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Research Article

Upadacitinib in the Treatment of Atopic Dermatitis: A Systematic Review and Meta-Analysis

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Background. The pathogenesis of atopic dermatitis (AD) is associated with proinflammatory cytokines and the JAK/STAT signaling pathway. Upadacitinib, an approved oral JAK1 inhibitor, has been investigated in some clinical trials and observational studies of AD. However, the efficacy and safety profile of upadacitinib for AD is still unclear, as few previous meta-analyses evaluated upadacitinib alone. *Purpose*. To assess the benefit and risk profile of upadacitinib for patients with AD based on evidence from current clinical trials and observational studies. *Methods*. The study was performed according to PRISMA guidelines. Efficacy outcomes included the proportion of AD patients achieving 50%, 75%, 90%, and 100% improvement in Eczema Area and Severity Index (EASI 50, 75, 90, and 100) and clear or almost clear in Investigator Global Assessment (IGA 0/1) following upadacitinib treatment. Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) was used for quality assessment, and Comprehensive Meta-Analysis (CMA) was used to analyze the extracted data. *Results*. We enrolled 12 studies from 11 articles, including 6 clinical trials and 6 observational studies. For efficacy, the overall pooled proportions of AD patients achieving EASI 50, EASI 75, EASI 90, and EASI 100 after upadacitinib therapy were 83.3%, 70.5%, 51.8%, and 25.0%, respectively. For safety, the most frequently reported adverse events during upadacitinib treatment were acne (13.2%), and the overall pooled rate of serious adverse events was acceptable (2.2%). The pooled rate of upadacitinib discontinuation was 1.5%, with adverse events (2.2%) and lack of efficacy (1.6%) as the major factors. The subgroup analysis based on dosage regimen revealed that upadacitinib 30 mg/d conferred superior efficacy in treating AD but higher risks of acne than 15 mg/d. *Conclusions*. Upadacitinib seems to be a promising drug with mild adverse effects in the treatment of AD. More high-quality, large-scale controlled trials are needed for further verification.

1. Introduction

Atopic dermatitis (AD) is a common, chronic, inflammatory cutaneous disease, affecting up to 20% of children and 1–3% of adults globally [1, 2]. Though AD is normally non-fatal, the physical signs and cutaneous symptoms including pruritus and pain of AD can largely impair patients' physical and mental health and eventually have a profound impact on the quality of life (QoL) of the patients, their caregivers, and their family members [3, 4]. Additionally, AD has proven to be associated with multiple extracutaneous disorders, such as atopic comorbidities, anxiety and depression, infections, and cardiovascular diseases [5]. Thus, the effective treatment and management of AD are challenging but crucially important for patients. In recent years, with the in-depth exploration of the pathogenic mechanism of AD, various biologics and molecular targeted drugs have been developed and used, providing novel therapeutic alternatives for moderate-to-severe AD. Dupilumab, a monoclonal antibody against the shared interleukin-4 (IL-4) receptor subunit α of IL-4 and IL-13 receptors, is the first approved biologic to treat moderate-to-severe AD [6, 7]. Although many patients

with AD benefit from dupilumab therapy, there remain unmet needs arising from dupilumab-associated conjunctivitis, facial redness, and certain population of non-responders [8]. Janus kinase (JAK) inhibitors emerge as a potentially promising alternative, with superior efficacy compared to dupilumab in clinical trials [9–11] and successful treatment outcomes in real-world studies for dupilumab-resistant AD patients [12, 13].

The pathogenesis of AD is driven by numerous proinflammatory cytokines, including IL-4, IL-13, IL-31, interferon-γ (IFN-γ), and thymic stromal lymphopoietin (TSLP), which interact with their corresponding receptors and initiate the subsequent JAK/signal transducer and activator of transcription (STAT) signaling pathway [14, 15]. The JAK/STAT pathway is marked by regulation of the immune system, encompassing aspects such as cell proliferation, survival, inflammation, and immune tolerance [16]. Upadacitinib is a highly selective JAK1 inhibitor that can suppress the related cytokine-mediated signaling pathways [17], and its efficacy and safety have been explored in a series of investigations, including clinical trials [9, 18–22] and observational studies [12, 23–29]. However, few meta-analyses exclusively integrated the current data on the efficacy and safety of upadacitinib for AD, and the benefit and risk profile of upadacitinib remains unclear. We therefore performed this systematic review and meta-analysis of available evidence from clinical trials as well as observational studies to quantify the benefits and risks of upadacitinib in treating AD and to have a more comprehensive assessment of this drug.

2. Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [30]. We registered the protocol of our study at PROSPERO, no. CRD42022361857.

2.1. Literature Search. Two independent reviewers searched PubMed, Embase, and the Cochrane Library databases from their inception to 13th September 2022 for eligible literature with language restricted to English. Keywords *upadacitinib and atopic dermatitis*, *upadacitinib and real-world,* and *upadacitinib and observational* were used as the search terms to identify potentially relevant studies. The investigators read the titles and abstracts of the retrieved articles for screening and further assessed the screened articles by reading their full text.

2.2. Selection Criteria. Studies were considered eligible for inclusion if they met the following criteria: (1) studies that enrolled patients with AD; (2) studies in which patients used upadacitinib for monotherapy or concomitant therapy; (3) studies that recorded efficacy outcomes including Eczema Area and Severity Index (EASI) or Investigator Global Assessment (IGA) scores or safety outcomes including the incidence of adverse events with corresponding time points; and (4) studies of clinical trials or observational studies including the retrospective study, prospective study, and case series with more than three patients. Exclusion criteria were as follows: (1) studies that did not report efficacy outcomes or safety outcomes with corresponding time points; (2) studies of case series with less than four people, and studies without complete original data, such as editorials, comments, reviews, protocols, and conference presentations; and (3) studies of publications from the same study group.

2.3. Data Extraction. Two reviewers accomplished the process of data extraction separately after screening the full text of the selected literature. Data extracted from the eligible studies included (1) study characteristics: study name, study type, number of patients, follow duration, treatment regimen, outcome parameters for efficacy, and study region; (2) patient characteristics: dosage regimen, disease duration, age, sex ratio, BMI, concomitant treatment, discontinuation of drug, and reasons for discontinuation; (3) data on efficacy outcomes: the number or proportion of patients achieving 50%, 75%, 90%, and 100% improvement in Eczema Area and Severity Index (EASI 50, 75, 90, and 100) and clear or almost clear in Investigator Global Assessment (IGA 0/1) at different time points; and (4) data on safety outcomes: the number of any/serious adverse events, specific types, and the respective number of the detailed adverse events. For studies that incorporated multiple groups with different dosage regimens, we only extracted the data from the groups that received upadacitinib 15 mg/d or 30 mg/d. For data that only existed in figures, Engauge Digitizer 11.1 software was applied for the extraction of data.

2.4. Quality Assessment. The risk of bias in the eligible studies was assessed using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I). As an emerging tool for quality assessment, ROBINS-I can evaluate the risk of bias from seven domains, including confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selective reporting [31]. For the selected studies, the overall risk of bias was rated as low, moderate, or serious based on each domain by two independent investigators. Any discrepancy was resolved by a senior investigator.

2.5. Statistical Analysis. The Comprehensive Meta-Analysis (CMA) software 3.4.0 (Biostat, Englewood, NJ) was used to analyze extracted data for meta-analysis. Proportions of patients achieving EASI 50, 75, 90, and 100 and IGA 0/1 across eligible studies were meta-analyzed for efficacy, while the incidence of adverse events was meta-analyzed for safety assessment. The heterogeneity was quantified with the Q test and the calculation of I^2: $P > 0.10$ or $I^2 < 50\%$ was considered an indication of low heterogeneity. The fixed-effect model

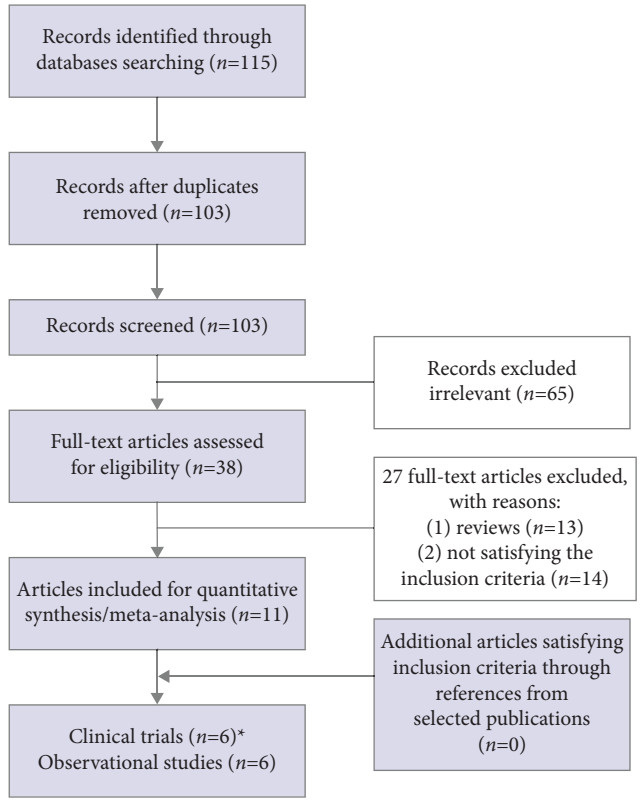
was used to calculate the pooled rates of outcome parameters with 95% confidence intervals when the heterogeneity was low, and the random-effect model was used when the heterogeneity was substantial. Based on the dosage regimen (15 mg/d or 30 mg/d), we performed the subgroup analysis to investigate the subgroup differences and the potential sources of heterogeneity. The P value was 2-tailed, with an alpha level of 0.05 regarded statistically significant.

3. Results

3.1. Study Selection, Characteristics, and Quality Assessment. Through the initial literature search, we yielded 103 articles after removing duplicates. Based on the screening of titles and abstracts, 38 articles were subsequently reviewed in full text for eligibility, and 27 articles were excluded according to inclusion and exclusion criteria. Ultimately, 11 articles including 6 clinical trials (two were from the same publication) and 6 observational studies were selected for the final quantitative synthesis. Figure 1 displays the flow of literature selection, and Tables 1 and 2 summarize the characteristics of the eligible studies and patients. Published as full text between 2020 and 2022, the selected studies were conducted in various regions including the Asian-Pacific, European, North and South American, Middle East, and Oceanian areas. The studies were composed of one Phase II study, five Phase III studies, one prospective study, and five retrospective studies. Except for one retrospective study using vIGA-AD for the efficacy outcome [26], all the remaining studies reported EASI scores as the outcome parameter for efficacy. The included studies mostly recorded the rates of detailed adverse events and discontinuation of drug during upadacitinib treatment apart from two retrospective studies [27, 28]. Among the eligible studies, 2 studies were with the 15 mg dosage regimen of upadacitinib, 3 studies were with the 30 mg dosage regimen, 5 studies followed either the 15 mg or 30 mg dosage regimen in different groups, and 2 studies did not unify the upadacitinib dosage in the same cohort. The follow-up duration of studies ranged from 8 to 24 weeks, and all of the studies provided data of EASI or IGA with corresponding time points.

Overall, 9 articles were at a moderate risk of bias and 2 showed a serious risk of bias in accordance with the ROBINS-I tool. The detailed assessment results of the risk of bias in each domain are summarized in Table 3.

3.2. Efficacy Outcomes. The efficacy outcome of EASI scores could be assessed in 11 included studies including 6 clinical trials and 5 observational studies. We divided 6 clinical trials into 11 individual groups according to different dosage regimens and study designs. The overall pooled rates of EASI 50, EASI 75, EASI 90, and EASI 100 responses were 83.3% (95% CI: 76.7%–88.3%), 70.5% (66.3%–74.4%), 51.8% (45.8%–57.7%), and 25.0% (20.5%–30.0%), respectively, with the random-effect model (Figure 2). Calculated from 5 clinical trials and 3 observational studies, the overall pooled rate of IGA 0/1 response was 48.0% (42.2%–53.8%) with the random-effect model, which is presented in Supplementary Figure S1. The proportions of patients achieving EASI 50 and



*Two of the included clinical trials were reported in the same article/publication.

Figure 1: Flow diagram of the search and screening of the literature.

EASI 100 across the observational studies were significantly higher than the clinical trials (98.9% vs. 82.4%, $P = 0.042$; 69.8% vs. 19.1%, $P < 0.01$), which implied a superior performance of upadacitinib in real-life use than in rigorous clinical trials.

3.3. Safety Outcomes. The detailed adverse events during upadacitinib treatment in each study are summarized in Supplementary Table S1. We analyzed the treatment-emergent adverse events (TEAE) in ≥5% of patients in either treatment group from the included clinical trials and found an overall pooled rate of 7.5% (6.9%–8.2%). Acne was the most frequent adverse event (13.2%, 11.1%–15.7%), followed by nasopharyngitis (9.5%, 7.6%–11.9%) and upper respiratory tract infection (URTI) (8.3%, 6.7%–10.2%) (Figure 3).

Safety analysis of any adverse events was based on 5 clinical trials and 3 observational studies, while analysis of serious adverse events was based on 6 clinical trials and 1 observational study. The overall pooled rate of any adverse events among 8 studies was 62.8% (57.6%–67.7%), and the pooled rate of serious adverse events across 7 eligible trials was 2.2% (1.7%–2.9%) (Supplementary Figure S2).

3.4. Discontinuation of Drug. The rates of upadacitinib discontinuation were investigated in 10 studies including 6 clinical trials and 4 observational studies (Figure 4). The

Table 1: Characteristics of included studies in this meta-analysis.

Study	Study type	Total patients	Follow-up duration	Treatment regimen	Treatment duration	Efficacy assessment	Region
Blauvelt et al. [9]	CT	348	February 21, 2019, to December 9, 2020	Once-daily upadacitinib 30 mg	24 weeks	EASI NRS	129 centers located in 22 countries across Europe, North and South America, Oceania, and the Asia-Pacific region
Guttman-Yassky et al. [19]	CT	126 Group 1: 42 Group 2: 42 Group 3: 42	November 21, 2016, to April 20, 2017	Once-daily upadacitinib oral monotherapy Group 1: 7.5 mg Group 2: 15 mg Group 3: 30 mg	16 weeks	EASI IGA NRS SCORAD BSA POEM	Australia, Canada, Finland, Germany, Japan, the Netherlands, Spain, and the United States
Guttman-Yassky et al. [19] (Measure up 1)	CT	566 Group 1: 281 Group 2: 285	August 13, 2018, to December 23, 2019	Once-daily upadacitinib oral monotherapy Group 1: 15 mg Group 2: 30 mg	16 weeks	EASI and IGA WP-NRS ADerm-IS, ADerm-SS POEM HADS DLQI	151 clinical centers in 24 countries across Europe, North and South America, Oceania, and the Asia-Pacific region
Guttman-Yassky et al. [19] (Measure up 2)	CT	558 Group 1: 276 Group 2: 282	July 27, 2018, to January 17, 2020	Once-daily upadacitinib oral monotherapy Group 1: 15 mg Group 2: 30 mg	16 weeks	EASI and IGA WP-NRS ADerm-IS, ADerm-SS POEM HADS DLQI	54 clinical centers in 23 countries across Europe, North America, Oceania, and the Asia-Pacific region
Katoh et al. [20]	CT	182 Group 1: 91 Group 2: 91	From November 17, 2018	Once-daily upadacitinib oral with medium-potency topical corticosteroids (TCSs) Group 1: 15 mg Group 2: 30 mg	24 weeks	EASI and IGA NRS	Japan
Chiricozzi et al. [24]	OS, P	43	October 2020 to June 2021	Once-daily upadacitinib 30 mg	16 weeks	EASI BSA NRS DLQI POEM	Italy
Bello et al. [27]	CS, R	10	NR	Mostly upadacitinib 15 mg	8 weeks	EASI and NRS	Italy
Hagino et al. [23]	OS, R	31	September 2021 to March 2022	Once-daily 15 mg upadacitinib oral with plus twice daily topical corticosteroids of medium to strongest classes	12 weeks	EASI IGA ADCT NRS	Japan

Table 1: Continued.

Study	Study type	Total patients	Follow-up duration	Treatment regimen	Treatment duration	Efficacy assessment	Region
Pereyra-Rodriguez et al. [25]	OS, R	43	October 2020 to March 2022	Mostly once-daily upadacitinib 30 mg (60%)	16 weeks	SCORAD EASI DLQI NRS BSA IGA	Spain
Napolitano et al. [28]	OS, R	9	From June 2021	Once-daily upadacitinib 30 mg	16 weeks	EASI DLQI NRS	Italy
Feraru et al. [26]	CS, R	12	July 2020 to November 2021	Once-daily upadacitinib 30 mg or 15 mg	24 weeks	vIGA	Israel

ADCT, atopic dermatitis control tool; ADerm-IS, atopic dermatitis impact scale; ADerm-SS, atopic dermatitis symptom scale; BSA, body surface area; CT, clinical trial; CS, case series; DLQI, dermatology life quality index; HADS, hospital anxiety and depression scale; NRS, numerical rating scale; OS, observational study; P, prospective; POEM, patient oriented eczema measure; R, retrospective; SCORAD, scoring atopic dermatitis; vIGA-AD, validated investigator's global assessment for atopic dermatitis.

Table 2: Characteristics of included patients in this meta-analysis.

Study	Dosage regimen (mg)	Disease duration	Age (y) (SD)	Sex (M: F)	BMI (kg/m^2) (SD)	Concomitant treatment	Discontinuation	Reason
Blauvelt et al. [9]	30	25.0 (14.8)	36.9 (14.09)	194:150	25.99 (5.72)	Monotherapy	32	Adverse event, 10 Withdrew consent, 8 Lost to follow-up, 4 Lack of efficacy, 6 Other, 2 COVID-19 logistics, 1
Guttman-Yassky et al. [18] (Group 1)*	7.5	30.4 (18.1)	41.5 (15.4)	28: 14	27.9 (6.3)	Monotherapy	11	Adverse event, 2 Lack of efficacy, 6 Withdrew consent, 1 Lost to follow-up, 1 Progressive disease, 1
Guttman-Yassky et al. [18] (Group 2)	15	22.6 (15.8)	38.5 (15.2)	30: 12	27.4 (6.7)	Monotherapy	5	Adverse event, 2 Lack of efficacy, 2 Withdrew consent, 1
Guttman-Yassky et al. [18] (Group 3)	30	24.2 (13.6)	39.9 (15.3)	22: 20	27.4 (6.0)	Monotherapy	4	Adverse event, 2 Lack of efficacy, 1 Other, 1
Guttman-Yassky et al. [19] (Measure up 1 Group 1)	15	20.5 (15.9)	34.1 (12–74)	157: 124	25.8 (6.1)	Monotherapy	8	Lost to follow-up, 3 Withdrew consent, 2 Poor efficacy, 2 Adverse event, 1
Guttman-Yassky et al. [19] (Measure up 1 Group 2)	30	20.4 (14.3)	33.6 (12–75)	155: 130	25.6 (5.9)	Monotherapy	15	Adverse event, 7 Withdrew consent, 4 Lost to follow-up, 2 Other, 1 Systemic rescue medication required, 1
Guttman-Yassky et al. [19] (Measure up 2 Group 1)	15	18.8 (13.3)	33.3 (12–74)	155: 121	25.8 (5.6)	Monotherapy	16	Adverse event, 7 Other, 4 Poor efficacy, 3 Withdrew consent, 1 Systemic rescue medication required, 1
Guttman-Yassky et al. [19] (Measure up 2 Group 2)	30	20.8 (14.3)	34.1 (12–75)	162: 120	25.9 (5.8)	Monotherapy	14	Withdrew consent, 5 Adverse event, 4 Other, 3 Lost to follow-up, 1 Systemic rescue medication required, 1

Table 2: Continued.

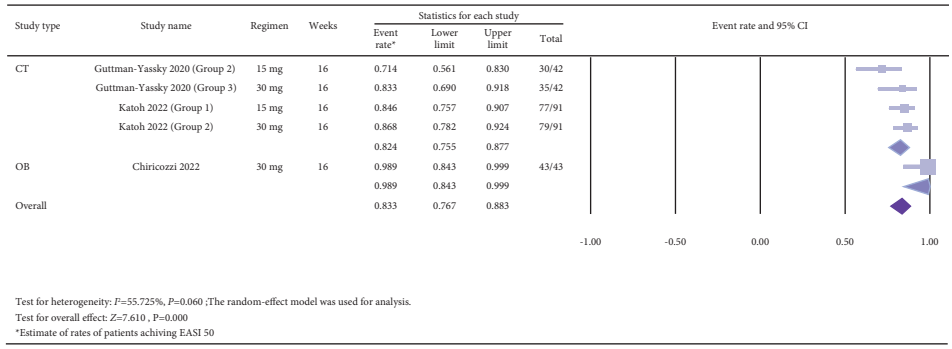
Study	Dosage regimen (mg)	Disease duration	Age (y) (SD)	Sex (M: F)	BMI (kg/m^2) (SD)	Concomitant treatment	Discontinuation	Reason
Katoh et al. [20] (Group 1)	15	23.0 (14.3)	35.9 (13.2)	68: 23	Weight: 65.1 (14.2)	In combination with medium-potency topical corticosteroids once daily	4	Adverse event, 2 Lost to follow-up, 1 Lack of efficacy, 1
Katoh et al. [20] (Group 2)	30	20.7 (14.1)	34.7 (12.7)	69: 22	Weight: 66.2 (14.4)	In combination with medium-potency topical corticosteroids once daily	6	Withdrew consent, 4 Adverse event, 1 Other, 1
Reich et al. [22] (Group 1)	15	22.9 (13.9)	32.5 (13–74)	179: 121	25.8 (6.2)	In combination with topical corticosteroids once daily	11	Withdrew consent, 3 Adverse event, 3 Poor efficacy, 2 Lost to follow-up, 2 Other, 1
Reich et al. [22] (Group 2)	30	23.1 (16.1)	35.5 (12–72)	190: 107	25.7 (5.4)	In combination with topical corticosteroids once daily	10	Other, 4 Adverse event, 3 Withdrew consent, 2 Lost to follow-up, 1
Chiricozzi et al. [24]	30	NA	45.91 (15.8)	28: 15	24.6 (3.5)	In combination with emollients daily, or with topical corticosteroids of different potencies or topical calcineurin inhibitors	4	Lost to follow-up, 2 Adverse event, 2
Bello et al. [27]	15	NA	35.4 (14.1)	8: 2	Weight: 77.2 (8.9)	NA	0	NA
Hagino et al. [23]	15	30.1 (14.3)	41.2 (16.5)	24: 7	24.5 (3.9)	In combination with twice daily topical corticosteroids of medium to strongest classes	1	Adverse event, 1
Pereyra-Rodriguez et al. [25]	15 or 30	21.1 (11.3)	34.4 (13.5)	23: 20	24.5 (4.9)	9.5% used topical corticosteroids, 6.9% used oral corticosteroids, 2.3% received phototherapy	1	Adverse event, 1
Napolitano et al. [28]	30	20.22 (5.21)	28.7 (10.3)	6: 3	NA	NA	NA	NA
Feraru et al. [26]	15 or 30	NA	51.3 (27–85)	9: 3	NA	Topical treatment for AD was offered and prescribed as needed	3	Lack of efficacy, 1 Sustained significant improvement, 2

*The dosage regimen of this group was upadacitinib 7.5 mg once daily, so we did not incorporate it in the subsequent statistical analysis. NA, not available.

Table 3: Quality assessment of the included observational studies with ROBINS-I.

Study	Study type	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall assessment
Blauvelt et al. [9]	CT	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Guttman-Yassky et al. [18]	CT	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Guttman-Yassky et al. [19]	CT	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Katoh et al. [20]	CT	Moderate	Low	Low	Moderate	Low	Moderate	Low	Moderate
Reich et al. [22]	CT	Moderate	Low	Low	Moderate	Low	Moderate	Low	Moderate
Chiricozzi et al. [24]	OS	Moderate	Low	Low	Moderate	Low	Moderate	Low	Moderate
Bello et al. [27]	CS	Serious	Low	Moderate	Moderate	Moderate	Moderate	Low	Serious
Hagino et al. [23]	OS	Moderate	Low	Low	Moderate	Low	Moderate	Low	Moderate
Pereyra-Rodriguez et al. [25]	OS	Moderate	Low	Moderate	Moderate	Low	Moderate	Low	Moderate
Napolitano et al. [28]	OS	Moderate	Low	Low	Moderate	Moderate	Moderate	Low	Moderate
Feraru et al. [26]	CS	Moderate	Low	Moderate	Moderate	Low	Moderate	Low	Moderate

CT, clinical trial; CS, case series; OS, observational study.



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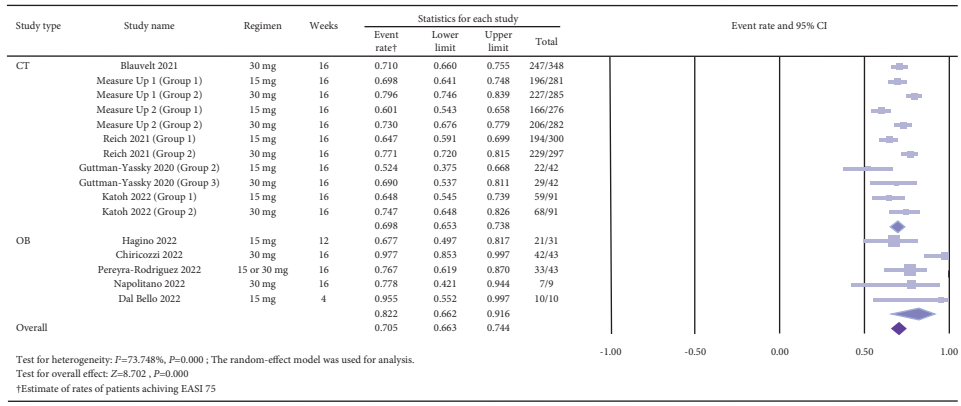

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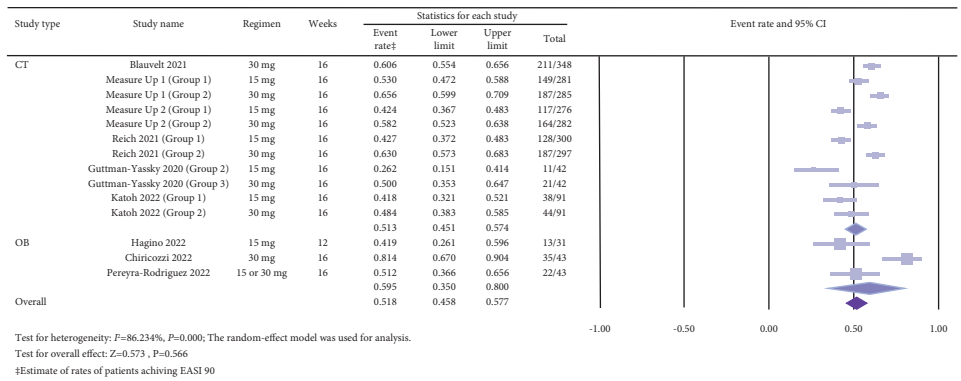

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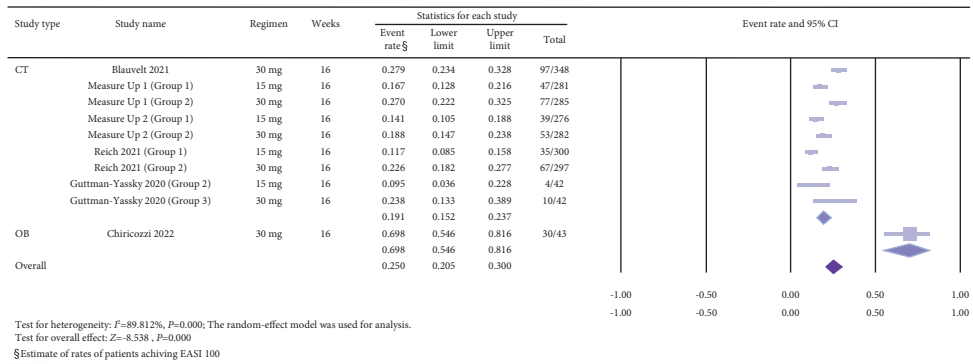
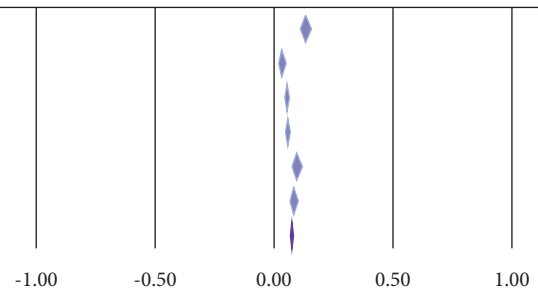


(d)

FIGURE 2: Pooled rates of patients achieving EASI 50, EASI 75, EASI 90, and EASI 100 following upadacitinib therapy: (a) pooled proportion of patients achieving EASI 50; (b) pooled proportion of patients achieving EASI 75; (c) pooled proportion of patients achieving EASI 90; (d) pooled proportion of patients achieving EASI 100.

Adverse event*	Statistics for each study			Event rate and 95% CI
	Event rate†	Lower limit	Upper limit	
Acne	0.132	0.111	0.157	
AD worsening	0.032	0.019	0.051	
Blood CPK increased	0.054	0.045	0.065	
Headache	0.057	0.048	0.068	
Nasopharyngitis	0.095	0.076	0.119	
URTI	0.083	0.067	0.102	
Overall	0.075	0.069	0.082	



Test for heterogeneity: I^2=79.443%, P=0.000 ; The random-effect model was used for analysis

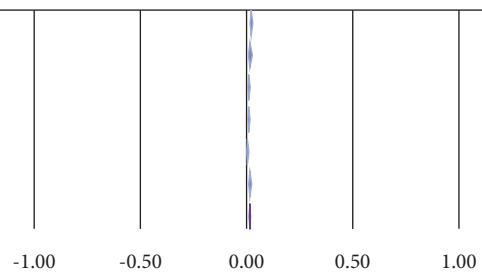
Test for overall effect: Z=-54.255 , P=0.000

*Only the adverse events reported in more than 2 studies were analyzed in the meta-analysis

†Estimate of rates of patients who experienced the corresponding adverse event

Figure 3: Pooled rates of adverse events in clinical trials.

Reasons for discontinuation	Statistics for each study			Event rate and 95% CI
	Event rate*	Lower limit	Upper limit	
Adverse event	0.022	0.017	0.029	
Lack of efficacy	0.016	0.010	0.025	
Lost to follow-up	0.010	0.006	0.016	
Other	0.010	0.006	0.017	
Systemic rescue medication use	0.004	0.001	0.011	
Withdrew consent	0.016	0.012	0.024	
Overall	0.015	0.013	0.018	



Test for heterogeneity: I^2=23.277%, P=0.075 ;The fixed-effect model was used for analysis.

Test for overall effect: Z=-46.836 , P=0.000

*Estimate of rates of patients who discontinued upadacitinib treatment for different reasons

Figure 4: Pooled rates of discontinuation of drug during upadacitinib therapy.

overall pooled proportion of upadacitinib discontinuation was 1.5% (1.3%–1.8%) with the fixed-effect model. The major factors leading to drug discontinuation were adverse events (2.2%, 1.7%–2.9%), lack of efficacy (1.6%, 1.0%–2.5%), and withdrawal of consent (1.6%, 1.2%–2.4%).

3.5. Subgroup Analysis. To explore the presence of subgroup differences for the efficacy and safety outcome of upadacitinib in treating AD, we carried out the subgroup analysis based on the dosage regimen (15 mg once daily or 30 mg once daily). Overall, the 30 mg/d regimen groups presented a superior performance in efficacy outcomes but with a higher incidence of most adverse events than the 15 mg/d regimen groups. For efficacy, significant differences in EASI 75 ($P < 0.001$), EASI 90 ($P < 0.001$), EASI 100 ($P < 0.001$), and IGA 0/1 ($P < 0.001$) between the subgroups were detected by dosage regimen. For safety, the test showed a statistically significant subgroup effect for the incidence of acne ($P = 0.007$) but detected no statistically significant difference for the incidence of other common adverse events such as nasopharyngitis ($P = 0.906$), URTI ($P = 0.734$), and increased CPK ($P = 0.325$) between different dosage groups (Table 4).

4. Discussion

4.1. Principal Findings. In this meta-analysis, 12 studies from 11 publications, including 6 clinical trials and 6 observational studies, were enrolled. The overall proportion of AD patients who achieved EASI 50, EASI 75, EASI 90, and EASI 100 after treatment with upadacitinib was 83.3%, 70.5%, 51.8%, and 25.0%, respectively. Additionally, the overall pooled rate of IGA 0/1 response was 48.0% following

Table 4: Subgroup analysis based on different dosage regimens (15 mg once daily or 30 mg once daily).

Characteristics	15 mg/d dosage group				30 mg/d dosage group				P value
	Number of groups	Event rate (%)	I^2	P	Number of groups	Event rate (%)	I^2	P	
EASI 50	2	79.1 (63.6–89.1)	67.654	0.079	3	87.6 (76.4–93.9)	46.365	0.155	0.266
EASI 75	7	64.3 (59.5–68.9)	46.872	0.080	8	75.3 (71.2–79.0)	53.785	0.034	<0.001
EASI 90	6	44.8 (41.7–47.9)	66.253	0.011	7	61.0 (58.3–63.5)	68.382	0.004	<0.001
EASI 100	4	14.0 (11.5–16.8)	20.397	0.288	6	29.0 (21.5–37.8)	88.189	0.000	<0.001
IGA 0/1	6	40.8 (36.5–45.2)	41.600	0.128	5	55.2 (49.8–60.4)	60.236	0.039	<0.001
Acne	6	10.4 (7.9–13.5)	42.362	0.123	7	15.5 (13.6–17.5)	2.491	0.406	0.007
Nasopharyngitis	5	9.4 (6.7–12.9)	57.441	0.052	6	9.6 (6.8–13.5)	73.332	0.002	0.906
URTI	4	7.9 (6.3–9.8)	0.000	0.569	5	8.8 (7.3–10.6)	70.095	0.010	0.734
Blood CPK increased	5	4.9 (3.7–6.6)	1.288	0.399	5	5.9 (4.7–7.4)	0.000	0.609	0.325

URTI, upper respiratory tract infection; CPK, creatine phosphokinase.

upadacitinib therapy. The findings on efficacy suggested that upadacitinib served as a satisfactory treatment option for patients with AD. With regard to safety, the most frequently reported adverse events were acne, followed by nasopharyngitis and URTI. The overall incidence of any adverse events was 62.8%, and the pooled rate of serious adverse events was 2.2%, signifying that the safety concerns regarding upadacitinib treatment were largely manageable. The pooled proportion of upadacitinib discontinuation was low (1.5%), primarily due to adverse events, lack of efficacy, and withdrawal of consent. The subgroup analysis based on dosage regimen revealed that the response rates of efficacy parameters, including EASI 75, EASI 90, EASI 100, and IGA 0/1, were statistically higher in the 30 mg/d groups compared to the 15 mg/d groups ($P < 0.001$), but the incidence of acne was also found to be statistically higher across the 30 mg groups ($P = 0.007$). These findings indicated that the higher dose of upadacitinib conferred greater benefits in efficacy but larger risks for adverse events.

4.2. Comparison with Other Studies. To the best of our knowledge, only one network meta-analysis, which comprised of three 16-week clinical trials, has been conducted to exclusively assess the efficacy and safety of upadacitinib in AD [32]. The present systematic review and meta-analysis has advantages over previous research by incorporating both clinical trials and observational studies, analyzing efficacy and safety beyond 16 weeks of treatment and the rate of drug discontinuation, and conducting subgroup analysis based on dosage regimen. Some of our findings were in agreement with the abovementioned meta-analysis: upadacitinib 30 mg/d groups present better performance in efficacy parameters but with an elevated incidence of acne than the 15 mg/d groups.

Acne was the most common adverse event during upadacitinib treatment for patients with AD in our study, with an incidence of 10.4% across 15 mg/d groups and 15.5% across 30 mg/d groups. This finding was consistent with the result from a post hoc analysis, which revealed an incidence of 9.8% in 15 mg/d groups and 15.2% in 30 mg/d groups [33]. Our result was also similar to a recent case series, in which 13.3% of the AD patients treated with JAK inhibitors experienced acne [34]. It should be noted that the higher incidence of acne after JAK inhibitor therapy is observed in patients with AD rather than other inflammatory diseases, such as rheumatoid arthritis and psoriatic arthritis [35, 36], which can be explained by an inference that the facial skin of patients with AD and other inflammatory diseases is fundamentally different [37]. The younger average ages of patients, more frequent skin examinations, and more often use of systemic immunosuppressants and topical corticosteroid or topical calcineurin inhibitors in the atopic dermatitis studies may also be the factors [22, 34].

4.3. Potential Underlying Mechanisms. AD is a condition caused by type 2 immune responses [38]. Type 2 cytokines, especially IL-4 and IL-13, play a key role in the pathogenesis of AD by activating the JAK/STAT pathway and driving the increased T helper (Th) 2 immunity [14, 39, 40]. Hence, blocking the JAK/STAT pathway can effectively suppress cytokine-mediated signaling pathways and inhibit the abnormal immune responses in AD [16]. Upadacitinib has a higher selectivity for JAK1 compared to other JAK family members [41]. Key cytokines that depend on JAK1 for signal transduction include the γc family (i.e., IL-4), the gp130 family (i.e., IL-6), and the class II cytokine receptor family (i.e., IFNα/β, IFN-γ, and IL-10), all of which contribute to the pathology of AD [42]. The understanding of the mechanism helps explain the satisfactory efficacy of upadacitinib as a JAK1 selective inhibitor in AD treatment. Additionally, the selective inhibition of JAK1 over JAK2 and JAK3 results in a more favorable benefit-risk profile, particularly in reducing the incidence of hematological adverse reactions [43].

The underlying mechanism of upadacitinib-associated acne in AD patients is unclear. One theory suggests that immune inhibition by JAK1 inhibitors may lead to changes in skin microbe colonization [37]. Another theory is that Th2 pathway inhibition leads to inflammatory lesions from an immune skew towards Th1 or Th17 [37]. However, a recent study showed the activation of JAK signaling pathway in acne lesions, conflicting with the acne occurrence after JAK1 inhibitor treatment [44]. As can be seen from above, the existing hypotheses for the pathogenesis of

upadacitinib-associated acne exhibit significant disparities, thus necessitating further research for clarification. Nasopharyngitis and URTI are linked to upadacitinib's mode of action, as JAK1 inhibitors can hinder cytokine signaling and cause infections [42]. Increased creatine phosphokinase (CPK) is another noticeable adverse event, probably caused by JAK inhibitors reversing inflammation-associated inhibition of myoblast differentiation, though the detailed mechanism is ambiguous [45].

4.4. Limitations. This systematic review has limitations. The first concern is the quality of the studies included, which were rated as either moderate or serious risk of bias. In addition, to gain a thorough comprehension of upadacitinib in both clinical trials and routine practice, we incorporated both randomized trials and observational studies without control groups, thus limiting our ability to compare efficacy with placebo and rendering the research a single-arm nature. Therefore, more large-scale, high-quality controlled trials are needed. Secondly, variations in study design, dosage regimen, duration covered, data material, and quality among the included studies caused heterogeneity in the meta-analysis, which we addressed with the random-effect or fixed-effect model and subgroup analysis. Finally, the majority of the included studies had a follow-up of 16–24 weeks and few provided long-term efficacy and safety evidence. It is expected that future updates will encompass more studies with extended follow-up durations.

5. Conclusion

In conclusion, upadacitinib presents potential as a promising drug for AD with favorable efficacy and manageable adverse effects. In comparison with upadacitinib 15 mg/d, upadacitinib 30 mg/d conferred superior efficacy but also a higher incidence of acne. Nevertheless, owing to the restrained quality and number of current studies, we need more high-quality, large-size trials with different dosage regimens, concomitant treatment, and follow-up durations to further verify the benefits and risks of upadacitinib.

Data Availability

All data generated or analyzed during this study are included within the supplementary information files.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yuanyuan Xu and Zhixuan Li contributed equally to this work.

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Supplementary Materials

Table S1: detailed adverse events during upadacitinib therapy. Figure S1: pooled rates of patients achieving IGA 0/1 following upadacitinib therapy. Figure S2: pooled rates of any adverse events and serious adverse events. (*Supplementary Materials*)

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