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

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Keywords
Janus kinase inhibitors · Atopic dermatitis · Meta-analysis

Abstract
Background: Current therapeutic options for atopic dermatitis (AD) are limited. Janus kinase (JAK) inhibitors may be viable alternatives. ***Objectives:*** To assess the efficacy and safety of JAK inhibitors for AD treatment. ***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. ***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 2.25–3.56, $p < 0.001$) and EASI score (WMD −28.82, 95% CI −34.48 to −23.16, $p < 0.001$). JAK inhibitor treatment achieved the largest improvement in both IGA response (RR 3.59, 95% CI 2.66–4.84, $p < 0.001$) and EASI score (WMD −42.00, 95% CI −48.64 to −35.36, $p < 0.001$) 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, $p < 0.001$). There was no difference in the frequency of adverse events (AEs) leading to discontinuation; however, JAK inhibitors use, especially abrocitinib, led to a higher incidence of treatment-emergent AEs (RR 1.25, 95% CI 1.10–1.42, $p = 0.001$). ***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.

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

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worldwide, affecting approximately 20% of children and 2.1–4.9% of adults [2, 3]. AD etiologies include environmental factors, genetic disposition, immune dysregulation, and impaired skin barrier function [1]. AD imposes psychological and social burdens, associated with a higher risk of depression, anxiety, work absenteeism, and suicidality [4–7].

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 after 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-

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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, week
						arms	sample size	age, y	females, *n* (%)	arms	sample size	age, years	females, *n* (%)		
Gooderham et al. [23], 2019	Multinational	NCT02780167	Phase 3, double-blinded RCT, 5 arms	Hanifin and Rajka [36]	Moderate to severe	Abrocitinib 10 mg QD Abrocitinib 30 mg QD Abrocitinib 100 mg QD Abrocitinib 200 mg QD	49 51 56 55	44.3 (15.9) 37.6 (15.9) 41.1 (15.6) 38.7 (17.6)	28 (57) 29 (57) 25 (45) 27 (49)	Placebo QD	56	42.6 (15.1)	35 (63)	IGA, EASI, adverse event	1, 2, 4, 8, 12, 16
Silverberg et al. [24], 2020	Multinational	NCT03575871	Phase 2, double-blinded RCT, 3 arms	Hanifin and Rajka [36]	Moderate to severe	Abrocitinib 100 mg QD Abrocitinib 200 mg QD	158 155	37.4 (15.8) 33.5 (14.7)	64 (41) 67 (43)	Placebo QD	78	33.4 (13.8)	31 (40)	IGA, EASI, adverse event	2, 4, 8, 12
Simpson et al. [25], 2020	Multinational	NCT03349060	Phase 3, double-blinded RCT, 3 arms	Hanifin and Rajka [36]	Moderate to severe	Abrocitinib 100 mg QD Abrocitinib 200 mg QD	156 154	32.6 (15.4) 33.0 (17.4)	66 (42) 73 (47)	Placebo QD	77	31.5 (14.4)	28 (36)	IGA, adverse event	2, 4, 8, 12
Bissonnette et al. [26], 2019	Canada and USA	NCT03139981	Phase 1, double-blinded RCT, 4 arms	NR	Moderate to severe	ASN002 20 mg QD ASN002 40 mg QD ASN002 80 mg QD	9 9 9	38.2 (14.36) 42.4 (13.88) 33.1 (10.42)	4 (44) 4 (44) 4 (44)	Placebo QD	9	29.9 (9.33)	6 (67)	IGA, adverse event	2, 4
Guttman-Yassky et al. [27], 2019	US and Japan	NCT02576938	Phase 2, double-blinded RCT, 3 arms	Hanifin and Rajka [36]	Moderate to severe	Baricitinib 2 mg QD plus TCS Baricitinib 4 mg QD plus TCS	37 38	42 (26.0-52.0) 32.5 (26.0-48.0)	15 (41) 16 (42)	Placebo QD plus TCS	49	35 (28.0–48.0)	25 (51)	IGA, EASI, adverse event	4, 8, 12, 16
NCT03733301 [28], 2020	Multinational	NCT03733301	Phase 3, double-blinded RCT, 3 arms	Eichenfield et al. [37]	Moderate to severe	Baricitinib 2 mg QD plus TCS Baricitinib 4 mg QD plus TCS	109 111	≥18	39 (36) 36 (32)	Placebo QD plus TCS	109	≥18	38 (35)	IGA, EASI, adverse event	4, 16
Simpson et al. BREEZE-AD1 [29], 2020	Multinational	NCT03334396	Phase 3, double-blinded RCT, 4 arms	Eichenfield et al. [37]	Moderate to severe	Baricitinib 1 mg QD Baricitinib 2 mg QD Baricitinib 4 mg QD	127 123 125	36 (12.4) 35 (13.7) 37 (12.9)	49 (39) 41 (33) 42 (34)	Placebo QD	249	35 (12.6)	101 (41)	IGA, EASI, adverse event	1, 2, 4, 16
Simpson et al. BREEZE-AD2 [29], 2020	Multinational	NCT03334422	Phase 3, double-blinded RCT, 4 arms	Eichenfield et al. [37]	Moderate to severe	Baricitinib 1 mg QD Baricitinib 2 mg QD Baricitinib 4 mg QD	125 123 123	33 (10.0) 36 (13.2) 34 (14.1)	45 (36) 58 (47) 41 (33)	Placebo QD	244	35 (13.0)	90 (37)	IGA, EASI, adverse event	1, 2, 4, 16
Nakagawa et al. [30], 2020	Japan	JapicCTI-173554	Phase 3, double-blinded RCT, 2 arms	Saeki et al. [38]	Moderate to severe	Delgocitinib 0.5% BID	106	31.4 (9.6)	42 (40)	Vehicle BID	52	32.3 (11.2)	18 (35)	IGA, EASI, adverse event	4
Nakagawa et al. [31], 2019	Japan	JapicCTI-173553	Phase 2, double-blinded RCT, 3 arms	Saeki et al. [38]	Mild to severe	Delgocitinib 0.25% BID Delgocitinib 0.5% BID	34 34	8.4 (3.8) 8.5 (4.4)	12 (35) 16 (47)	Vehicle BID	35	8.6 (4.0)	17 (49)	IGA, EASI, adverse event	4
Nakagawa et al. [32], 2018	Japan	JapicCTI-152887	Phase 2, double-blinded RCT, 6 arms	Saeki et al. [38]	Moderate to severe	Delgocitinib 0.25% BID Delgocitinib 0.5% BID Delgocitinib 1% BID Delgocitinib 3% BID	69 65 66 65	31.5 (10.5) 29.5 (9.2) 28.6 (8.7) 32.3 (10.6)	21 (30) 26 (40) 18 (27) 23 (35)	Vehicle BID	31	31.6 (9.6)	12 (39)	IGA, EASI, adverse event	4
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% QD Ruxolitinib 0.5% QD Ruxolitinib 1.5% QD Ruxolitinib 1.5% BID	51 51 52 50	38.0 (18.0-69.0) 37.0 (18.0-70.0) 37.0 (18.0-65.0) 35.5 (18.0-70.0)	26 (51) 27 (53) 31 (60) 24 (48)	Vehicle BID	52	31.5 (18.0∼69.0)	32 (62)	IGA, EASI, adverse event	2, 4, 8
Bissonnette et al. [34], 2016	Canada	NCT02001181	Phase 2, double-blinded RCT, 2 arms	Hanifin and Rajka [36]	Mild to moderate	Tofacitinib 2% BID	35	32.4 (9.8)	19 (54)	Vehicle BID	34	30.4 (10.4)	18 (53)	PGA, EASI, adverse event	1, 2, 4
Guttman-Yassky et al. [35], 2020	Multinational	NCT02925117	Phase 2, double-blinded RCT, 4 arms	Hanifin and Rajka [36]	Moderate to severe	Upadacitinib 7.5 mg QD Upadacitinib 15 mg QD Upadacitinib 30 mg QD	42 42 42	41.5 (15.4) 38.5 (15.2) 39.9 (15.3)	14 (33) 12 (29) 20 (48)	Placebo QD	41	39.9 (17.5)	17 (41)	EASI, adverse event	2, 4, 8, 12, 16

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.

tomeris.io/wpd/index.zh_CN.html) was used to extract data from the figure. In studies without a placebo or vehicle comparator arm, where patients subsequently entered an open-label period, we extracted data from the placebo/vehicle-controlled period. When there was an active control arm, we only extracted data from the placebo or vehicle-control arm.

We evaluated the quality of included articles and the risk of bias using the Cochrane Collaboration's Risk of Bias assessment tool [22]. Quality parameters assessed were (1) random sequence generation; (2) allocation concealment; (3) blinding of participant and personnel; (4) incomplete outcome data; (5) selective reporting; and (6) other bias.

Statistical Analyses

Statistical analyses were performed using Review Manager, version 5.4 (The Cochrane Collaboration) and Stata version 12.0 (StataCorp LP). We calculated relative risk (RR) with 95% CIs for dichotomous outcomes and weighted mean difference (WMD) with 95% CIs for continuous outcomes. $p < 0.05$ (2-tailed) was considered statistically significant. I^2 was used to assess heterogeneity ($I^2 \geq 50\%$ considered significant). If significant heterogeneity was present, the data were assessed using a random-effects model; otherwise, a fixed-effects model was utilized. We conducted subgroup analyses based on treatment duration, administration route, baseline severities of AD and types of JAK inhibitors. Funnel plots and Egger tests assessed publication bias.

Results

Search Results and Study Characteristics

The database search identified 878 relevant records. After removing 221 duplicates, an additional 625 records were excluded based on title and abstract review. Nineteen records were excluded on full-text assessment. Fourteen RCTs published in 13 studies [23–35] were included in the systematic review and meta-analysis (online supplementary Fig. 1).

The study included 3,822 patients. Both topical and oral administration of JAK inhibitors was assessed. All studies used placebo or vehicle ointment as controls. The vehicle used was the base cream or ointment without active ingredient. The detailed characteristics of the selected 13 studies are summarized in Table 1 [23–35].

Quality Assessment

While 12 studies specified methods of random sequence generation [23–28, 30–35], one study had an "unclear" bias [29]. Further, 9 studies had described allocation concealment [23–25, 27–29, 31, 34, 35], and 4 studies had an "unclear" bias [26, 30, 32, 33]. Next, 8 studies had blinded outcome assessment [23–26, 28, 33–35], and 11 studies had reported a "low" risk of incomplete outcome data [24–26, 28–35]. All 13 studies had a "low" risk of performance bias and reporting bias, but an "unclear" risk of other biases [23–35] (online supplementary Fig. 2).

Efficacy Outcomes

Overall Clinical Efficacy

As measurement time points were different in each of the 13 studies, we pooled data for the last time point of each study during primary analysis.

IGA Response of Patients

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-

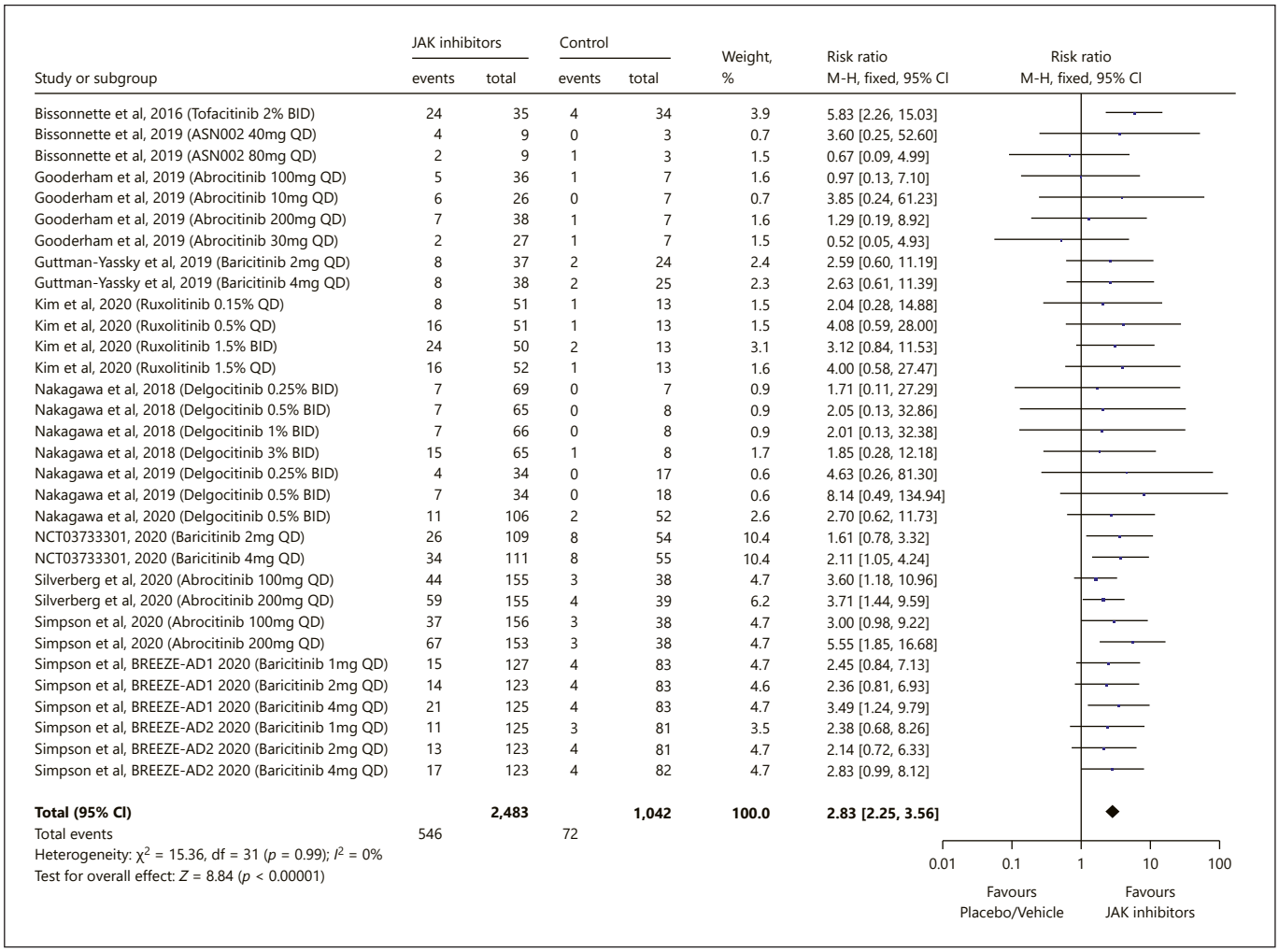

Fig. 1. Meta-analysis for overall efficacy of treatment with Janus kinase (JAK) inhibitors in patients achieving Investigator's Global Assessment response versus placebo/vehicle.

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, ASN002, baricitinib, delgocitinib, rux-

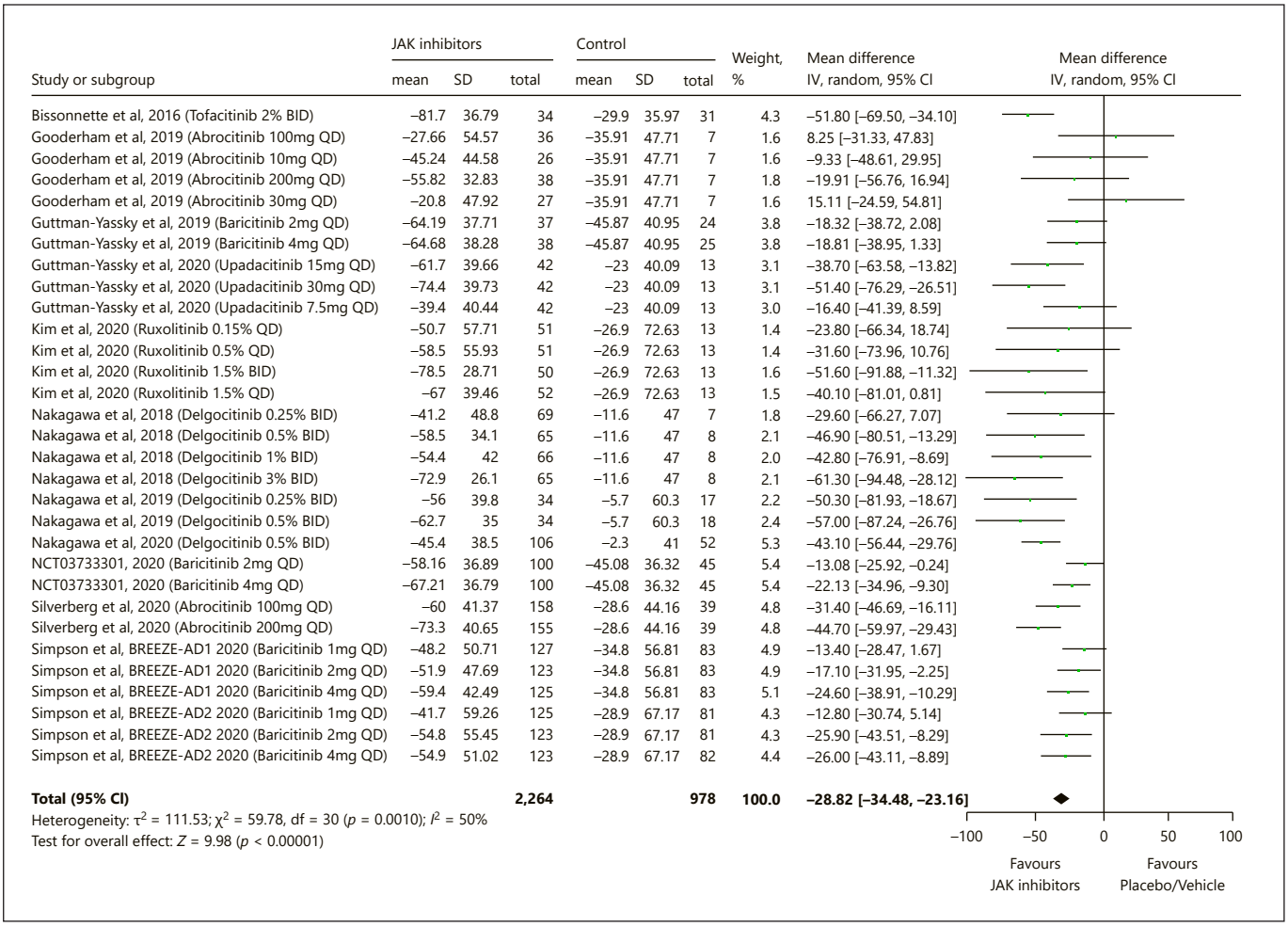

Fig. 2. Meta-analysis for overall efficacy of treatment with Janus kinase (JAK) inhibitors in percent change from baseline on the Eczema Area and Severity Index versus placebo/vehicle.

olitinib, tofacitinib); among them, abrocitinib showed the most significant improvement in IGA response 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 ($I^2 = 31\%$) 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 ($I^2 = 34\%$; 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,

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

Subgroup	Comparison, *n*	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
ASN002	3	27/9	1.61 [0.34, 7.69]	0.55	0
Baricitinib	10	1,041/651	2.99 [1.92, 4.65]	<0.001	0
Topical	12	678/204	3.43 [2.04, 5.78]	<0.001	0
Delgocitinib	7	439/118	2.84 [1.23, 6.56]	0.01	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

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 3. Subgroup analysis of JAK inhibitors for treatment of atopic dermatitis in percent change from baseline in the eczema area and severity index (EASI)

Subgroup	Comparison, *n*	Treatment/ Control participants, *n*	WMD (95% CI)	*p* value	I^2, %
At week 1					
Total	5	240/88	−15.97 [−31.09, −0.85]	0.04	78
Oral	4	205/54	−10.23 [−22.82, 2.36]	0.11	56
Abrocitinib	4	205/54	−10.23 [−22.82, 2.36]	0.11	56
Topical	1	35/34	−36.80 [−49.75, −23.85]	<0.001	NA
Tofacitinib	1	35/34	−36.80 [−49.75, −23.85]	<0.001	NA
At week 2					
Total	14	876/259	−32.09 [−40.89, −23.29]	<0.001	67
Oral	9	637/173	−28.30 [−39.92, −16.69]	<0.001	77
Abrocitinib	6	511/133	−21.69 [−36.69, −6.69]	0.005	82
Upadacitinib	3	126/40	−42.61 [−54.47, −30.74]	<0.001	2
Topical	5	239/86	−41.67 [−52.22, −31.11]	<0.001	0
Ruxolitinib	4	204/52	−39.95 [−54.85, −25.04]	<0.001	0
Tofacitinib	1	35/34	−43.40 [−58.36, −28.44]	<0.001	NA
At week 4					
Total	21	1,312/369	−42.00 [−48.64, −35.36]	<0.001	40
Oral	9	635/168	−37.66 [−49.06, −26.27]	<0.001	70
Abrocitinib	6	509/128	−30.59 [−43.54, −17.65]	<0.001	69
Upadacitinib	3	126/40	−53.92 [−69.26, −38.58]	<0.001	31
Topical	12	677/201	−46.82 [−54.56, −39.08]	<0.001	0
Delgocitinib	7	439/118	−45.98 [−55.46, −36.49]	<0.001	0
Ruxolitinib	4	204/52	−44.06 [−64.51, −23.61]	<0.001	0
Tofacitinib	1	34/31	−51.80 [−69.50, −34.10]	<0.001	NA
At week 8					
Total	13	818/211	−33.41 [−43.20, −23.62]	<0.001	47
Oral	9	614/159	−32.33 [−44.33, −20.34]	<0.001	63
Abrocitinib	6	488/119	−25.92 [−39.32, −12.52]	<0.001	58
Upadacitinib	3	126/40	−46.66 [−68.94, −24.38]	<0.001	61
Topical	4	204/52	−37.24 [−57.98, −16.49]	<0.001	0
Ruxolitinib	4	204/52	−37.24 [−57.98, −16.49]	<0.001	0
At week 12					
Total	9	632/169	−33.30 [−45.96, −20.63]	<0.001	63
Oral	9	632/169	−33.30 [−45.96, −20.63]	<0.001	63
Abrocitinib	6	506/130	−26.95 [−42.05, −11.85]	<0.001	63
Upadacitinib	3	126/39	−46.49 [−68.64, −24.35]	<0.001	60
At week 16					
Total	17	1,274/699	−19.82 [−24.71, −14.94]	<0.001	9
Oral	17	1,274/699	−19.82 [−24.71, −14.94]	<0.001	9
Abrocitinib	4	127/28	−2.20 [−21.60, 17.20]	0.82	0
Baricitinib	10	1,021/632	−19.05 [−24.01, −14.08]	<0.001	0
Upadacitinib	3	126/39	−35.53 [−55.55, −15.50]	<0.001	48

NA, not applicable; WMD, weighted mean difference

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/JAK 3 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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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.

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