

# Effectiveness and Safety of Upadacitinib in Combination with Topical Corticosteroids in Adolescent Patients with Moderate-to-Severe Atopic Dermatitis

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**Purpose:** To investigate the therapeutic effectiveness and safety of Janus kinase 1 inhibitor upadacitinib in adolescent patients with atopic dermatitis (AD).

**Patients and Methods:** This study examined therapeutic effectiveness and safety of upadacitinib for 39 Japanese adolescent patients (aged 12–17 years) diagnosed with moderate-to-severe AD from August 2021 to January 2023. The patients were treated with upadacitinib 15 mg/day plus twice daily topical corticosteroids. Total eczema area and severity index (EASI) or EASI on head and neck, upper limbs, lower limbs, and trunk or for erythema, edema/papulation, excoriation, or lichenification, atopic dermatitis control tool (ADCT), peak pruritus-numerical rating scale (PP-NRS), and laboratory indexes were assessed at weeks 0, 4, and 12 of treatment. Treatment-emergent adverse events were recorded.

**Results:** Total EASI or EASI on 4 anatomical sites or for 4 rash types, ADCT, and PP-NRS were significantly reduced at week 4 and 12 compared to week 0. The achievement rates at weeks 4 or 12 were 64.1% or 62.5% for EASI 75, 93.5% or 73.1% for ADCT <7-point, and 80.6% or 60% for PP-NRS  $\geq$ 4-point improvement, respectively, indicating their peak at week 4 and slight decrease at week 12. The percent reduction of EASI for excoriation was higher than that for lichenification or edema/papulation at week 4 or week 12, respectively. The percent reductions of EASI for erythema and edema/papulation on head and neck were lower than those on lower limbs at week 12. Total eosinophil counts (TEC) and IgE reduced at week 4 compared to week 0 while TARC, IgE, TEC, and LDH increased at week 12 compared to week 4.

**Conclusion:** These results suggest therapeutic effectiveness and tolerability of upadacitinib and support its therapeutic usefulness for adolescent AD patients.

**Keywords:** atopic dermatitis, upadacitinib, adolescent, effectiveness, safety

## Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by recalcitrant eczema, type 2-skewed immune responses, disrupted skin barrier, and severe pruritus.<sup>1,2</sup> AD is associated with disease burden, and lack of disease control induces persistent itch, sleep disturbance, depression, anxiety, impairment of daily activities, and reduces quality of life (QOL) of patients.<sup>3–5</sup> In the skin lesions with AD, the levels of cytokines transducing intracellular Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signals are increased, such as interleukin (IL)-4, IL-5, IL-13, IL-31, thymic stromal lymphopoietin (TSLP) or IL-22, which contribute to the development and exacerbation of AD.<sup>6–9</sup> Recently in Japan, the approval of the IL-4R $\alpha$  antibody, dupilumab, for patients with AD post six months of age has expanded the therapeutic options especially for pediatric AD patients, including those aged 12 and above. Dupilumab is a well-balanced antibody preparation with substantial evidence

supporting its safety and effectiveness.<sup>10</sup> JAK inhibitors including upadacitinib can suppress the effects of above cytokines and are approved as therapeutic options for AD.<sup>11</sup> Previous real-world clinical studies have revealed the therapeutic effectiveness and safety and resultant good disease control by upadacitinib 15 mg/day plus topical corticosteroids for patients with AD, mainly in adult patients.<sup>12–15</sup> However, there are few studies specifically examining the effectiveness and safety of this treatment in adolescent patients with moderate-to-severe AD. Adolescents face challenges in managing AD that are distinct from adults, such as heightened sensitivity to skin irritation, increased social and emotional pressures by appearance, and reduced compliance with treatment regimens.<sup>16</sup> Therefore, it is necessary to establish treatment options for adolescent AD patients. This study aims to evaluate the therapeutic effectiveness and safety of upadacitinib 15 mg/day plus topical corticosteroids for adolescent patients with moderate-to-severe AD in real-world clinical practice.

## Materials and Methods

### Study Design and Data Collection

A retrospective study was conducted on 39 Japanese patients (aged 12 to 17 years) diagnosed with moderate-to-severe AD between August 2021 and January 2023. The patients were treated with oral upadacitinib 15 mg/day plus twice daily topical corticosteroids of moderate to strongest classes. The diagnosis of moderate-to-severe AD (eczema area and severity index [EASI]  $\geq 16$  or EASI of head and neck  $\geq 2.4$ ) was done based on the Japanese Atopic Dermatitis Guidelines 2021.<sup>17</sup> This study was conducted in accordance with the Declaration of Helsinki (2004) and was approved by the Ethics Committee of Chiba Hokusoh Hospital. Patients were recruited from the dermatology department of Chiba Hokusoh Hospital based on medical record reviews, ensuring that none had been part of any clinical trials. Given the retrospective nature of this study, a control group was not included. The 12-week duration was chosen as an initial evaluation period to discern the immediate effects and safety of the treatments, understanding the chronic nature of AD. Prior to this treatment, all patients had been treated with topical corticosteroids alone and did not respond adequately. Lastly, this study was not registered on any clinical trial site due to its retrospective design. The written informed consent was obtained from the patients and their parents. The demographic information of the patients, such as sex, age, body mass index, duration of AD, and history of allergic diseases, was recorded.

### Assessment of Therapeutic Effectiveness

We analyzed eczema area and severity index (EASI), investigator's global assessment (IGA), IgE, thymus and activation-regulated chemokine (TARC), lactate dehydrogenase (LDH), and total eosinophil count (TEC) at weeks 0, 4, and 12 of treatment. The reference values are as follows: for IgE, the typical range is 0–170 (IU/mL); for TARC, the range varies with age, being less than 450 pg/mL for adults and under 743 (pg/mL) for children aged 2 years and above; LDH falls within the range of 124–222 (IU/mL); and for TEC, the standard value lies between 70 and 450 (/mL). Patients reported the atopic dermatitis control tool (ADCT) and peak pruritus-numerical rating score (PP-NRS) simultaneously.<sup>18,19</sup> We analyzed the EASI scores on head and neck, upper limbs, lower limbs, and trunk, or for erythema, edema/papulation, excoriation, and lichenification at weeks 0, 4, and 12 of treatment. We calculated the proportions of patients whose EASI decreased by at least 75%, 90%, or 100% from baseline (EASI 75, EASI 90, or EASI 100, respectively). We examined the proportion of patients whose PP-NRS was reduced by  $\geq 4$ -point from baseline (PP-NRS 4) among the patients with baseline PP-NRS  $\geq 4$ . We investigated the proportion of patients who achieved an ADCT score  $< 7$ -point (ADCT 7), which is the threshold for control of AD, among patients with baseline ADCT  $> 7$ -point. We investigated the proportion of patients who achieved IGA = 0 (clear) or 1 (almost clear) with  $\geq 2$  grades of reduction from baseline (IGA 0/1).

### Assessment of Safety

Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that emerged or worsened during the follow-up survey period (from the start of upadacitinib treatment until 30 days after the final administration).

## Statistical Analysis

For variables with a normal distribution, results were shown as mean  $\pm$  standard deviation (SD), and for variables with a nonparametric distribution, the results are shown as median [interquartile range]. The differences between measurements at weeks 0, 4, and 12 were analyzed using Friedman test with Bonferroni post-hoc test for variables with a nonparametric distribution. Differences in frequencies were analyzed by Fisher's exact test. Statistical significance was set at  $p < 0.05$ . All statistical analyses were performed using Easy R (EZR) (Saitama Medical Center, Jichi Medical University).

## Results

### Patient Demographics and Baseline Characteristics

We enrolled 39 adolescent patients (aged 12 to 17 years) with moderate-to-severe AD (26 males and 13 females). Table 1 shows the comorbidities, baseline total EASI score, EASI scores on head and neck, upper limbs, lower limbs, and trunk, or for erythema, edema/papulation, excoriation or lichenification, IGA, ADCT, PP-NRS, and baseline serum IgE, TARC, LDH, and TEC.

**Table 1** Demographics and Baseline Characteristics of Adolescent Patients with Atopic Dermatitis (n = 39)

Sex, n (%)	
Male	26 (67)
Age (years) <sup>a</sup>	14 [13–16]
Body mass index (kg/m <sup>2</sup> ) <sup>b</sup>	21.3 $\pm$ 3.3
Disease duration (years) <sup>b</sup>	11.5 $\pm$ 4.0
Comorbidities, n (%)	
Allergic conjunctivitis	9 (23)
Allergic rhinitis	9 (23)
Asthma	9 (23)
Cataract	1 (3)
Pretreatment, n (%)	
Topical corticosteroids	39 (100)
Clinical indexes	
Total EASI <sup>a</sup>	21.3 [17.0–29.8]
EASI on head and neck <sup>a</sup>	3 [1.4–4]
EASI on upper limbs <sup>a</sup>	4.8 [4–6]
EASI on lower limbs <sup>a</sup>	8.4 [6.4–11.2]
EASI on trunk <sup>a</sup>	7.2 [4.5–8.4]
EASI for erythema <sup>a</sup>	4.1 [3.2–7.7]
EASI for edema/papulation <sup>a</sup>	4.8 [4.0–7.7]
EASI for excoriation <sup>a</sup>	6.0 [4.3–8.1]
EASI for lichenification <sup>a</sup>	5.0 [4.3–7.4]

(Continued)

**Table 1** (Continued).

IGA <sup>a</sup>	3 [3–3]
ADCT <sup>a</sup>	10 [7.5–14]
PP-NRS <sup>a</sup>	8 [7–8]
Laboratory parameters	
IgE (IU/mL) <sup>a</sup>	2440 [928–8277.5]
TARC (pg/mL) <sup>a</sup>	996 [437–2198]
LDH (IU/mL) <sup>a</sup>	243 [188.5–277.5]
TEC (/mL) <sup>a</sup>	353.4 [239.8–669.1]

**Notes:** <sup>a</sup>Data provided as the median [interquartile range]. <sup>b</sup> Data provided as the mean ± standard deviation.

**Abbreviations:** EASI, eczema area and severity index; ADCT, atopic dermatitis control tool; PP-NRS, peak pruritus-numerical rating score; IGA, investigator's global assessment; IgE, immunoglobulin E; TARC, thymus and activation-regulated chemokine; LDH, lactate dehydrogenase; TEC, total eosinophil count.

## Improvement of EASI, IGA, ADCT, and PP-NRS at Weeks 4 and 12 of Treatment with 15 mg/Day Upadacitinib Plus Topical Corticosteroids

All clinical indexes, EASI, IGA, ADCT, and PP-NRS, significantly decreased at weeks 4 and 12 compared to week 0 (Table 2). There were no differences in EASI, IGA, ADCT, and PP-NRS between week 12 versus week 4. The percent reductions from baseline at week 4 or 12 were median [interquartile] 77.3 [72.7–83.5] % or 77.7 [62.7–87.5] % for EASI, 76 [47.8–84.7] % or 65.5 [34.8–90] % for ADCT, and 62.5 [50–75] % or 75 [42.9–87.5] % for PP-NRS, respectively. There were no significant differences in the percent reductions of EASI, ADCT, and PP-NRS between week 4 versus 12. The achievement rates at week 4 or 12 were 64.1% or 62.5% for EASI 75, 93.5% or 73.1% for ADCT 7, and 80.6% or 60% for PP-NRS 4, respectively, indicating the peak at week 4 and modest decrease at week 12 without significant differences (Figure 1), while those were 12.8% or 15.6% for EASI 90, 12.8% or 15.6% for EASI 100, and 11.6% or 18.6% for IGA 0/1, indicating their

**Table 2** The Clinical Indexes and Laboratory Parameters at Week 0, 4 and 12 of Upadacitinib Treatment, and the Significance of Differences Between the Stages (n = 39)

	Median [Interquartile Range]			p		
	Week 0	Week 4	Week 12	Week 0 versus Week 4	Week 0 versus Week 12	Week 4 versus Week 12
Total EASI	21.3 [17.0–29.8]	4.4 [3.7–6.3]	4.4 [3–7.4]	< 0.01**	< 0.01**	1
EASI on head and neck	3 [1.4–4]	0.8 [0.4–1.5]	0.8 [0.4–1.5]	< 0.01**	< 0.01**	0.88
EASI on upper limbs	4.8 [4–6]	0.8 [0.4–1.2]	1.2 [0.4–1.75]	< 0.01**	< 0.01**	1
EASI on lower limbs	8.4 [6.4–11.2]	1.6 [0.8–2.4]	0.8 [0.5–2.4]	< 0.01**	< 0.01**	0.53
EASI on trunk	7.2 [4.5–8.4]	1.2 [0.9–1.8]	1.2 [0.6–2.7]	< 0.01**	< 0.01**	1
EASI for erythema	4.1 [3.2–7.7]	1.0 [0.3–1.6]	1.1 [0.5–1.6]	< 0.01**	< 0.01**	0.91
EASI for edema/papulation	4.8 [4.0–7.7]	1.3 [0.8–2.1]	1.6 [1.2–2.4]	< 0.01**	< 0.01**	0.74
EASI for excoriation	6.0 [4.3–8.1]	0.8 [0–1.5]	1.2 [0–2.1]	< 0.01**	< 0.01**	1

(Continued)

Table 2 (Continued).

	Median [Interquartile Range]			p		
	Week 0	Week 4	Week 12	Week 0 versus Week 4	Week 0 versus Week 12	Week 4 versus Week 12
EASI for lichenification	5.0 [4.3–7.4]	1.8 [1.0–2.2]	1.4 [1.0–2.2]	< 0.01**	< 0.01**	1
IGA	3 [3–3]	1 [1–2]	1 [1–2]	< 0.01**	< 0.01**	1
ADCT	10 [7.5–14]	2.5 [1–4.8]	3 [1–7.25]	< 0.01**	< 0.01**	0.32
PP-NRS	8 [7–8]	3 [2–3]	2 [1–4.5]	< 0.01**	< 0.01**	1
IgE (IU/mL)	2440 [928–8277.5]	2075 [788.5–6514.5]	3431 [2036–10,794]	< 0.01**	0.047*	< 0.01**
TARC (pg/mL)	996 [437–2198]	681 [362.5–1321.25]	1188 [593–6229]	1	0.14	< 0.01**
LDH (IU/mL)	243 [188.5–277.5]	198 [178–230]	220 [195–258]	0.25	1	< 0.01**
TEC (/ $\mu$ L)	353.4 [239.8–669.1]	248.5 [133.3–339.2]	249.6 [198–494]	< 0.01**	1	0.015*

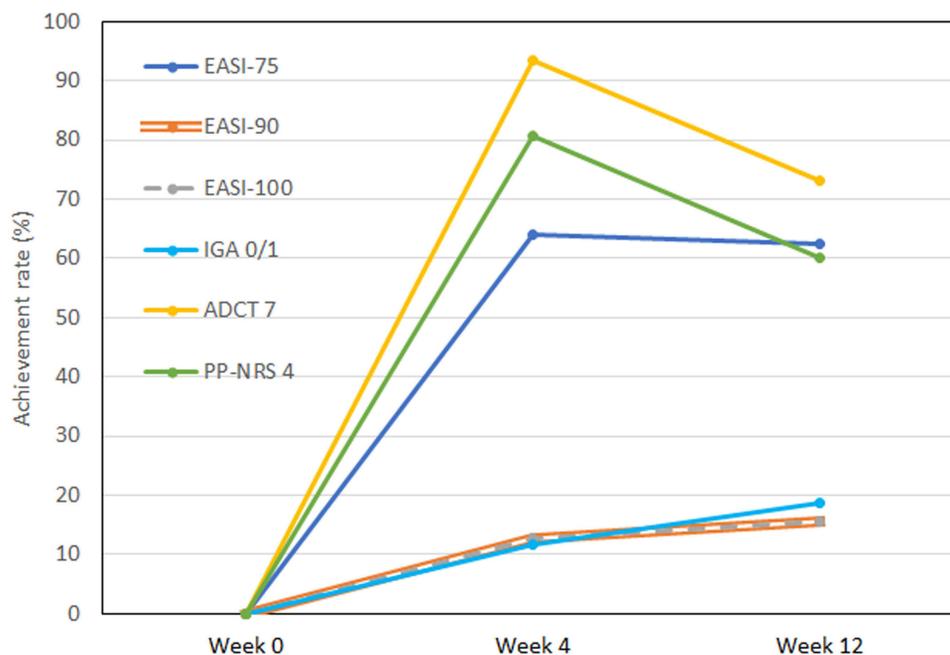
**Notes:** Data provided as the median [interquartile range]. \*Statistically significant at  $p < 0.05$ , \*\* at  $p < 0.01$ , analyzed by Friedman test with Bonferroni post-hoc test.

**Abbreviations:** EASI, eczema area and severity index; ADCT, atopic dermatitis control tool; PP-NRS, peak pruritus-numerical rating score; IGA, investigator's global assessment; IgE, immunoglobulin E; LDH, lactate dehydrogenase; TARC, thymus and activation-regulated chemokine; TEC, total eosinophil count.

gradual increase until week 12 without significant differences from those at week 4 (Figure 1). The transitions of EASI 90, EASI 100 and IGA0/1 were very close to one another.

## Improvement of EASI on Different Anatomical Sites at Weeks 4 and 12 of Treatment

The EASI scores on all four anatomical sites decreased at weeks 4 and 12 compared to week 0 (Table 2). There were no significant differences in EASI scores on 4 anatomical sites at week 12 compared to week 4.



**Figure 1** The achievement rates of eczema area and severity index (EASI) 75, EASI 90, EASI 100, atopic dermatitis control tool (ADCT) 7, peak pruritus-numerical rating score (PP-NRS) 4, and investigator's global assessment (IGA) 0/1 during treatment with upadacitinib 15 mg/day plus topical corticosteroids for adolescent patients with atopic dermatitis ( $n = 39$ ).

The median percent reductions of EASI from baseline at week 4 or 12 were 70% or 68.8% on head and neck, 80% or 80.6% on upper limbs, 78.6% or 87.5% on lower limbs, and 81.3% or 83.3% on trunk, respectively (Figure 2a). The percent reduction of EASI on head and neck was lower than that on upper limbs at week 4, and that on head and neck was lower than that on lower limbs at week 12, indicating lower treatment responsiveness on head and neck compared to upper or lower limbs.

## Improvement of EASI for Individual Clinical Components on the Whole Body at Weeks 4 and 12 of Treatment

The EASI scores for erythema, edema/papulation, excoriation or lichenification decreased at weeks 4 and 12 compared to week 0 (Table 2). There were no significant differences in EASI scores for all four clinical components at week 12 compared to week 4.

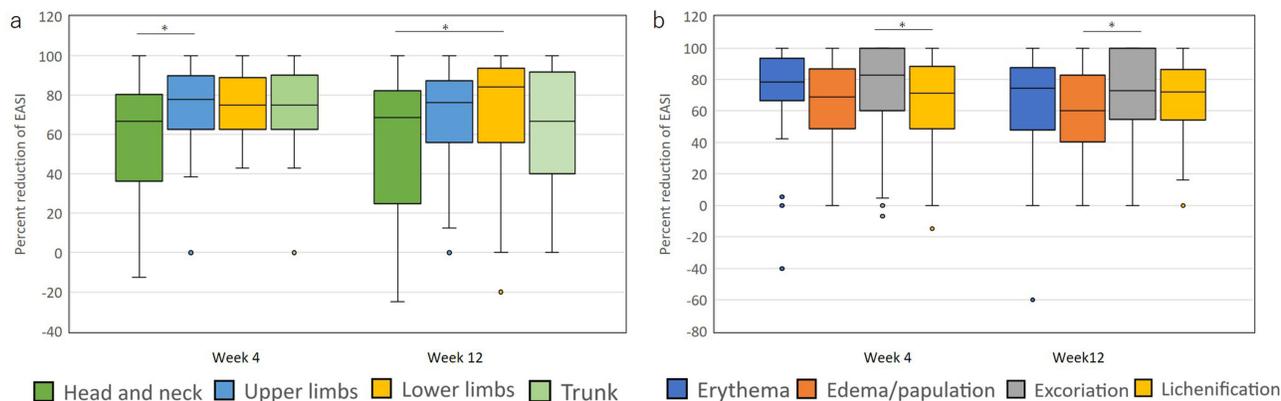
The median percent reductions of EASI from baseline at weeks 4 or 12 were 74.2% or 69.5% for erythema, 62.7% or 54.1% for edema/papulation, 77.7% or 73.4% for excoriation, and 68.6% or 71.4% for lichenification, respectively (Figure 2b). The percent reduction of EASI for excoriation was significantly higher than that for lichenification at week 4 and was higher than that for edema/papulation at week 12.

## Improvement of EASI for Individual Clinical Components on Different Anatomical Sites at Weeks 4 and 12 of Treatment

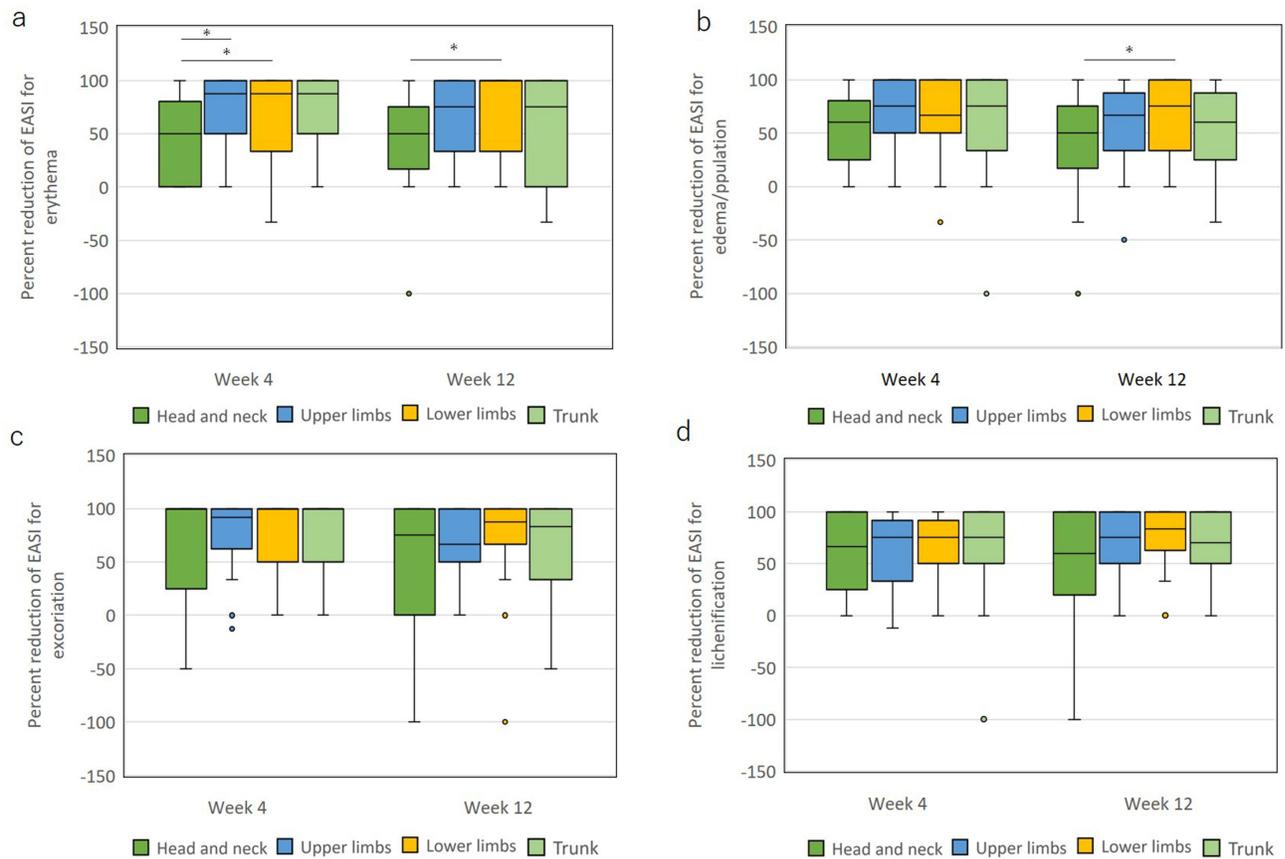
We then assessed if the percent reduction of EASI for erythema, edema/papulation, excoriation, or lichenification might differ with different anatomical sites. The percent reduction of EASI for erythema on head and neck at week 4 (48.9%) was lower than that on upper limbs (83.3%) and on lower limbs (76.8%), and that on head and neck at week 12 (57.4%) was lower than that on lower limbs (80.6%) (Figure 3a). The percent reduction of EASI for edema/papulation on head and neck at week 12 (46.7%) was lower than that on lower limbs (73.3%) (Figure 3b). There were no site-dependent differences in percent reduction of EASI for excoriation or lichenification (Figure 3c and d). These results indicate that the therapeutic effectiveness of upadacitinib for erythema and for edema/papulation on head and neck might be lower than those on lower limbs in adolescent patients.

## The Alteration of Laboratory Parameters During Upadacitinib Treatment

TEC and IgE significantly decreased at week 4 compared to week 0, while TARC and LDH appeared to decrease at week 4 compared to week 0; however, the differences were not significant (Table 2). IgE, TARC, LDH, and TEC significantly increased at week 12 compared to week 4 though the median TEC at week 12 appeared unchanged.



**Figure 2** % reductions of eczema area and severity index (EASI) from baseline on different anatomical sites (a) or for different individual clinical components of the EASI score (b) at week 4 and 12 of treatment with upadacitinib 15 mg/day plus topical corticosteroids for adolescent patients with atopic dermatitis (n = 39). Percent reductions of EASI from baseline on head and neck, upper limbs, lower limbs, and trunk (a) or for erythema, edema/papulation, excoriation, or lichenification (b) are shown as median [interquartile range]. \*p < 0.05, analyzed by Friedman test with Bonferroni post-hoc test.



**Figure 3** % reductions of eczema area and severity index (EASI) from baseline for individual rash types at weeks 4 and 12 of treatment with oral upadacitinib plus topical corticosteroids on different anatomical sites. Percent reductions of EASI from baseline for erythema (a), edema/papulation (b), excoriation (c), and lichenification (d) on head and neck, upper limbs, lower limbs, and trunk are shown as median [interquartile range]. \*  $p < 0.05$ , analyzed by Friedman test with Bonferroni post-hoc test.

## Safety Profile

The safety profile of upadacitinib in this real-world study (Table 3) was mostly equivalent to that observed in Phase 3 clinical trials (Measure Up 1, Measure Up 2, AD Up, and Rising Up).<sup>20–23</sup> No novel AEs were identified in this study. Adverse events occurred in 25 adolescent patients (64.1%). Neither serious AEs nor AEs leading to death were observed.

**Table 3** Treatment-Emergent Adverse Events (TEAEs) Through Week 12 After Treatment with Upadacitinib Plus Topical Corticosteroids for Adolescent Patients with Atopic Dermatitis (n = 39)

TEAE	n (%)
All TEAEs	25 (64.1)
Serious AE	0
AE leading to discontinuation of upadacitinib	2 (5.1)
AE leading to death	0
AEs of special interest	
Kaposi's varicelliform eruption	1 (2.6)

(Continued)

**Table 3** (Continued).

TEAE	n (%)
TEAEs frequently reported (> 5%)	
Atopic dermatitis	2 (5.1)
Acne	8 (20.5)
Elevation of creatine phosphokinase value	7 (17.9)
Herpes labialis	3 (7.7)
Herpes zoster	2 (5.1)

**Abbreviation:** AE, adverse event.

Kaposi's varicelliform eruption occurred in 1 patient (2.6%), herpes labialis occurred in 3 patients (7.7%), and herpes zoster occurred in 2 patients (5.1%). Acne occurred in 8 patients (20.5%). These AEs were mild in severity and improved with appropriate treatment. AEs leading to discontinuation of upadacitinib were worsening of AD in 2 patients (5.1%); one patient improved with increasing upadacitinib dose up to 30 mg/day while in the other patient, treatment was switched to dupilumab and topical corticosteroids. The elevation of serum creatine phosphokinase values was observed in 7 patients (17.9%), which was mild in severity and improved without treatment.

## Discussion

In this study, total EASI of adolescent AD patients remarkably reduced at week 4 and did not further reduce at week 12. The achievement rate of EASI 75 was also peaked at week 4 and was plateaued at week 12. The results were slightly different from those of our previous study mainly for adult AD patients, whose EASI score and achievement rate of EASI 75 continued to improve until week 12.<sup>12</sup> The faster improvement of EASI by upadacitinib in adolescent patients than in adults may be attributable to the smaller body weight of the former, leading to higher per kg dosage of upadacitinib, which might provide higher local concentrations of upadacitinib at sites of inflammation, and provide longer time above half maximum inhibitory concentration for STAT phosphorylation by JAK-linked cytokines,<sup>24</sup> and higher average daily percent STAT inhibition in adolescent patients compared to adult patients. Another possible reason for the faster improvement of EASI in adolescent patients may be altered immunological profiles; fold increase of expression in lesional versus normal skin for type 2 inflammation-related (*IL13*, *CCL17*, *CCL22*) or epidermal hyperplasia-related genes (*IL22*, *IL20*), whose expression or function can be suppressed by JAK inhibitors, was lower in adolescent AD patients compared to adult AD patients.<sup>25–27</sup> Thus type 2 inflammation or epidermal hyperplasia in adolescent AD patients, at least in the context of these genes, may be more susceptible to the suppression by upadacitinib treatment compared to adult AD patients.

Upadacitinib improved all four individual clinical components of the EASI score in adolescent AD patients; however, there were some differences in its effectiveness between these components. The therapeutic effectiveness for excoriation was higher than that for edema/papulation or lichenification. This trend was also revealed in our previous study for mainly adult patients.<sup>28</sup>

The higher responsiveness of excoriation to upadacitinib treatment might be caused by its rapid and direct suppression on IL-4, IL-13, IL-31, and TSLP-induced pruritus<sup>5,29</sup> and on IL-31-induced elongation of sensory nerves<sup>30</sup> through JAK1/STAT pathway. On the other hand, the lower responsiveness of lichenification might be due to the extremely high levels of molecules promoting epidermal growth such as keratin 6B, keratin 16, or IL-36 $\gamma$  and of molecules promoting remodeling and fibrosis such as IL-33, whose effects are resistant to JAK inhibitors, in chronic phase of AD.<sup>31</sup> The lower responsiveness of edema/papulation may be its promotion by cytokines resistant to JAK inhibitors such as IL-33 or vascular endothelial growth factor (VEGF), which suppresses the expression<sup>32</sup> or alignment of vascular endothelial-

cadherin,<sup>33</sup> respectively, damaging endothelial barrier and increasing vascular permeability and efflux of plasma components.

The present results indicate that the treatment responsiveness to upadacitinib on head and neck was lower than that on upper or lower limbs in adolescent AD patients. The lower treatment responsiveness of head-and-neck clinical components was similarly observed in our previous study of upadacitinib treatment for mainly adult patients,<sup>14</sup> and also in JAK1/2 inhibitor baricitinib treatment for mainly adult patients<sup>13</sup> or previous study of dupilumab treatment for adult patients.<sup>34</sup> These results indicate that the lower treatment responsiveness of head-and-neck clinical components compared to the other body sites might be independent of age or treatment modalities. Further, the lower responsiveness of erythema or edema/papulation on head and neck compared to lower limbs (Figure 3a and b) indicate that the lower responsiveness of head-and-neck clinical components to upadacitinib treatment in adolescent patients might be attributable to the lower responsiveness of erythema and/or edema/papulation on this site. The treatment resistance of head-and-neck erythema or edema/papulation is possibly because the skin of head-and-neck is more exposed to external stimuli such as aeroallergens, sunlight, or cosmetics, and is more likely to be affected by specific pathogens, such as *Malassezia*<sup>35</sup> or *Demodex*.<sup>36,37</sup> Especially severity scores of erythema and edema/papulation are known to correlate with stratum corneum VEGF levels.<sup>38</sup> Both *Malassezia*<sup>35</sup> and *Demodex*<sup>39,40</sup> induce the production of VEGF in keratinocytes or mast cells, which increases dermal vasculature and blood flow, exacerbating erythema, and disrupts the alignment of vascular endothelial-cadherin around the endothelial cell borders<sup>33,38,41</sup> and promotes the leakage of plasma proteins and leukocytes, exacerbating edema/papulation.

In this study, all the laboratory parameters, IgE, TARC, TEC, and LDH, increased at week 12 compared to week 4 in adolescent AD patients (Table 2) though the levels of clinical indexes at week 12 were similar to those at week 4. The reason for the reversal of laboratory parameters after clinical improvement should further be elucidated. It is hypothesized that the reversal of TARC, TEC, and LDH levels after clinical improvement might be mediated by upadacitinib-induced decrease of endogenous IL-17A level since JAK1 siRNA or JAK inhibitors suppress IL-17A secretion in anti-CD3/28-stimulated human CD4+T cells in the presence of IL-2, IL-1 $\beta$ , IL-6, and IL-23, indicating that suppression of JAK1 might reduce the production of IL-17A in T cells.<sup>42</sup> IL-17A suppresses TARC production in dendritic cells and allergen-stimulated production of IL-5, which induces eosinophilia via promoting survival of eosinophils, in mediastinal lymph node cells of asthma model mice.<sup>43</sup> Thus, the possible upadacitinib-induced reduction of endogenous IL-17A may diminish the IL-17A-mediated suppression of TARC and IL-5 production, leading to the increase of TARC and TEC levels irrespective of clinical improvement of AD.

The leakage of LDH from keratinocytes may be induced by the intracellular accumulation of reactive oxygen species (ROS) associated with increased mitochondrial activity.<sup>44,45</sup> Since IL-17A induces nuclear translocation of transcription factor NF-E2-related factor 2 (Nrf2) and Nrf2-dependent expression of heme oxygenase-1 (HO-1)<sup>46</sup> which suppresses accumulation of ROS in keratinocytes, upadacitinib-induced decrease of endogenous IL-17A might lead to the down-regulation of Nrf2/HO-1 pathway, inducing accumulation of ROS, which activates inflammasome cascade and resultant release of cytoplasmic LDH.<sup>47,48</sup> The reversal of IgE level after clinical improvement by upadacitinib treatment may be mediated by upadacitinib-induced inhibition of IL-21-mediated JAK1/JAK3/STAT3 pathway<sup>24</sup> since IL-21 suppresses IgE class switch recombination in human B cells through this pathway.<sup>49</sup>

We should analyze the transition of these laboratory parameters for further long-term treatment with upadacitinib in adolescent AD patients. The reversal of levels of these parameters after clinical improvement by upadacitinib was not prominent in our previous study whose participants are mainly adult patients.<sup>12</sup> Whether the reversal is specific to adolescent patients should further be studied by comparing the results between adolescent versus adult patients strictly.

The safety profile of upadacitinib for adolescent AD patients in this real-world study was mostly similar to that of previous phase 3 clinical trials<sup>23</sup> and also to that of our previous real-world study mainly for adult AD patients.<sup>12</sup> The incidence of acne was slightly higher in this study for adolescent patients versus that in our previous study mainly for adult patients (20.5% versus 16.1%), and the elevation of serum creatine phosphokinase values also more frequently occurred in adolescent patients (17.9% versus 9.7%).<sup>12</sup> The results may possibly be because adolescence is peak age of onset of acne and because adolescents tend to exercise harder compared to adults. Neither novel nor serious AEs occurred in the present study. The safety profile supports the tolerability of upadacitinib in adolescent AD patients.

In the broader context of systemic treatments available for AD in Japan, particularly for patients aged 12 and above, the choices remain limited. Alongside the JAK1 inhibitor upadacitinib, other therapies have recently been approved, including the JAK1 inhibitor abrocitinib, the IL-4R $\alpha$  antibody dupilumab, and the IL-31R antibody nemolizumab. Each drug exhibits unique safety characteristics. Specifically, abrocitinib is often linked with headaches and nausea, while conjunctivitis is a commonly observed side effect with dupilumab.<sup>10</sup> As our study highlights, for upadacitinib, clinicians should be vigilant for occurrences of acne and herpes zoster.<sup>15</sup> It is imperative that clinicians meticulously evaluate the risk-benefit profile of these therapies, tailoring their choice to the individual needs of the patient.

Our study has several limitations. Firstly, the patients' population was limited to Asians. The results for adolescent patients of the other races should further be studied. Secondly, our study was done for a relatively short duration ( $\leq 12$  weeks), and effectiveness and safety of longer-term treatment should further be evaluated. Thirdly, the effectiveness and safety of upadacitinib were assessed in combination with topical corticosteroids. The comparison between combination therapy versus monotherapy should further be conducted.

## Conclusion

In conclusion, upadacitinib treatment significantly reduced EASI, ADCT, and PP-NRS at weeks 4 and 12 compared to week 0, with mild manageable AEs in adolescent patients with moderate-to-severe AD. The improvement of EASI was peaked at early point of time (week 4). Though TEC and IgE decreased at week 4 compared to week 0, TEC, IgE, LDH, and TARC increased at week 12 compared to week 4. The therapeutic effectiveness for erythema or edema/papulation on head and neck was lower than that on lower limbs. These findings suggest the therapeutic effectiveness and tolerability of upadacitinib in adolescent patients with AD and support its potentiality as a promising treatment option for adolescent AD patients. However, further long-term studies are necessary to fully dissect its effectiveness and efficacy in adolescent AD patients.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Nippon Medical School Chiba Hokusoh Hospital (protocol code H-2022-945 and February 10, 2022 of approval).

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