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Original Article

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Real-World Efficacy and Safety of Upadacitinib in Korean Patients With Atopic Dermatitis

So Yun Park[1], **Seok-Jae Heo**[2], **Ho Eun Gwag**[1], **Narang Hong**[1], **Hyung Don Kook**[1], **Hye Jung Jung**[1], **Mi Youn Park**[1], **Jiyoung Ahn**[1*]

[1]Department of Dermatology, National Medical Center, Seoul, Korea
[2]Division of Biostatistics, Department of Biomedical Systems Informatics, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

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Correspondence to
Jiyoung Ahn, MD, PhD
Department of Dermatology, National Medical Center, 245 Eulji-ro, Jung-gu, Seoul 04564, Korea.
Tel: +82-2-2260-7315
Email: jiyoung.ahn@nmc.or.kr

ORCID iDs
So Yun Park
https://orcid.org/0000-0003-4747-0248
Seok-Jae Heo
https://orcid.org/0000-0002-8764-7995
Ho Eun Gwag
https://orcid.org/0000-0001-6640-2705
Narang Hong
https://orcid.org/0000-0002-6542-4811
Hyung Don Kook
https://orcid.org/0000-0001-6687-2125

ABSTRACT

Purpose: Upadacitinib is an oral selective Janus kinase (JAK) 1 inhibitor that has demonstrated high efficacy in clinical trials for patients with atopic dermatitis (AD). However, clinical trial settings may not always reflect real-world practice. This study aimed to assess the real-world efficacy and safety of upadacitinib in AD patients.
Methods: One hundred fifteen AD patients treated with upadacitinib were retrospectively analyzed using medical records. Patients who received treatment for at least 16 weeks were included. In the moderate-to-severe AD group, efficacy was assessed by the proportion of patients achieving Eczema Area and Severity Index (EASI) 50, EASI 75, and EASI 90 at weeks 2 and 16 compared to baseline, whereas efficacy in the mild AD group was evaluated based on the reduction in patient-reported outcomes.
Results: The mean EASI score significantly decreased after 16 weeks of upadacitinib treatment. At week 2, 67%, 35%, and 6% of moderate-to-severe AD patients achieved EASI 50, EASI 75 and EASI 90, respectively. At week 16, 88%, 71%, and 31% of moderate-to-severe AD patients achieved EASI 50, EASI 75 and EASI 90, respectively. Patient-reported outcome measures improved rapidly within 2 weeks and were sustained through week 16. The most common adverse event was acne, occurring in 35 patients (41.2%) with mild severity. No serious adverse events occurred.
Conclusions: Upadacitinib is effective and safe for AD patients in a real-world clinical setting.

Keywords: Dermatitis, atopic; upadacitinib; Janus kinase inhibitors; treatment outcome; observational study

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition that poses therapeutic challenges and significantly impacts patients' quality of life.[1] Recently, the advent of novel systemic agents has transformed the therapeutic paradigm in the management of AD. Dupilumab is the first approved biologic that inhibits the signaling of interleukin (IL)-4 and

Hye Jung Jung
https://orcid.org/0000-0003-0995-5711
Mi Youn Park
https://orcid.org/0000-0002-1824-8309
Jiyoung Ahn
https://orcid.org/0000-0002-6766-9978

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IL-13 by blocking the IL-4 receptor alpha subunit.[2] More recently, small molecule agents including upadacitinib, baricitinib, and abrocitinib have demonstrated significant efficacy in the treatment of AD by selectively targeting the intracellular Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway.[3] Upadacitinib, an oral JAK1 inhibitor, has exhibited high efficacy in clinical trials for AD.[4] However, clinical trials are conducted under controlled and standardized conditions, which may not fully reflect the complex and variable nature of real-world clinical practice. Consequently, assessment of drug effectiveness and adverse events (AEs) within real-world clinical contexts is imperative.

To date, several real-world studies on upadacitinib have been published. Hagino *et al.*[5] in Japan reported a single-center study involving 31 patients, whereas Chiricozzi *et al.*[6] in Italy described a multicenter study comprising 146 patients. However, single-center studies are often limited by small sample sizes. Therefore, we present a relatively large single-center cohort comprising 115 patients treated with upadacitinib in Korea.

MATERIALS AND METHODS

Study design

This retrospective study was performed using electronic medical records (EMRs) of patients with AD treated with upadacitinib at the National Medical Center in Korea between October 2021 and December 2022. All consecutive patients diagnosed with AD and prescribed upadacitinib during the study period were screened for eligibility to minimize selection bias.

A total of 115 patients were enrolled in this study, of whom 85 completed 16 weeks of upadacitinib treatment. Thirty patients discontinued the treatment before 16 weeks and were therefore excluded from the final analysis. The reasons for discontinuation were as follows: loss to follow-up (14/30), treatment cessation due to financial burden (8/30), achievement of complete remission before 16 weeks (4/30), and voluntary withdrawal of consent (4/30). The baseline demographic and clinical characteristics of the excluded patients did not significantly differ from those who completed 16 weeks of treatment, suggesting minimal attrition bias.

Inclusion criteria were consistent with the Korean Ministry of Food and Drug Safety (MFDS) labeling for upadacitinib, which approves its use in patients aged 12 years or older with clinically diagnosed AD who were deemed eligible for systemic therapy by their dermatologist. Additionally, both mild and moderate-to-severe cases were included to better reflect real-world treatment patterns. However, patients with incomplete baseline laboratory or clinical data were excluded. All data were extracted from the hospital's EMR system, and data completeness was independently verified by two investigators.

Patients were treated with 30 or 15 mg of upadacitinib daily, depending on the severity of AD. For patients receiving 30 mg, the dosage was reduced to 15 mg upon clinical improvement. In most cases, patients used topical tacrolimus as needed for symptom control. Patients demonstrating sufficient symptom improvement before 16 weeks received a maintenance regimen with reduced dosing frequency to alleviate financial burden.

Data regarding height, weight, AD onset, previous treatment, and history of comorbidities were obtained using a questionnaire. Before initiating upadacitinib treatment, patients

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underwent baseline assessments, including complete blood count, biochemical analysis, total eosinophil count (TEC), lactate dehydrogenase (LDH), uric acid, and immunoglobulin E (IgE) levels. For patients who had not undergone a Multiple Allergen Simultaneous Test (MAST) within the preceding 2 years, MAST was also performed at baseline to identify potential allergen triggers. Furthermore, follow-up testing was performed after 16 weeks of treatment to assess both efficacy and AEs. This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of the National Medical Center (approval number NMC-2023-12-133).

Efficacy measurements

All patients were assessed for objective improvement of skin lesions using the Eczema Area and Severity Index (EASI) at baseline, 2 weeks, and 16 weeks after upadacitinib administration. Subjective symptom improvement was evaluated using patient-reported outcome (PRO) tools, including the Peak Pruritus Numerical Rating Scale (ppNRS), Patient-Oriented Eczema Measure (POEM), Dermatology Quality of Life Index (DLQI), and Atopic Dermatitis Control Tool (ADCT).

The primary outcome was based on the initial severity of AD. In the moderate-to-severe AD group, efficacy was evaluated based on the proportion of patients achieving EASI 50, EASI 75, and EASI 90 scores at weeks 2 and 16 compared to baseline. In the mild AD group, efficacy was assessed using reductions in PROs, given the limited sensitivity of the EASI score reduction in this population.[7,8]

Safety analysis

Safety assessments included physical examinations and systematic assessment for AEs at each outpatient visit throughout the study period. Changes in laboratory parameters were monitored throughout upadacitinib administration. Although the primary efficacy assessment was conducted at week 16, safety data were continuously reviewed throughout the treatment and follow-up period using EMRs to capture delayed-onset AEs. This comprehensive approach aimed to identify the potential safety concerns, including common AEs and significant changes in laboratory parameters that could indicate the systemic effects of the treatment. AEs were recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis

Demographic variables are presented as mean ± standard deviation for continuous variables or number (percentage) for categorical variables. Statistical analysis was conducted using the Wilcoxon signed-rank test, a non-parametric method, to assess changes in efficacy outcomes and laboratory parameters between baseline and weeks 2 and 16 with Bonferroni correction. Univariate and multivariate logistic regression analyses were conducted to determine factors associated with the achievement of EASI 75 after 16 weeks of treatment. The independent variables included in the model were age, sex, body mass index (BMI), AD onset, prior treatment, IgE, TEC, LDH, and uric acid levels. This analysis is essential for identifying potential predictors of treatment response, thereby facilitating the optimization of therapeutic strategies for distinct patient subgroups according to demographic and clinical characteristics. All statistical analyses were performed using the R software (version 4.1.2; www.r-project.org; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a P value less than 0.05.

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RESULTS

Demographics and baseline characteristics

A total of 85 patients with AD (48 males and 37 females) were included in the analysis. Seventy-three adults and 12 adolescents were recruited, with a mean age of 30.6 ± 9.2 years. The majority (59 patients, 74.7%) were diagnosed with AD in childhood. Allergic rhinitis (38 patients, 44.7%) was the most common comorbidity, with *Dermatophagoides* (31 patients, 36.5%) the most prevalent allergen . Before upadacitinib treatment, all patients had received at least one systemic therapy; 16.5% had been treated with other JAK inhibitors, and 14.1% had received dupilumab. The proportion was higher in patients with mild (36/85, 42.4%) and moderate AD (34/85, 40%) than in those with severe AD (15/85, 17.6%). The demographic and baseline characteristics of the patients are presented in **Table 1**.

Table 1. Baseline demographics, history of prior treatments and baseline severity of the patients

Variables	Values
Total	85 (100.0)
Age (yr)	30.6 ± 9.2
Adult	73 (85.9)
Adolescent	12 (14.1)
Sex	
Male	48 (56.5)
Female	37 (43.5)
Disease onset	
At birth	27 (34.2)
Childhood	32 (40.5)
Adolescence	5 (6.3)
Adult	15 (19.0)
Past allergic history	
Allergic conjunctivitis	19 (22.4)
Allergic contact dermatitis	2 (2.4)
Allergic rhinitis	38 (44.7)
Asthma	9 (10.6)
Cholinergic urticaria	1 (1.2)
Urticaria	7 (8.2)
Allergen sensitization	
Dermatophagoides	31 (36.5)
Fungus	11 (12.9)
Dog	6 (7.1)
Cat	3 (3.6)
Others	13 (15.3)
Prior treatment	
Dupilumab	12 (14.1)
Other JAK inhibitors	14 (16.5)
Cyclosporine	39 (45.9)
Methotrexate	6 (7.1)
Systemic steroid	48 (56.5)
Topical steroid	75 (88.2)
Topical calcineurin inhibitor	50 (58.8)
Phototherapy	22 (25.9)
Korean traditional medicine	29 (34.1)
Baseline severity	
Mild (EASI < 7)	36 (42.4)
Moderate (7 ≤ EASI < 23)	34 (40.0)
Severe (EASI ≥ 23)	15 (17.6)

Values are presented as mean ± standard deviation or number (%).
JAK, Janus kinase; EASI, Eczema Area and Severity Index.

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Efficacy of treatment

Mild AD group

All PROs improved significantly within 2 weeks. The ppNRS (0–10) was reduced by 67% of baseline at week 2 and was maintained until week 16. The POEM score (0–28) was decreased by 70% of baseline at week 2 and 64% at week 16. The DLQI and ADCT scores was reduced by 63% of baseline and 69% at week 2, respectively, and were maintained until week 16. At week 16, 58%, 33%, and 11% of patients achieved EASI 50, EASI 75, and EASI 90, respectively (**Table 2**, **Fig. 1**).

Moderate-to-severe AD group

The primary outcome in the moderate-to-severe AD group was assessed based on the proportion of patients achieving EASI 50, EASI 75, and EASI 90 at weeks 2 and 16. The EASI scores declined rapidly over time. EASI 50 was achieved by 66.7% of patients at week 2 and 87.8% at week 16. The corresponding rates were 35.4% and 71.4% for EASI 75, and 6.2% and 30.6% for EASI 90 (**Fig. 2B**). All PROs also markedly improved, with ppNRS decreasing by 71.4% of baseline and DLQI decreasing by 75.8% at week 16. POEM and ADCT scores were reduced by 81.0% and 77.8%, respectively, at week 16 (**Table 3**, **Fig. 2**).

EASI breakdown

The EASI scores showed a considerable reduction from baseline across all body regions and symptom domains after 16 weeks. The most pronounced reduction was observed in the lower extremities, where the median EASI score decreased by 90%, followed by the upper extremities (88.3%), trunk (80.0%), and head (74.2%), all of which were statistically significant ($P < 0.05$). Symptom analysis demonstrated significant improvements, with the greatest reduction observed in excoriation (88.0%), followed by induration (86.2%), lichenification (81.0%), and erythema (69.2%) (all $P < 0.001$; **Fig. 3**).

Safety of treatment

Overall, 47 patients (55.3%) reported at least one AE during the treatment period. The most frequently reported AE was acne, observed in 35 patients (41.2%), followed by herpes simplex (H. simplex) infection in 15 patients (17.6%). Other AEs included folliculitis and urticaria (5 patients each, 5.9%), nausea (4 patients, 4.7%), and abnormal vaginal bleeding, cellulitis, diarrhea, dyspepsia, elevated creatine kinase, epistaxis, hair loos, and herpes zoster (1 patient each, 1.2%). All AEs were graded according to the CTCAE version 5.0 and were mild to moderate in severity (Grade 1–2). No patients discontinued treatment due to AEs, and no severe AEs were reported during the study period (**Table 4**).

Table 2. Efficacy of mild group presenting median and percentage change of PRO and EASI at week 2 and week 16 from baseline

Outcome	Baseline	2 wk	16 wk
ppNRS	6.0	2.0 (67)	2.0 (67)
POEM	16.5	5.0 (70)	6.0 (64)
DLQI	13.5	5.0 (63)	5.0 (63)
ADCT	13.0	4.0 (69)	4.0 (69)
EASI	3.9	1.6 (59)	1.1 (72)

Values are presented as median (percentage reduction from baseline).
PRO, patient-reported outcome; EASI, Eczema Area and Severity Index; ppNRS, Peak Pruritus Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; ADCT, Atopic Dermatitis Control Tool; EASI, Eczema Area and Severity Index.

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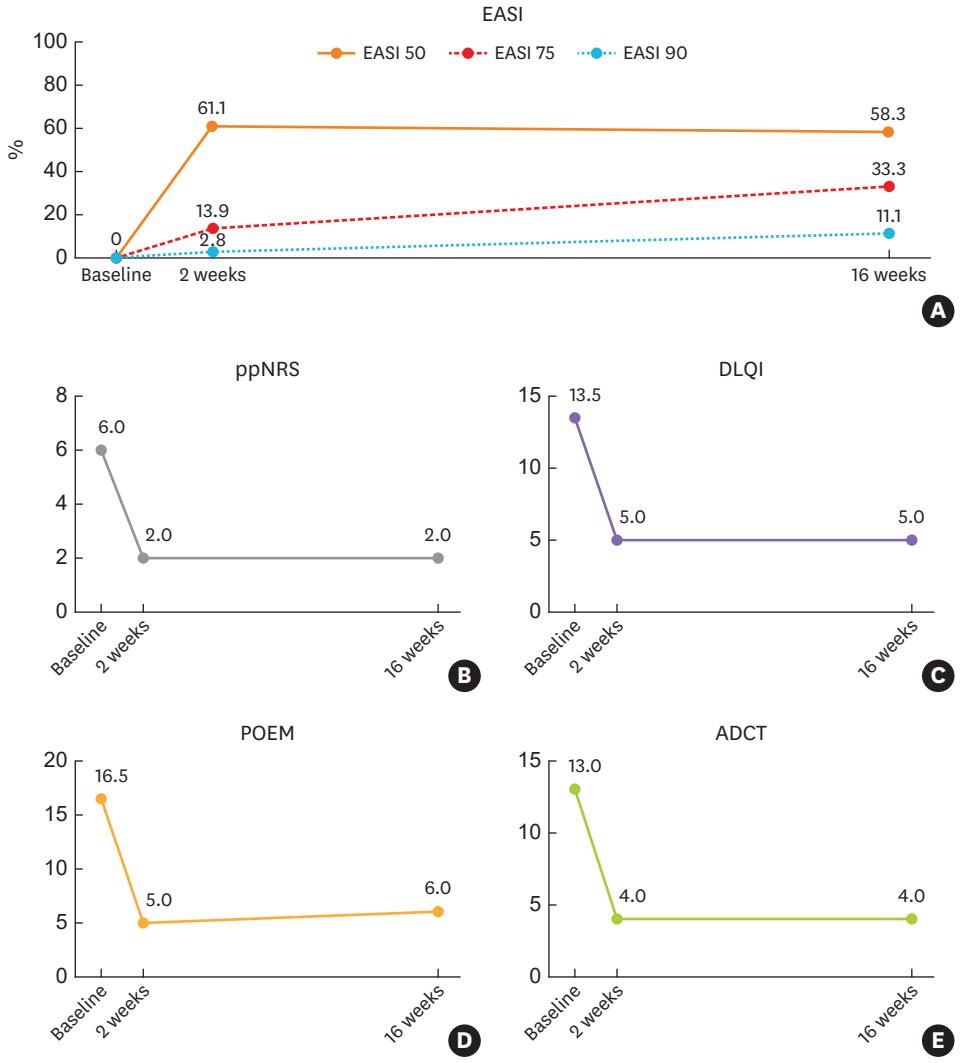

Fig. 1. Changes in (A) EASI, (B) ppNRS, (C) DLQI, (D) POEM, and (E) ADCT in the mild AD group at baseline, week 2, and week 16.
EASI, Eczema Area and Severity Index; ppNRS, Peak Pruritus Numerical Rating Scale; DLQI, Dermatology Quality of Life Index; POEM, Patient-Oriented Eczema Measure; ADCT, Atopic Dermatitis Control Tool; AD, atopic dermatitis.

Acne

The average onset of acne was 7 weeks after treatment initiation. Analysis of acne incidence by age revealed a significantly higher rate of 69.2% (9/13) among patients younger than 20 years. Acne manifestations tended to decrease with advancing age; however, this predisposition was not statistically significant. Among the patients, 63% (22/35) had pre-existing acne before upadacitinib treatment, and 60% experienced aggravation of their pre-existing condition. Acne was more prevalent in spring and summer than in fall and winter. Oral isotretinoin was the primary acne treatment, administered to 57% (20/35) of the patients, whereas 34.3% (12/35) experienced spontaneous improvement without any specific therapy (**Table 5**). The severity of acne was mild to moderate, and none of the patients discontinued upadacitinib owing to acne.

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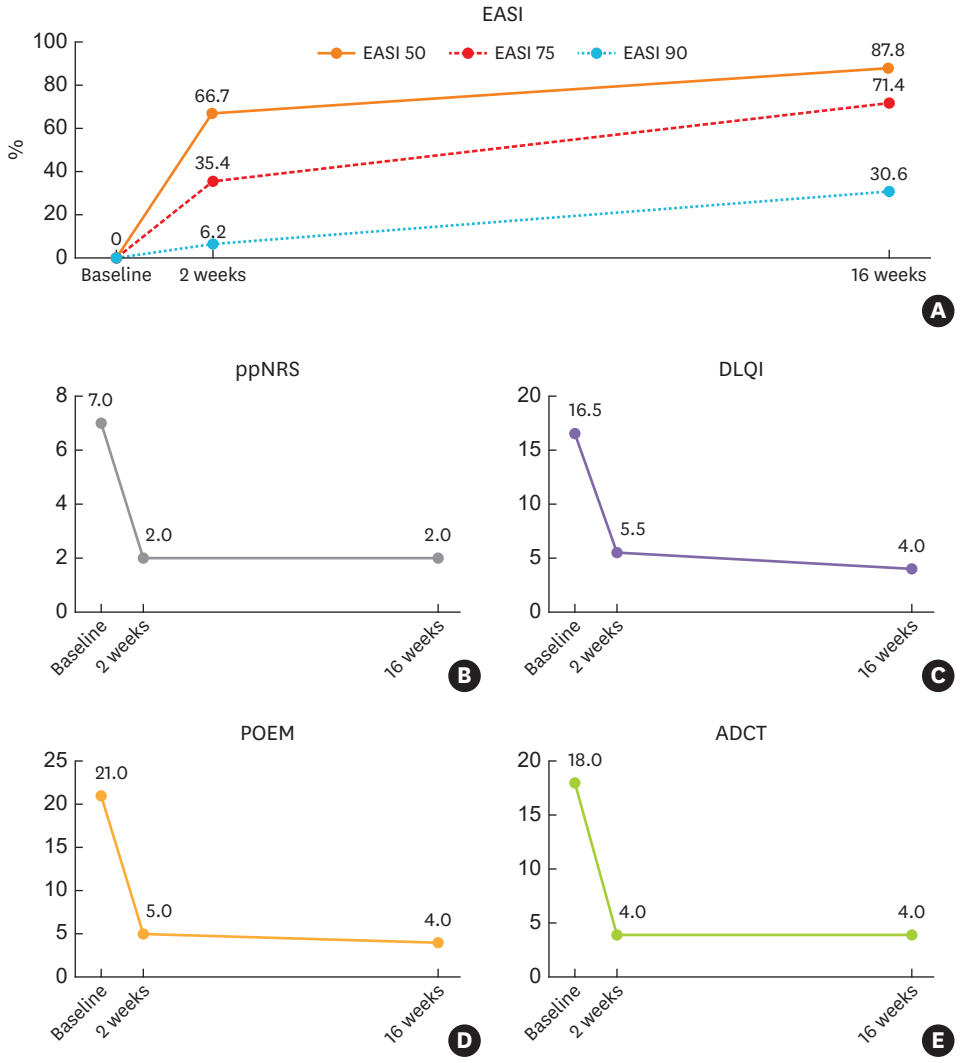

Fig. 2. Changes in (A) EASI, (B) ppNRS, (C) DLQI, (D) POEM, and (E) ADCT at baseline, and after 2 and 16 weeks in the moderate-to-severe AD group.
EASI, Eczema Area and Severity Index; ppNRS, Peak Pruritus Numerical Rating Scale; DLQI, Dermatology Quality of Life Index; POEM, Patient-Oriented Eczema Measure; ADCT, Atopic Dermatitis Control Tool; AD, atopic dermatitis.

Table 3. Efficacy of moderate-to severe group presenting median and percentage change of EASI and PROs at week 2 and week 16 from baseline

Outcome	Baseline	2 wk	16 wk
EASI	13.00	4.80 (63.1)	1.90 (85.4)
ppNRS	7.00	2.00 (71.4)	2.00 (71.4)
POEM	21.00	5.00 (76.2)	4.00 (81.0)
DLQI	16.50	5.50 (66.7)	4.00 (75.8)
ADCT	18.00	4.00 (77.8)	4.00 (77.8)

Values are presented as median (percentage reduction from baseline).
EASI, Eczema Area and Severity Index; PRO, patient-reported outcome; ppNRS, Peak Pruritus Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; ADCT, Atopic Dermatitis Control Tool.

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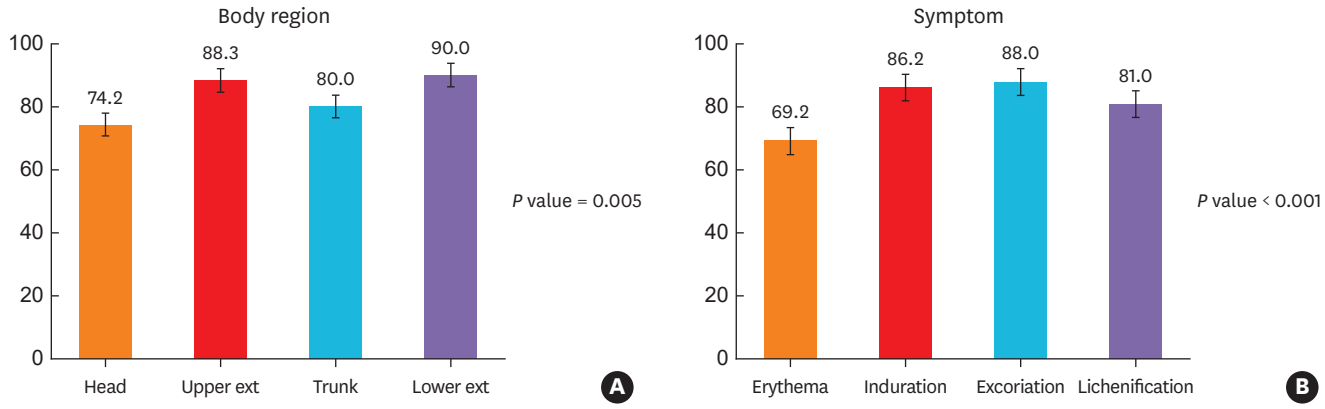

Fig. 3. Percentage improvement in EASI scores by (A) body region and (B) symptoms.
EASI, Eczema Area and Severity Index.

Table 4. Safety profile of upadacitinib up to 16 weeks

Variables	No. (%)
Total	85 (100.0)
Acne	35 (41.2)
Herpes simplex	15 (17.6)
Folliculitis	5 (5.9)
Urticaria	5 (5.9)
Nausea	4 (4.7)
Headache	2 (2.4)
Abnormal vaginal bleeding	1 (1.2)
Cellulitis	1 (1.2)
Diarrhea	1 (1.2)
Dyspepsia	1 (1.2)
Elevated creatine kinase	1 (1.2)
Epistaxis	1 (1.2)
Hair loss	1 (1.2)
Herpes zoster	1 (1.2)

Table 5. Characteristics and management of acne during upadacitinib treatment

Category	Subgroup	No. (%)	*P* value
Age group	< 20	9 (69.2)	0.008
	20–29	14 (38.9)	0.704
	30–39	16 (41.0)	0.946
	40–49	2 (11.1)	0.021
	≥ 50	0 (0.0)	0.999
Preexisting acne	Present	22 (62.9)	
	Absent	13 (37.1)	
Onset pattern	Aggravation of preexisting	21 (60.0)	
	New-onset	14 (40.0)	
Season of presentation	Spring (Mar–May)	13 (37.1)	
	Summer (Jun–Aug)	10 (28.6)	
	Autumn (Sep–Nov)	5 (14.3)	
	Winter (Dec–Feb)	7 (20.0)	
Treatment	Isotretinoin	20 (57.1)	
	Minocycline	1 (2.9)	
	Topical	2 (5.7)	
	Observation	12 (34.3)	

P values were calculated only for age group comparisons; other variables are presented descriptively.

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H. simplex

H. simplex infection was the second most common AE (15 patients), with an average onset of 16 weeks. Among these patients, 7 (47%) experienced multiple episodes, with a mean of three episodes and a maximum of 5 recurrences.

Laboratory change and variables associated with treatment response

To assess the prognostic factors, multiple clinical and laboratory variables associated with treatment response were examined, including age, sex, BMI, number of prior treatments, previous biological therapy, prior JAK inhibitor use, and baseline laboratory parameters (IgE, TEC, LDH, and uric acid). IgE, TEC, LDH, and uric acid levels decreased after 16 weeks of therapy, with TEC demonstrating the most pronounced decline and reaching statistical significance (**Table 6**). The achievement rate of EASI 75 was significantly high in patients with elevated baseline TEC in univariate analysis. However, when adjusted for multiple clinical covariates in the multivariate model, the association between baseline TEC and achieving EASI 75 was attenuated and did not reach statistical significance ($P = 0.158$), although a positive trend was maintained. Patients with prior biologic or JAK inhibitor exhibited lower odds of achieving EASI 75 at week 16; however, these differences were not significant (**Table 7**).

Table 6. Mean laboratory changes of the patient treated with upadacitinib throughout 16 weeks

Outcome	Baseline	After 16 wk	Percentage change	
			After 16 wk	*P* value
IgE (IU/mL)	1,581.00	809.00	−20.96	0.095
TEC (/uL)	286.00	143.00	−27.69	0.049
LDH (U/L)	213.00	192.00	−4.33	0.100
Uric acid (mg/dL)	4.60	4.70	−3.37	0.892

IgE, immunoglobulin E; TEC, total eosinophil count; LDH, lactate dehydrogenase.

Table 7. The univariate logistic regression analysis about variables associated with achieving EASI 75

Variable	Univariable		Multivariable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.998 (0.953–1.046)	0.948	1.020 (0.958–1.091)	0.542
Sex				
Female	reference		reference	
Male	1.111 (0.468–2.652)	0.812	0.450 (0.098–1.744)	0.267
Number of prior treatments	0.642 (0.380–1.043)	0.082	0.727 (0.323–1.625)	0.428
BMI	0.950 (0.816–1.103)	0.500	0.981 (0.824–1.168)	0.824
Biologic experience				
No	reference		reference	
Yes	0.769 (0.255–2.319)	0.637	0.692 (0.169–2.577)	0.584
Previous JAK inhibitor use				
No	reference		reference	
Yes	0.574 (0.196–1.636)	0.300	0.650 (0.125–3.047)	0.593
Baseline IgE				
≤ 450	reference		reference	
> 450	3.778 (0.940–19.047)	0.074	4.755 (0.913–24.767)	0.064
Baseline TEC				
≤ 250	reference		reference	
> 250	5.714 (1.614–27.187)	0.013	3.742 (0.600–23.343)	0.158
Baseline LDH				
≤ 100	reference		reference	
> 100	1.540 (0.497–5.130)	0.462	1.221 (0.332–4.733)	0.766
Baseline uric acid				
< 3.4 or > 7	reference		reference	
3.4–7	0.775 (0.147–3.480)	0.744	0.685 (0.101–4.175)	0.689

EASI, Eczema Area and Severity Index; OR, odds ratio; CI, confidence interval; BMI, body mass index; JAK, Janus kinase; IgE, immunoglobulin E; TEC, total eosinophil count; LDH, lactate dehydrogenase.

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DISCUSSION

Although several real-world studies of upadacitinib have been conducted, single-center studies often lack sufficiently large cohorts. In multicenter studies, variability among evaluators across sites can pose challenges in maintaining consistency in efficacy and safety assessment due to differing criteria, thereby potentially compromising the reliability of data collection. However, a notable advantage of conducting multicenter studies is to increase sample size, which can lead to statistically significant results. Given these considerations, this study aimed to report a single-center, real-world investigation of upadacitinib therapy in patients with AD, with a relatively large cohort. All assessments were conducted by the same evaluator using consistent criteria to ensure that both the efficacy and safety of the treatment were evaluated consistently.

Significant improvements in symptoms and skin lesions were observed across all AD severities in the study. All PROs improved rapidly, with more than a 50% reduction within 2 weeks, consistent with the rapid onset reported in a pivotal trial.[4] The rapid symptom alleviation provided by upadacitinib may be attributed to its direct and simultaneous inhibition of multiple pathways involved in pruritus. Although a rapid decrease in PROs was observed within the first 2 weeks, no further reduction was noted up to 16 weeks. The absence of an additional decline beyond the initial period could be because many patients reached a ppNRS of 0–1 within 2 weeks or achieved sufficient symptom improvement by 4–8 weeks. Consequently, a maintenance regimen with reduced dosing frequency was implemented in some patients. In the moderate-to-severe AD group, 71% of patients achieved EASI 75, aligning with outcomes reported in phase 3 clinical trials.[4] Notably, this response was achieved despite flexible dose tapering once disease control was reached. This may suggest the feasibility of dose reduction in real-world practice; however, further studies are needed to evaluate long-term durability and cost-effectiveness.

These outcomes are broadly consistent with recent international real-world cohorts, including a 52-week Italian study demonstrating sustained efficacy and favorable tolerability in routine clinical care, even with individualized dosing strategies.[9] This alignment supports the external validity of our findings and suggest the clinical relevance of flexible dose adjustments in real-world settings.

At 16 weeks, the EASI breakdown revealed an improvement of more than 70% across all body regions. These findings indicate that upadacitinib provides consistent and substantial improvement across multiple anatomical sites, including regions that are traditionally challenging to manage, such as the head, neck, hands, and feet. Some previous clinical reports have described limited responses to dupilumab in these regions, suggesting potential differences in treatment responsiveness among anatomical sites.[10] Nevertheless, as the present study did not involve direct comparison with dupilumab and was limited to a 16-week observation period, these interpretations should be made with caution. The relatively short duration and indirect nature of this comparison may not fully reflect long-term or treatment-specific variations in efficacy. Further comparative and longitudinal studies are needed to validate these findings.

In terms of symptom-specific improvements, induration and excoriation, predominantly representing acute inflammatory lesions, demonstrated marked improvement rates exceeding 85%. These results suggest that upadacitinib is effective in alleviating the acute and active inflammatory components of AD, supporting its role as a rapid-acting systemic therapy.

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In this study, the most frequently observed AE was acne, reported at a significantly higher rate of 41.2% compared to 17% in the phase 3 clinical trial.[4] Although younger age was associated with higher acne occurrence, this trend was not statistically significant. The mean age of our cohort was 30.6 years, younger than the 34.1 years reported in the phase 3 cohort, which may have contributed to the higher incidence. Additionally, many participants had pre-existing acne before upadacitinib treatment, which may have influenced the increased incidence, whereas the rate of new-onset acne was comparatively low. Acne occurred mainly in spring and summer, likely due to increased sebum production at higher temperatures, consistent with previous studies.[11,12] Importantly, all acne events were nonserious and manageable with many resolving spontaneously or with conventional acne therapy, suggesting that these events may have been influenced by demographic and environmental factors rather than drug-specific toxicity.

However, the underlying pathogenesis of upadacitinib-induced acne in patients with AD remains unclear. A previous study revealed that JAK1 and JAK3 are upregulated in acne lesions relative to non-lesional skin, indicating a potential link between JAK pathway activation and acne.[13] Another proposed mechanism is that JAK inhibitors might exacerbate acne through their impact on the JAK-STAT signaling pathway, which interacts with epidermal growth factors (EGFs) and contributes to abnormal follicular keratinization.[14] Nevertheless, further investigation is required to better understand the pathophysiological mechanisms through which JAK inhibitors may precipitate acne development.

Considering the emotional stress experienced by the patients, early intervention with oral isotretinoin was implemented. Most patients exhibited rapid improvement in acne after isotretinoin treatment. Furthermore, spontaneous improvement was observed in 34% of the patients who did not receive any treatment for acne.

Opportunistic infection, particularly viral infection, was among the common non-serious AEs observed in patients treated with upadacitinib.[4] This susceptibility can be attributed to the drug's inhibition of interferon-γ via the JAK1-STAT1 pathway, which plays a crucial role in innate antiviral defense.[15] In our cohort, 17.6% of patients experienced an average of three recurring episodes of H. simplex infections after upadacitinib administration. Clinicians should should be aware of the potential risk of H. simplex reactivation during upadacitinib treatment.

Eosinophils are primary effector cells in the pathophysiology of AD, often associated with the disease severity and chronicity.[16] In 52-week real-world data for dupilumab, patients with a high baseline TEC had an odds ratio of 0.25 for achieving EASI 90, indicating a lower likelihood of response.[9] In contrast, for upadacitinib, several recent real-world studies have demonstrated that reductions in TEC are closely linked to clinical improvement. Hagino *et al.*[17,18] reported that a greater decline in TEC was strongly correlated with reductions in EASI and pruritus scores during 48 weeks of treatment, highlighting TEC as a dynamic biomarker reflecting treatment efficacy. Long-term follow-up studies further confirmed that TEC decreased rapidly within 4–12 weeks and remained below baseline up to 96 weeks, irrespective of patient age or dose, supporting its reliability as a sustained marker of upadacitinib response.[19,20]

In our cohort, a higher baseline TEC was significantly associated with achieving EASI 75 in the univariate analysis, consistent with prior reports suggesting that eosinophilic inflammation may predict favorable outcomes with JAK inhibitors. Although this association

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was attenuated and did not reach statistical significance in the multivariate model, a positive association was observed. This attenuation may be influenced by the inclusion of multiple covariates and should not be interpreted as diminishing the biological relevance of TEC. Collectively, these findings suggest the role of TEC as a biomarker for predicting response to upadacitinib. Even in the context of reduced statistical significance after adjustment, the biological plausibility and consistent positive trends reinforce that TEC is a clinically meaningful parameter. Incorporating TEC into treatment decision-making may assist clinicians in identifying patients who are more likely to benefit from upadacitinib. Further prospective studies with larger cohorts are warranted to confirm its predictive value and elucidate its role in the precise management of AD. This single-center real-world study included a relatively large cohort evaluated by consistent assessors, allowing for reliable assessment of both efficacy and safety. The use of TEC as a predictive biomarker may offer promising avenues for personalized treatment strategies.

However, the limitations of the study include its retrospective nature, which may introduce biases that could affect outcomes, and the lack of distinct categorization between patients treated with 15 and 30 mg of upadacitinib, as dosages were adjusted based on symptom severity rather than a standardized protocol. Additionally, patients who experienced symptom improvement did not adhere to a consistent daily regimen of upadacitinib, leading to non-continuous drug administration. In addition, interim clinical assessments between weeks 4 and 8 were not systematically collected in this retrospective study; thus, the early response dynamics within this interval could not be evaluated. Moreover, detailed information on concomitant topical or systemic therapies and washout periods was not consistently available for all patients, which may have limited the ability to fully distinguish the independent therapeutic effect of upadacitinib from potential concomitant treatments. These real-world dosing variations, while clinically reflective, may influence treatment consistency; therefore, future prospective studies with standardized dosing and prolonged follow-up periods are warranted.

In conclusion, this study demonstrated the efficacy and safety of upadacitinib in AD with rapid improvement across all severities. Outcomes were comparable to those of phase 3 trials, despite inconsistent adherence, with no serious AEs. Multicenter studies are needed to validate long-term safety and efficacy.

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