Abrocitinib | 4/207/54                                 | 0.96 [0.21, 4.51] | 0.96 | 0       |
| Baricitinib | 6/746/493                                   | 1.99 [0.65, 6.14] | 0.23 | 0       |
| Topical  | 1/35/34                                     | 14.58 [0.87, 245.80] | 0.06 | NA      |
| Tofacitinib | 1/35/34                                    | 14.58 [0.87, 245.80] | 0.06 | NA      |
| At week 2 |                                             |             |         |         |
| Total    | 19/1,809/787                                | 2.82 [1.75, 4.52] | <0.001 | 0       |
| Oral     | 14/1,570/701                                | 2.60 [1.49, 4.54] | <0.001 | 0       |
| Abrocitinib | 8/824/208                                  | 3.53 [1.44, 8.66] | 0.006 | 0       |
| Baricitinib | 6/746/493                                  | 1.99 [0.98, 4.03] | 0.06 | 0       |
| Topical  | 5/239/86                                    | 3.53 [1.43, 8.73] | 0.006 | 0       |
| Ruxolitinib | 4/204/52                                   | 1.85 [0.51, 6.74] | 0.35 | 0       |
| Tofacitinib | 1/35/34                                     | 6.80 [1.67, 27.70] | 0.007 | NA      |
| At week 4 |                                             |             |         |         |
| Total    | 33/2,566/1,072                              | 3.59 [2.66, 4.84] | <0.001 | 0       |
| Oral     | 21/1,888/868                                | 3.65 [2.53, 5.27] | <0.001 | 0       |
| Abrocitinib | 8/820/208                                  | 5.47 [2.74, 10.93] | <0.001 | 0       |
| Baricitinib | 3/27/9                                     | 1.61 [0.34, 7.69] | 0.55 | 0       |
| Topical  | 10/1,041/651                                | 2.99 [1.92, 4.65] | <0.001 | 0       |
| Delgocitinib | 12/678/204                        | 3.43 [2.04, 5.78] | <0.001 | 0       |
| Ruxolitinib | 4/204/52                                   | 2.68 [1.01, 7.15] | 0.05 | 0       |
| Tofacitinib | 1/35/34                                     | 5.83 [2.26, 15.03] | <0.001 | NA      |
| At week 8 |                                             |             |         |         |
| Total    | 14/1,104/309                                | 2.93 [2.01, 4.28] | <0.001 | 0       |
| Oral     | 10/900/257                                  | 2.85 [1.87, 4.35] | <0.001 | 0       |
| Abrocitinib | 8/825/208                                  | 3.37 [2.09, 5.41] | <0.001 | 0       |
| Baricitinib | 2/75/49                                    | 0.98 [0.37, 2.58] | 0.97 | 0       |
| Topical  | 4/204/52                                    | 3.27 [1.40, 7.67] | 0.006 | 0       |
| Ruxolitinib | 4/204/52                                   | 3.27 [1.40, 7.67] | 0.006 | 0       |
| At week 12 |                                            |             |         |         |
| Total    | 10/887/254                                  | 3.59 [2.33, 5.54] | <0.001 | 0       |
| Oral     | 10/887/254                                  | 3.59 [2.33, 5.54] | <0.001 | 0       |
| Abrocitinib | 8/812/205                                  | 3.86 [2.40, 6.19] | <0.001 | 0       |
| Baricitinib | 2/75/49                                    | 2.13 [0.74, 6.14] | 0.16 | 0       |
| At week 16 |                                            |             |         |         |
| Total    | 14/1,168/679                                | 2.22 [1.64, 3.00] | <0.001 | 0       |
| Oral     | 14/1,168/679                                | 2.22 [1.64, 3.00] | <0.001 | 0       |
| Abrocitinib | 4/127/28                                   | 1.33 [0.46, 3.83] | 0.6  | 0       |
| Baricitinib | 10/1,041/651                               | 2.32 [1.69, 3.18] | <0.001 | 0       |

NA, not applicable; RR, relative risk
Publication Bias Assessment

Funnel plot analysis and Egger linear regression test demonstrated no evidence of publication bias for IGA response (bias −0.14, 95% CI −0.80 to 0.52, \( p = 0.67 \)) and percent change from baseline in EASI (bias −0.53, 95% CI −1.90 to 0.83, \( p = 0.43 \)) (online supplementary Fig. 3).

Discussion

To the best of our knowledge, this is the first meta-analysis to assess both the efficacy and safety of JAK inhibitors for treating AD. Our results show that, compared to placebo, JAK inhibitor treatment can significantly improve AD with acceptable safety.
The use of JAK inhibitors to treat AD is gaining attention. A qualitative synthesis by Nusbaum et al. [39] demonstrated promising results in AD patients treated with oral or topical JAK inhibitors; however, that study lacked quantitative data analysis. A pooled meta-analysis of 4 RCTs [26, 31, 32, 34] by Arora et al. [40] included 534 patients and showed greater effectiveness of JAK inhibitors in AD treatment; however, the number of patients included was too small to draw strong conclusions. In our study, 10 RCTs [23–25, 27–30, 33, 35] including 3,288 patients were assessed for the first time, adding to the statistical power of the study to determine efficacy and safety. Given the wide spectrum of immunosuppressive effects of JAK inhibition [41], the safety of JAK inhibitor treatment was also assessed. Further, there was no detectable publication bias in the efficacy and safety of the outcomes. Our study confirms the effectiveness and safety of JAK inhibitors for AD treatment and is more believable.

There were some new findings from our subgroup analyses that had not been investigated in previous reports. First, a treatment duration analysis showed that JAK inhibitors exhibited significant effects as early as week 1 of treatment. The optimal duration was 4 weeks, implying that JAK inhibitors may be highly efficacious with rapid onset of action and clinically meaningful improvement. This rapid onset of action may be due to inhibition of JAK-cytokine receptor binding, which simultaneously blocks multiple cytokine signal transduction pathways [42, 43]. Analysis of available data shows that the best effect of treatment with JAK inhibitors occurs at the fourth week. However, as most studies on topical JAK inhibitors had a treatment duration of 4 weeks, we could not confirm if this result will persist in longer treatment duration, and further trials with longer duration are needed to validate this result. Beyond 4 weeks, a decreasing trend in the clinical improvement of AD was observed in both IGA response and EASI score, except at week 12, which reached the same IGA response as in week 4. As AD has a chronic and relapsing disease course, additional studies are necessary to address whether JAK inhibitor treatment can be effective for longer than 16 weeks.

Second, we found that topical JAK inhibitors were associated with higher efficacy than oral therapy in improving both EASI score and IGA response at timepoints before week 12 except for week 4, where a discrepancy was found in improving IGA response. This discrepancy may be due to an inherent limitation in the IGA measurement tool, namely, lower interobserver reliability [44–46]. Nevertheless, as EASI has adequate validity and responsiveness [47, 48], our results on the greater efficacy of topical JAK inhibitors remain credible. Next, subgroup analysis of the efficacy of topical versus oral administration, based on baseline severity of the treated subjects, showed that topical administration was more effective than oral administration in the moderate-to-severe subgroup in EASI. However, due to the paucity of data, efficacy was assessed only at week 4 in the moderate-to-severe group. Though oral administration displayed a better effect than topical administration with respect to IGA response, the number of participants in the oral administration group was much larger than the number of participants in the topical administration group; therefore, firm conclusions based on IGA response cannot be drawn.

Moreover, this observation has been confirmed in a murine model of allergic dermatitis, in which topical JAK inhibitors showed promising results against both pruritic and inflammatory responses; in contrast, oral JAK inhibitors could only decrease pruritus [49]. Nonetheless, it is noteworthy that the efficacy gap between oral and topical therapy gradually decreased over time. As data on the long-term efficacy of topical JAK inhibitors in AD treatment are not yet available, it remains unclear if topical administration will remain more effective than oral therapy after 12 weeks of treatment or later. Therefore, clinical trials on the long-term efficacy of topical JAK inhibitors in AD treatment are required.

This meta-analysis indicated that, based on the EASI score, upadacitinib for 4 weeks was the most effective treatment. For the outcome of IGA response, we preferred the result that abrocitinib for 4 weeks achieved the optimal efficacy. Although topical application of tofacitinib for 2 weeks was the most effective treatment in improving the IGA response at all measurement time points. However, this should be interpreted with caution because the number of patients included in this subgroup was relatively small. Further, the reason for the variance in the clinical performance of the involved JAK inhibitors remains unknown, but variations in affinity and selectivity profile among JAK inhibitors for JAK isoforms may contribute to the observed variation in clinical performance [50, 51]. When two JAK isoforms are involved in signaling from a given cytokine, e.g. JAK1/JAK3 binds to IL-2R, selective inhibition of one cytokine significantly impacts that cytokine’s function [52, 53]. Thus, studies and clinical trials on AD treatment that compare different combinations of JAK inhibitors are needed to assess this phenomenon better.

Except for abrocitinib, with significantly more TEAEs than placebo, all other JAK inhibitors displayed a favorable safety profile during short-term treatment. Never-
theless, JAKs play a role in immune function and hematopoietic systems, including thromboembolic risks [54], and additional data from long-term studies are needed to adequately assess such risks.

Our study has some limitations. First, all included studies were short-term RCTs; only 5 were on topical JAK inhibitor treatment and had small sample sizes. Second, no firm conclusions could be drawn based on baseline severity because of insufficient data and significant differences in participant numbers. Third, both IGA and EASI are physician-assessed instruments, which measure only clinical signs and do not address patient experience with pruritus and sleeplessness. A simple assessment of lesions does not represent a comprehensive evaluation of AD severity, and patient-assessable instruments with a health-related quality of life survey are also needed in future studies.

Conclusion

The results of this study support the efficacy and safe use of JAK inhibitors for AD treatment. Further trials with longer duration and head-to-head comparisons of different JAK inhibitors are needed to establish the most appropriate treatment for AD using JAK inhibitors.

Key Message

JAK inhibitors are effective and safe for AD treatment.

Statement of Ethics

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and registered in PROSPERO with registration number CRD42020215945.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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No funding was received for this study.

Author Contributions

C.L. conceptualized the study, interpreted data, and drafted the initial manuscript; X.S. and K.Z. conceptualized ideas and edited the manuscript; F.M. and L.L. supervised the analysis; Z.M. helped in data extraction and analysis; X.H. conceptualized the study and reviewed the manuscript; all authors approved the final manuscript for submission.
JAK Inhibitors for the Treatment of Atopic Dermatitis

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