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Brief Communication

Combined Dupilumab and Allergen-Specific Immunotherapy in Severe Refractory Atopic Dermatitis

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ABSTRACT

Although combining allergen immunotherapy with biologics has shown promise in treating atopic diseases such as asthma and allergic rhinitis, atopic dermatitis (AD) remains notably underexplored in this context. This study aimed to investigate the efficacy and safety of combining dupilumab with subcutaneous immunotherapy (SCIT) for severe AD refractory to standard treatments. This was a single-center retrospective analysis assessing patients with severe AD treated with combined dupilumab and SCIT, dupilumab, or SCIT alone at the Severance Hospital, Seoul, Korea. The inclusion criteria encompassed severe AD diagnosis, specific immunoglobulin (Ig) E levels to house dust mite allergens, and treatment follow-up for at least 18 months. Eczema Area and Severity Index (EASI) scores, serum biomarker levels, and adverse event records were regularly collected. Forty-eight patients with AD were analyzed, showing significant improvement in EASI scores and favorable changes in serum biomarkers over 144 weeks. The combination therapy led to a sustained reduction in AD severity, a significant reduction in total IgE and specific IgE levels, and an increment in allergen-specific IgG4. All patients experienced only mild and temporary side effects, not requiring treatment discontinuation. Combining dupilumab with SCIT offers a promising therapeutic option for patients with severe, treatment-refractory AD, reducing disease severity and inducing favorable immunological changes without increasing adverse effects.

Keywords: Atopic dermatitis; dupilumab; immunotherapy; house dust mite; safety; treatment outcome

INTRODUCTION

Atopic dermatitis (AD), characterized by chronic relapses and intense itchiness, is an inflammatory skin disorder, frequently co-occurring with allergic conditions such as rhinitis and asthma.[1] Allergen-specific immunotherapy (AIT) targeting house dust mite (HDM) has been introduced for AD cases sensitized to HDM and refractory to standard treatments.[1,2] Meta-analyses and long-term follow-up studies have confirmed its effectiveness as a disease-modifying therapy for AD.[2-4] Meanwhile, dupilumab, a fully human monoclonal antibody targeting the interleukin (IL)-4 receptor α-subunit (IL-4Rα), inhibits IL-4 and IL-13 signaling.

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There are no financial or other issues that might lead to conflict of interest.

This biological drug has led to a substantial decrease in disease severity and increase in quality of life for patients suffering from moderate-to-severe AD.[5-8] Additionally, recent trials investigating the efficacy and safety of AIT and biologics combination therapy in atopic diseases such as allergic rhinitis or asthma have reported favorable outcomes with tolerable side-effect profiles.[9-12] Therefore, our study aimed to evaluate the efficacy and safety of combining subcutaneous immunotherapy (SCIT) with dupilumab in the management of severe refractory AD in a real-world clinical setting.

MATERIALS AND METHODS

Patients and data collection

This single-center retrospective study was approved by the Institutional Review Board of Yonsei University Health System (No. 4-2023-1528), and the requirement for informed consent was waived due to the study's retrospective nature. The study included patients with severe AD treated between January 2015 and September 2023 at the Severance Hospital in Seoul, S. Korea. The inclusion criteria were: a) patients with severe AD, with an Eczema Area and Severity Index (EASI) score > 23 and a disease history of > 3 years before treatment; b) serum specific immunoglobulin (Ig) E levels to *Dermatophagoides pteronyssinus* (d1) and/or *Dermatophagoides farinae* (d2) allergens of ≥ 3.5 kU/L (class 3), as verified by CAP immunoassay; and c) regular follow-up for ≥ 18 months after treatment initiation. The study participants were divided into 3 treatment groups: 1) the SCIT group, consisting of patients who received SCIT only during the study period; 2) the dupilumab/SCIT group, which included patients who started dupilumab concurrently with SCIT after failing to achieve a 50% reduction in EASI scores after 6 months of SCIT treatment; 3) the dupilumab group, comprising patients who received dupilumab without SCIT.

Patients received SCIT with an HDM allergen extract composed of a 1:1 mixture of d1 and d2 extracts, adsorbed to tyrosine (Tyrosine-s®; Allergy Therapeutics Inc., Worthing, United Kingdom). This treatment was administered in accordance with the manufacturer's guidelines and detailed escalation protocols as previously described.[2,13] Alongside SCIT, patients were administered adjunct treatments including topical therapy, oral antihistamines, and short-term immunosuppressants (cyclosporine or methotrexate) or systemic steroids. Dupilumab was introduced as an initial 600-mg injection, followed by 300 mg biweekly.

Data collected included patient demographics, disease onset, allergic comorbidities, EASI scores, and serum levels of d1/d2-specific IgE, d1/d2-specific IgG4, and total IgE. EASI scores and serum biomarkers were measured at regular intervals for up to 144 weeks from baseline. The measurement baseline was defined as the point at which each group began their treatments. For the dupilumab/SCIT group, the baseline was the time when dupilumab was added to their ongoing SCIT treatment. Additionally, adverse events such as injection-site reactions, upper respiratory tract infections, conjunctivitis, herpes simplex infections, and dupilumab-associated head and neck dermatitis (DAHND) defined in elsewhere[14] (≥ 50% worsening of head and neck EASI score after dupilumab treatment) were recorded during the treatment period.

Statistical methods

Categorical variables were evaluated using the Fisher's exact test. Continuous variables were compared using the Wilcoxon signed-rank test and the Mann–Whitney *U* test. Analyses were

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conducted using Python, version 3.9.0 (Python Software Foundation, Wilmington, DE, USA), and statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics

Table 1 presents patient demographics and clinical characteristics, initial serum biomarkers, and treatment-related adverse events from the chart review. Of the 48 patients assessed, majority were male (n = 31; 64.5%), with an average age of 28.9 ± 7.99 years. Most had experienced AD since infancy or childhood (n = 37; 77.1%), and a significant number had histories of other allergic comorbidities (n = 35; 72.9%). Among the participants, 34 received SCIT, of which 14 required dupilumab during SCIT due to an insufficient treatment response. The remaining 14 participants received only dupilumab without SCIT during the study period. These 3 groups showed no significant difference in initial EASI scores and serum biomarkers. Demographics and clinical features also showed similar trends in these groups; only the dupilumab/SCIT group demonstrated a higher incidence of allergic comorbidities compared to the SCIT group. However, this difference was not statistically significant (85.7% and 55.0%, respectively; $P = 0.08$).

Treatment response and temporal changes in serum biomarkers

Fig. 1 and **Table 2** present the temporal changes in EASI scores and serum biomarker levels from baseline through week 144. From weeks 24 to 144, the dupilumab/SCIT group consistently showed a significantly greater reduction in EASI scores compared to the SCIT group. Additionally, the dupilumab/SCIT group showed a significantly greater decrease in EASI scores compared to the dupilumab group at week 96 (**Fig. 1A**). Furthermore, patients receiving dupilumab/SCIT experienced a continued significant decrease in EASI scores

Table 1. Baseline patient demographics, clinical features, initial serum biomarkers, and treatment-related adverse events in study participants

Features	Dupilumab/SCIT (n = 14)	Dupilumab (n = 14)	SCIT (n = 20)	Total (n = 48)	*P* value	
					Dupilumab/SCIT vs. dupilumab	Dupilumab/SCIT vs. SCIT
Male (sex)	10 (71.4)	9 (64.3)	12 (60.0)	31 (64.5)	> 0.99	0.72
Age at the initial treatment (yr)	26.9 ± 7.94	32.2 ± 8.40	28.1 ± 7.38	28.9 ± 7.99	0.09	0.54
Allergic comorbidities	12 (85.7)	12 (85.7)	11 (55.0)	35 (72.9)	> 0.99	0.08
Disease onset					0.68	0.67
Infancy or childhood	11 (78.6)	9 (64.3)	17 (85.0)	37 (77.1)		
Adolescence or adulthood	3 (21.4)	5 (35.7)	3 (15.0)	11 (22.9)		
Initial EASI	32.1 ± 7.79	32.8 ± 8.02	32.9 ± 6.72	32.6 ± 7.28	0.84	0.64
Initial serum allergy markers						
Total IgE (kU/L)	3,856.7 ± 1,910.9	4,463.4 ± 868.6	3,187.8 ± 1,848.9	3,755.0 ± 1,700.0	0.91	0.20
d1 specific IgE (kU/L)	68.8 ± 33.0	77.5 ± 30.0	70.4 ± 32.5	72.0 ± 31.5	0.33	0.62
d2 specific IgE (kU/L)	79.4 ± 30.7	85.3 ± 27.1	82.9 ± 29.9	82.6 ± 28.8	0.70	0.83
d1 specific IgG4 (mg/L)	0.71 ± 0.65	0.93 ± 1.78	0.35 ± 0.31	0.62 ± 1.04	0.91	0.26
d2 specific IgG4 (mg/L)	0.84 ± 0.78	1.20 ± 2.61	0.40 ± 0.44	0.76 ± 1.50	0.95	0.20
Adverse events						
Injection site reactions	2 (14.3)	0 (0.0)	4 (20.0)	6 (12.5)	0.48	> 0.99
Upper respiratory tract infections	2 (14.3)	0 (0.0)	2 (10.0)	4 (8.3)	0.48	> 0.99
Conjunctivitis	3 (21.4)	4 (28.6)	0 (0.0)	7 (14.6)	> 0.99	0.06
Herpes simplex infections	3 (21.4)	3 (21.4)	3 (15.0)	9 (18.8)	> 0.99	0.67
DAHND	3 (21.4)	7 (50.0)	NA	NA	0.24	NA

Data are presented as number (%) or mean ± standard deviation.
SCIT, subcutaneous immunotherapy; EASI, Eczema Area and Severity Index; Ig, immunoglobulin; d1, *Dermatophagoides pteronyssinus*; d2, *Dermatophagoides farinae*; DAHND, dupilumab-associated head and neck dermatitis; NA, not available.

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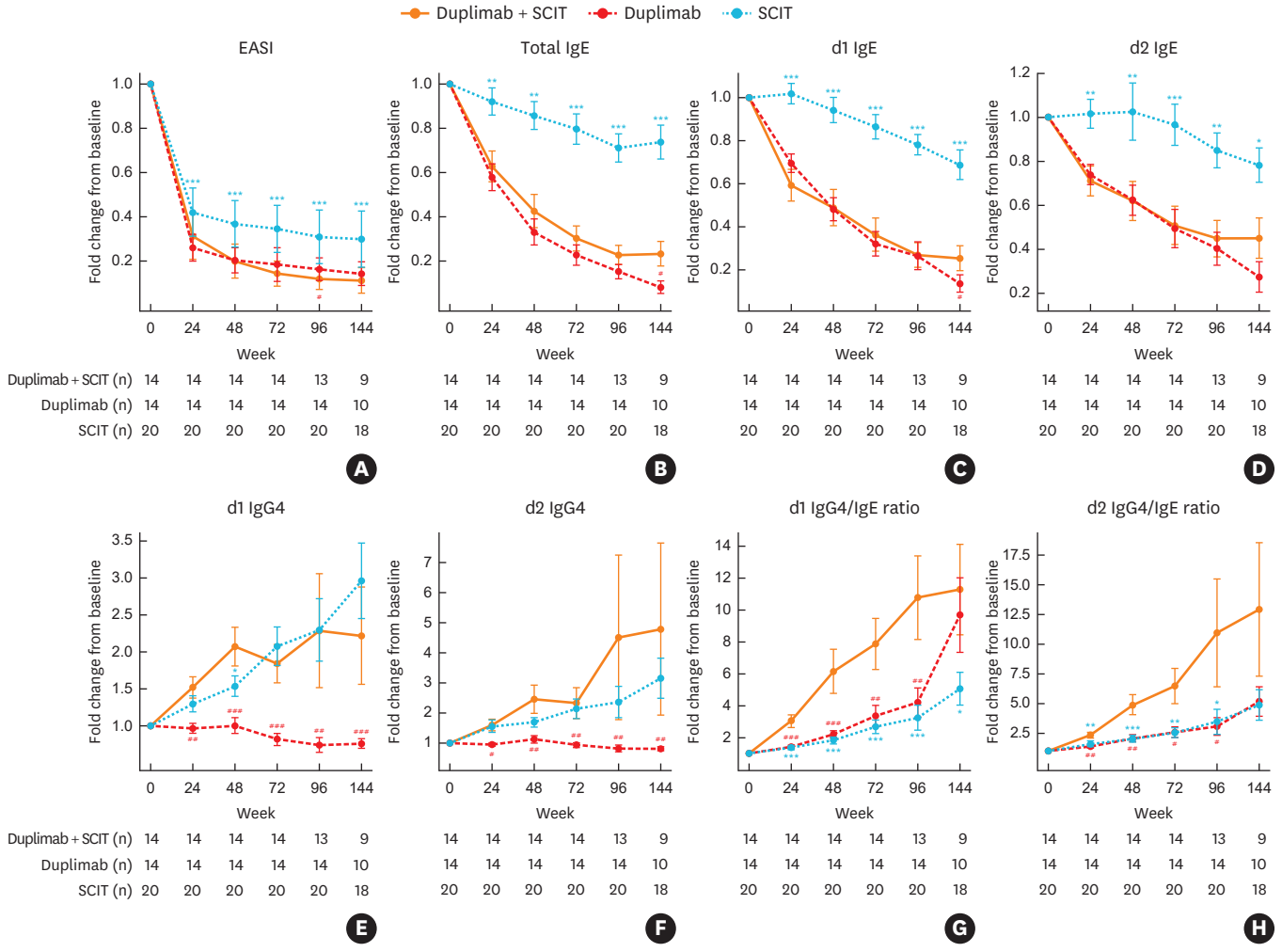

Fig. 1. Longitudinal changes in EASI scores and serum biomarker levels. Fold change from baseline in (A) EASI, (B) total IgE, (C) d1-specific IgE, (D) d2-specific IgE, (E) d1-specific IgG4, (F) d2-specific IgG4, (G) d1-specific IgG4/IgE ratios, (H) d2-specific IgG4/IgE ratios. Data shown as means with 95% confidence intervals.
EASI, Eczema Area and Severity Index; Ig, immunoglobulind1, *Dermatophagoides pteronyssinus*; d2, *Dermatophagoides farinae*.
$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ for cross sectional comparisons of dupilumab/SCIT vs. SCIT, and $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ for cross sectional comparisons of dupilumab/SCIT vs. dupilumab.

up to week 96 compared to the previous time interval, whereas the dupilumab group only maintained a significant reduction until week 48 (**Table 2**).

Throughout the study period, both the dupilumab/SCIT and dupilumab groups experienced a continuous reduction in total IgE and d1/d2-specific IgE levels, with a significantly lower fold change compared to the SCIT group (**Fig. 1B-D**). In contrast, serum d1/d2-specific IgG4 levels increased in both the dupilumab/SCIT and SCIT groups, with a significant difference observed between the dupilumab/SCIT and dupilumab groups (**Fig. 1E and F**).

The d1/d2-specific IgG4/IgE ratio increased across all 3 groups during treatment. However, the dupilumab/SCIT group exhibited a significantly higher fold change at most time points compared to both the dupilumab and SCIT groups (**Fig. 1G and H**).

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Table 2. Crude data of continuous variables in the study over follow-up periods

Features	Initial	24 weeks	48 weeks	72 weeks	96 weeks	144 weeks
Group 1: dupilumab/SCIT						
EASI	32.1 ± 7.79	9.75 ± 3.01	6.33 ± 2.57	4.61 ± 2.37	3.78 ± 2.20	3.71 ± 2.45
P value	NA	< 0.001	< 0.001	< 0.001	0.006	0.65
Total IgE (kU/L)	3,856.7 ± 1,841.4	2,625.6 ± 1,758.5	1,809.4 ± 16,145.0	1,265.3 ± 1,181.0	918.2 ± 896.2	958.8 ± 915.5
P value	NA	0.003	0.001	< 0.001	< 0.001	0.004
d1 specific IgE (kU/L)	68.8 ± 31.8	44.7 ± 31.5	36.9 ± 31.5	27.4 ± 27.1	20.0 ± 21.3	18.7 ± 18.2
P value	NA	0.001	0.02	0.002	0.001	0.004
d2 specific IgE (kU/L)	79.4 ± 29.5	60.2 ± 34.7	55.1 ± 38.5	45.5 ± 35.5	39.9 ± 32.0	39.1 ± 30.8
P value	NA	0.005	0.01	0.006	0.02	0.004
d1 specific IgG4 (mg/L)	0.71 ± 0.63	1.20 ± 1.23	1.48 ± 1.48	1.26 ± 1.21	1.14 ± 0.85	1.23 ± 0.90
P value	NA	0.003	0.06	0.049	0.31	0.30
d2 specific IgG4 (mg/L)	0.84 ± 0.75	1.41 ± 1.61	1.84 ± 1.92	1.47 ± 1.37	1.45 ± 1.06	1.60 ± 1.06
P value	NA	0.01	0.002	0.10	0.75	0.25
Group 2: duplimab						
EASI	32.8 ± 7.73	8.61 ± 2.63	6.69 ± 2.29	5.99 ± 2.67	5.16 ± 1.77	4.68 ± 1.81
P value	NA	< 0.001	< 0.001	0.12	0.3	0.06
Total IgE (kU/L)	4,463.4 ± 837.0	2,611.9 ± 1,242.0	1,537.4 ± 1,156.0	1,048.9 ± 832.3	698.1 ± 618.3	347.0 ± 414.2
P value	NA	0.002	< 0.001	< 0.001	< 0.001	0.002
d1 specific IgE (kU/L)	77.5 ± 29.0	55.1 ± 25.2	39.1 ± 24.2	26.1 ± 23.1	21.7 ± 25.1	11.2 ± 12.3
P value	NA	< 0.001	< 0.001	< 0.001	0.009	0.002
d2 specific IgE (kU/L)	85.3 ± 26.2	63.5 ± 25.2	53.0 ± 25.3	41.3 ± 24.9	33.9 ± 24.1	22.5 ± 16.7
P value	NA	0.002	0.004	0.003	0.001	0.006
d1 specific IgG4 (mg/L)	0.93 ± 1.71	0.83 ± 1.32	0.71 ± 0.85	0.53 ± 0.53	0.46 ± 0.46	0.34 ± 0.22
P value	NA	0.86	0.36	< 0.001	0.04	0.19
d2 specific IgG4 (mg/L)	1.20 ± 2.52	1.01 ± 1.83	0.89 ± 1.10	0.66 ± 0.71	0.58 ± 0.61	0.40 ± 0.27
P value	NA	0.71	0.76	0.002	0.02	0.13
Group 3: SCIT						
EASI	32.9 ± 6.55	13.7 ± 4.05	12.0 ± 4.17	11.3 ± 4.66	10.0 ± 4.31	9.61 ± 4.26
P value	NA	< 0.001	0.01	0.10	0.01	0.06
Total IgE (kU/L)	3,187.8 ± 1,802.1	2,808.4 ± 1,624.7	2,576.1 ± 1,595.5	2,454.2 ± 1,563.7	2,187.6 ± 1,501.3	2,343.7 ± 1,825.1
P value	NA	0.049	0.16	0.26	0.15	0.80
d1 specific IgE (kU/L)	70.4 ± 31.7	72.3 ± 31.7	69.2 ± 34.6	65.0 ± 33.9	60.9 ± 35.5	51.2 ± 33.5
P value	NA	0.75	0.056	0.04	0.12	0.11
d2 specific IgE (kU/L)	82.9 ± 29.2	81.4 ± 29.8	78.1 ± 32.7	76.9 ± 32.2	69.6 ± 32.7	63.9 ± 33.7
P value	NA	0.31	0.21	0.51	0.049	0.13
d1 specific IgG4 (mg/L)	0.35 ± 0.31	0.42 ± 0.36	0.52 ± 0.43	0.79 ± 0.88	0.78 ± 0.80	0.98 ± 0.82
P value	NA	0.01	0.005	< 0.001	0.61	0.10
d2 specific IgG4 (mg/L)	0.40 ± 0.43	0.53 ± 0.46	0.60 ± 0.49	0.90 ± 1.12	0.84 ± 0.82	1.10 ± 1.00
P value	NA	0.006	0.20	0.01	0.41	0.01

Data are presented as number (%) or mean ± standard deviation. *P* values at each time point were calculated by comparing to the immediately preceding measurement using the Wilcoxon signed-rank test on matched samples.
SCIT, subcutaneous immunotherapy; EASI, Eczema Area and Severity Index; NA, not available; Ig, immunoglobulin; d1, *Dermatophagoides pteronyssinus*; d2, *Dermatophagoides farina*.

Adverse events

Adverse events were comparable between the treatment groups, although conjunctivitis tended to be more prevalent in the dupilumab/SCIT and group. Although not statistically significant, the dupilumab monotherapy group had a higher incidence of DAHND compared to the dupilumab/SCIT group (50.0% and 21.4%, respectively; $P = 0.24$). However, all side effects were mild and transient not requiring cessation of treatment.

DISCUSSION

Our study results suggest that combining SCIT with dupilumab for up to 144 weeks significantly improves EASI scores in patients with severe AD, alongside inducing

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favorable shifts in serum biomarkers of AIT. Similarly, recent retrospective case series showed significant clinical improvements up to 52 weeks with the combined application of dupilumab and SCIT in patients with moderate-to-severe AD.[15,16] However, these studies had heterogeneous sequencing of dupilumab and SCIT administration, lacked regular monitoring of serum biomarkers related to AIT, and did not include control groups for comparing efficacy and safety profiles. Therefore, we believe our results provide a more systematic approach and evaluation for the combination treatment of dupilumab and SCIT.

Clinically, patients receiving dupilumab/SCIT showed EASI score improvements comparable to those observed in previous studies on the long-term efficacy of dupilumab, with a similar side-effect profile.[5,6,17] Furthermore, during the long-term administration period beyond 48 weeks, the dupilumab/SCIT group showed continuous decreases in EASI scores and exhibited a better response at week 96 compared to dupilumab monotherapy. The combined treatment of dupilumab and SCIT may offer long-term benefits via the disease-modifying effect of AIT, including sustained remission and reduced reliance on biologics. Notably, 3 patients in the dupilumab/SCIT group continued to show improvement in clinical severity and serum allergic parameters even after adjusting their dupilumab dosing interval to every 4 weeks, 1 year into treatment.

We also monitored serum biomarkers related to AIT response to observe their temporal changes.[18,19] The combination of dupilumab and SCIT or dupilumab monotherapy resulted in a substantial decrease in total and d1/d2-specific IgE compared to SCIT alone. Conversely, a substantial elevation of d1/d2-specific IgG4 levels was noted in both the dupilumab/SCIT and SCIT groups, whereas the dupilumab monotherapy group showed no significant change in IgG4 levels. Similar trends have been observed in other studies, leading us to believe that the combination of dupilumab and SCIT may offer a complementary effect.[9,10] Moreover, the application of AIT is thought to induce proliferation of regulatory T cell subsets, which dampen T_H2-driven responses and promote the production of allergen-specific IgG4 antibodies.[19] Meanwhile, dupilumab suppresses the production of allergen-specific and total IgE by inhibiting IL-4/IL-13 signaling.[10,15] Our study also supported this, as patients receiving dupilumab consistently showed a decreasing trend in IgE levels. Nonetheless, there is concern that dupilumab's mechanism might theoretically interfere with SCIT's efficacy by affecting IL-4 or IL-13-dependent IgG4 production.[20] However, recent opinions suggest that even with continuous dupilumab administration, some IL-4 and IL-13 remain in a free secretion form.[21] Thus, despite IL-4Rα blockade via dupilumab, significant dampening of IgG4 production by IL-4 and IL-13 might not occur. Moreover, our study showed that the dupilumab/SCIT group experienced an increase in allergen-specific IgG4, similar to the SCIT monotherapy group. This suggests that regulatory T cells and IL-10 pathways might be more crucial in allergen-specific IgG/IgG4 production, independent of dupilumab's action mechanism.[19,22] We have summarized the suggested mechanisms of dupilumab and SCIT in **Fig. 2**.

Nevertheless, the present study had some limitations, including its retrospective design, limited sample size, and the inclusion of patients with AD sensitized to other allergens along with HDM. The limited sample size and heterogeneous sensitization profiles made it challenging to determine whether specific serum biomarkers could predict clinical response. Moreover, the study lacked measures of subjective symptoms and quality of life for patients with AD.

In summary, this study provided evidence that patients with severe recalcitrant AD exhibit sustained treatment response to a combination of dupilumab and SCIT. Future prospective

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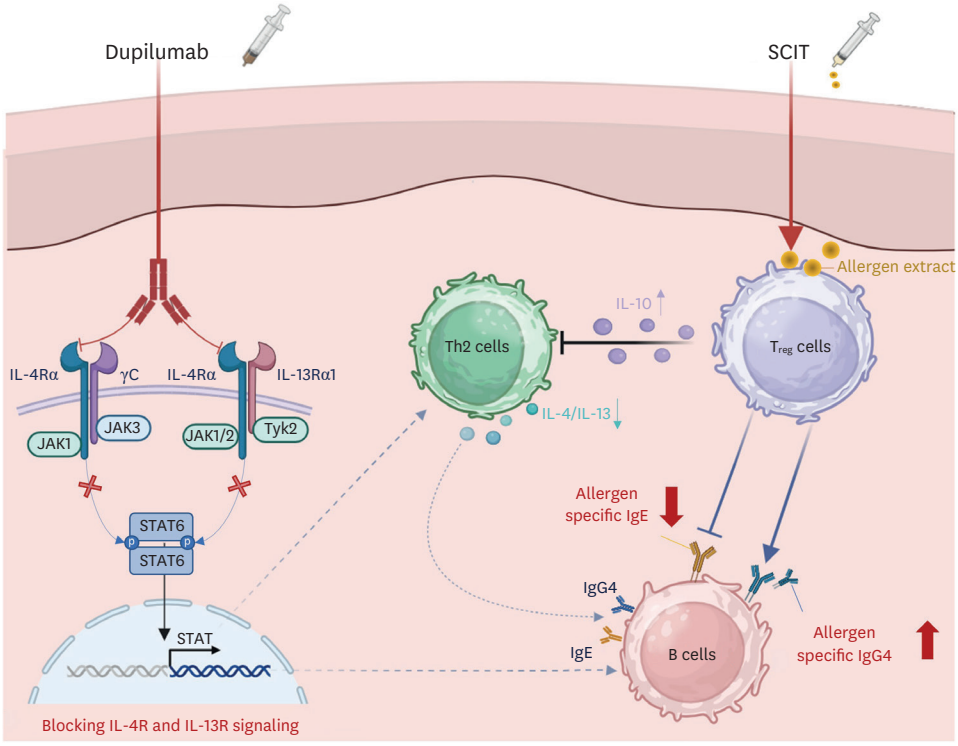

Fig. 2. Mechanisms of combined treatment of allergen-specific immunotherapy and dupilumab.
SCIT, subcutaneous immunotherapy; IL, interleukin; γC, common γ-chain; JAK, Janus kinase; Th, T helper; Treg, regulatory T; STAT, signal transducers and activators of transcription; Ig, immunoglobulin.

controlled trials with larger cohorts are necessary to further evaluate the efficacy and safety of dupilumab and SCIT combination therapy in patients with AD. Additionally, long-term follow-up studies are required to determine whether sustained remission continues after discontinuing the combination therapy.

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