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LETTER TO THE EDITOR

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Effectiveness and safety of upadacitinib in patients with face and neck atopic dermatitis unresponsive to dupilumab

Dear Editor,

Atopic dermatitis (AD) is an inflammatory skin condition that afflicts millions worldwide, resulting in chronic pruritus that affects both children and adults (1). Dupilumab is a monoclonal antibody that targets the IL-4Rα-subunit of the IL-4 and IL-13 receptor, thereby reducing type 2 inflammation. Real-world studies have documented the safety and efficacy of dupilumab for AD patients (2). However, some individuals exhibit improvement in trunk and limb skin lesions, but experience suboptimal improvement in facial and neck skin lesions after receiving dupilumab treatment (3,4). Upadacitinib, a selective small-molecule inhibitor of Janus kinase 1 (JAK1), has been recommended for the treatment of moderate-to-severe AD (5). Herein, we present a case series of six AD patients (3 male and 3 female; mean age: 18.67 ± 7.7 years, range 12-35 years) who received upadacitinib treatment for 12 weeks following an initial 14-20 weeks of dupilumab treatment without significant improvement in their facial and neck skin lesions (Table 1). Upadacitinib was administered at a once-daily dose of 15 mg to six AD patients. The effectiveness of the upadacitinib treatment was evaluated by measuring Eczema Area Severity Index (EASI, range: 0-72), Dermatology Life Quality Index (DLQI, range: 0-30), Atopic Dermatitis control tool (ADCT, range: 0-24), and Pruritus Numerical Rating Scale (P-NRS, range: 0-10) scores at baseline, week 4, week 8, and week 12. Besides, levels of pro-inflammatory cytokines (interleukin (IL)-4, IL-5, IL-13, IL-17, IL-22, IL-31, and IFN-γ), total IgE, and peripheral blood eosinophils were performed at baseline and after 12 weeks of upadacitinib treatment. Safety assessments included monitoring adverse events and conducting laboratory assessments such as blood count, liver and kidney function, lactate dehydrogenase and creatine phosphokinase, serum creatinine, and lipid status tests every 4 weeks. Continuous variables were given as mean ± standard error. Baseline characteristics were analyzed by t-test, and analysis of variance (ANOVA) using SPSS version 26.0, with a significance level of < 0.05.

These patients had a mean AD disease course of 12.5 ± 3.5 years. Only one (16.7%) patient had a personal atopic history of allergic rhinitis. After 14-20 weeks of treatment with dupilumab, the skin lesions on the trunk and limbs of the patients noticeably subsided, leaving only erythema, papules, and itching on the face and neck (Figure 1). At baseline (prior to upadacitinib treatment), the mean EASI, DLQI, ADCT, and P-NRS scores were 8.1 ± 0.66, 12.5 ± 6.24, 11.5 ± 3.15, and 6.83 ± 0.37, respectively. A statistically significant improvement in EASI score was observed at week 4 (3.95 ± 0.75), week 8 (1.9 ± 0.89), and week 12 (0.73 ± 0.56) compared with baseline ($p < 0.001$). At week 12, all patients achieved EASI 75, and three (50%) even reached EASI 90. In addition, the DLQI, ADCT, and P-NRS scores of all patients showed significant improvement from baseline to 12 weeks after upadacitinib treatment ($p < 0.001$). The number of eosinophil in peripheral blood also significantly decreased from baseline (2.65 ± 3.24) to week 12 (1.42 ± 2.42). After 12 weeks of upadacitinib treatment, biomarkers of AD, including serum levels of IL-4, and IL-31 levels decreased, whereas total IgE, serum levels of IL-5, IL-13, IL-22, and IFN-γ remained unchanged and serum levels of IL-17 increased (Table 2). No patients reported adverse events during the treatment period.

Based on current literature and clinical practice, it is evident that dupilumab is effective in treating Atopic Dermatitis (2,5). However, some reports suggest that in some adolescents and adults with AD, the use of Dupilumab may not improve or may exacerbate head and neck dermatitis (4,6). Therefore, our study aims to explore the clinical effectiveness of upadacitinib treatment in AD patients with facial and neck skin lesions who have not responded to dupilumab treatment. One study reached similar conclusion using upadacitinib on dupilumab-associated head and neck dermatitis, with a significant reduction of EASI scores, total IgE and Malassezia-specific IgE. However, our study observed no significant difference in total serum IgE levels after 12 weeks of upadacitinib treatment when compared to baseline levels. Nonetheless, the study revealed a decrease in eosinophil count and serum levels of Interleukin-31 (IL-31) and Interleukin-4 (IL-4). These findings suggest that eosinophils may play critical roles in AD rash and itch symptoms by secreting IL-4/IL-13 or IL-31, which bind to their respective receptors on sensory nerve endings, IL-4Rα or IL-31RA, and activate the JAK1/STAT pathway (7). Upadacitinib may suppress the effects of IL-31 or IL-4/IL-13 and block the communication between nerves and eosinophils, reducing pruritus. In addition, dual blockade of IL-4/IL-13 may lead to Th1/Th17 skewing (8), thus contributing to the increase in serum IL-17 levels observed after 12 weeks of upadacitinib treatment. An increase in Th17 cytokines' expression may induce a psoriasiform reaction pattern (9) and promote Demodex colonization, leading to the development of rosacea (10). However, the exact mechanism of action of upadacitinib in treating AD is still unclear and requires further extensive prospective studies to confirm. In conclusion, upadacitinib may be a promising option for AD patients with recalcitrant facial and neck dermatitis who do not respond to dupilumab. The dynamic changes observed in serum levels of IL-4 and IL-31 and eosinophils may serve as useful biomarkers to evaluate upadacitinib's efficacy for treating AD.

Table 1. Clinical data of six AD cases.

Patient No.	Age, Gender	Duration of AD (Years)	Personal atopic history	Previous treatment method	Treatment	Duration of Upadacitinib (Weeks)	Complications
1	14, female	10	None	Dupilumab 16 weeks + Topical medications	Upadacitinib 15 mg/day	12	None
2	15, male	9	None	Dupilumab 14 weeks + Topical medications	Upadacitinib 15 mg/day	12	None
3	16, male	12	None	Dupilumab 14 weeks + Topical medications	Upadacitinib 15 mg/day	12	None
4	35, female	15	Allergic rhinitis	Dupilumab 18 weeks + Topical medications	Upadacitinib 15 mg/day	12	None
5	12, male	10	None	Dupilumab 16 weeks + Topical medications	Upadacitinib 15 mg/day	12	None
6	20, female	19	None	Dupilumab 20 weeks + Topical medications	Upadacitinib 15 mg/day	12	None

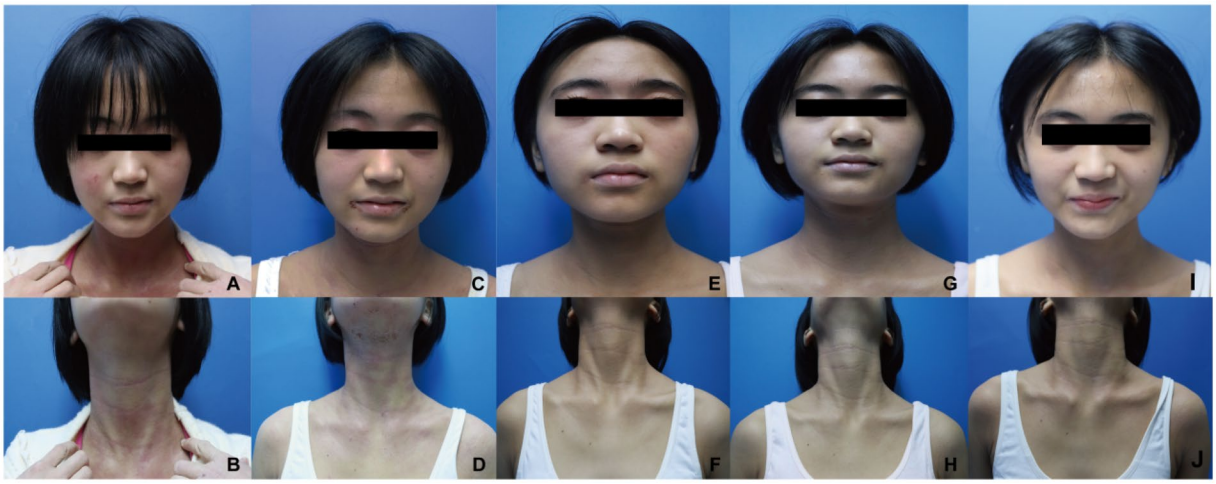

Figure 1. (A, B) Face and neck lesions before treatment with dupilumab. (C, D) no significant improvement in the skin lesions of the face and neck after 12 weeks of dupilumab treatment. (E, F) Clinical improvement after 4 weeks of upadacitinib. (G, H) Marked improvement with clearing of face and neck lesions after 8 weeks of upadacitinib. (I, J) Clinical complete resolution after 12 weeks with upadacitinib without recurrence.

Table 2. Summary of the treatment efficacy of upadacitinib after 12 weeks of treatment.

Category	Before Upadacitinib Treatment	4 week	8 week	12 week	P
EASI	8.1 ± 0.66	3.95 ± 0.75	1.9 ± 0.89	0.73 ± 0.56	<0.001
DLQI	12.5 ± 6.24	3.83 ± 1.07	1.67 ± 0.75	0.67 ± 0.75	<0.001
ADCT	11.5 ± 3.15	4 ± 2.71	2.33 ± 2.36	0.33 ± 0.75	<0.001
P-NRS	6.83 ± 0.37	2 ± 1	0.67 ± 0.47	0	0.0001
IgE (IU/mL)	3855.05 ± 3990.98			3083.12 ± 3066.23	0.5213
Eosinophils count (×109 /L)	2.65 ± 3.24			1.42 ± 2.42	0.0375
IL-4 (pg/ml)	6.83 ± 3.79			5.28 ± 3.42	0.0024
IL-5 (pg/ml)	1.27 ± 1.1			1.14 ± 0.62	0.8239
IL-13 (pg/ml)	1.84 ± 2.3			1.44 ± 1.16	0.7426
IL-17 (pg/ml)	0.46 ± 0.23			1.73 ± 0.76	0.0082
IL-22 (pg/ml)	0.38 ± 0.16			0.28 ± 0.04	0.1547
IL-31 (pg/ml)	5.11 ± 2.68			2.83 ± 1.37	0.0426
IFN-γ (pg/ml)	2.06 ± 2.86			1.46 ± 1.56	0.4003

Note: EASI, Eczema Area Severity Index (range: 0–72); DLQI, Dermatology Life Quality Index (range: 0–30); ADCT, Atopic Dermatitis control tool (range: 0-24); P-NRS, Pruritus Numerical Rating Scale (range: 0–10).

Disclosure statement

None.

Ethics statement

The patients in this manuscript have given written informed consent to the publication of their case details.

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Data available statement

Data available on request from the authors.

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