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Original Article

Efficacy of subcutaneous immunotherapy for patients with asthma and allergic rhinitis in Korea: effect on eosinophilic inflammation

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Conflict of Interest
The authors have no financial conflicts of interest.

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Conceptualization: Chang Keun Kim. Formal analysis: Zak Callaway, Chang Keun Kim. Investigation: Chang Keun Kim, Jin-Sung

ABSTRACT

Background: Atopic asthma (AA) and allergic rhinitis (AR) are often seen as comorbidities and specific immunotherapy (SIT) is considered evidence-based treatment for them both.
Objective: The purpose of this study was to evaluate the efficacy of multiallergen subcutaneous SIT (SCIT) in reducing nasal and sputum eosinophilia, symptom scores, and impaired lung function in Korean pediatric patients with AR and AA.
Methods: Children aged 6–15 years with a documented history of bronchial asthma and seasonal/perennial AR were recruited then randomly selected to 1 of 2 groups: "immunotherapy group" (inhaled corticosteroids [ICS] and short-acting beta$_2$-agonist [SABA] + subcutaneous injection of standardized extracts of up to 4 allergens [n = 53]) or "drug only group" (ICS and SABA only [n = 19]). All data were collected retrospectively.
Results: Comparing the 2 treatment groups, the immunotherapy group showed a significantly (p = 0.006) greater reduction in nasal eosinophilia over the 3-year treatment period. Only the immunotherapy group exhibited a significant reduction in sputum eosinophilia over the 3-year treatment period (p = 0.003). Fifty-one point one percent of patients in the immunotherapy group showed significant improvement in the methacholine challenge test negative conversion rate compared to only 17.65% in the drug only group (p = 0.0168). There were significantly greater improvements in symptom scores in the immunotherapy group compared to the drug only group. For all allergens tested, only house dust mite reactivity changed significantly over the treatment period and only in the immunotherapy group (*Dermatophagoides pteronyssinus* [p < 0.0001] and *Dermatophagoides farina* [p = 0.035]).
Conclusion: SCIT was associated with greater improvements in lung function and bronchial hyperresponsiveness and reductions in nasal and sputum eosinophilia and allergen reactivity. Changes in symptom scores were also much greater in patients receiving SCIT when compared to those who did not receive it. Korean children with AA and AR respond well to long-term multiallergen SCIT.

Keywords: Allergen immunotherapy; Child; Desensitization; Eosinophilia

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INTRODUCTION

Specific immunotherapy (SIT) is an evidence-based therapy for both allergic rhinitis (AR) and asthma [1, 2], and involves administering gradually increasing doses of offending allergens to a person with allergic disease, with the eventual goal of reducing or eliminating adverse clinical responses to future allergen exposures [3]. SIT has been shown to reduce symptoms and medication use in patients with AR; however, the mechanisms of action are unclear. One proposed mode of action is that SIT causes a significant decrease in Th2 cytokines and Th2 effector cell activity, increased secretion of anti-inflammatory cytokines such as interleukin (IL)-10 and transforming growth factor-beta, as well as increased numbers and activity of T regulatory cells, consequently diminishing the allergic reaction to specific allergens [4]. It has been speculated that the Th2-associated allergic inflammation found in both AR and allergic asthma (AA) is best characterized by eosinophils [5], which are known to infiltrate the upper and lower airways, releasing proinflammatory mediators and correlating well with spirometric findings forced expiratory volume in 1 second (FEV_1) and bronchial hyperresponsiveness (BHR) [6, 7]. Studies have shown SIT may inhibit increases in nasal eosinophilia in seasonal AR [8]; however, reductions in sputum eosinophilia have not been found [9, 10].

There is strong evidence the upper and lower airways function as one unit [1], so there may be merit in treating AR and AA as 2 parts of the same disease (i.e., allergic airway disease). However, the number of studies using this approach is limited.

There are a number of administration routes for SIT, each with its advantages and disadvantages. Subcutaneous SIT (SCIT) presents the risk of inducing local and systemic side effects as a result of allergen injection. Studies monitoring large numbers (>10,000) of patients have shown a small but potential risk of adverse reaction [11, 12]. Consequently, several recommendations have been made to minimize the risk of side effects [13]. Furthermore, there is a paucity of studies on the safety and efficacy of multiallergen SCIT for allergic disease.

We aim to assess SCIT's efficacy in reducing nasal and sputum eosinophilia, symptom scores, and impaired lung function in Korean pediatric patients with AR and AA.

MATERIALS AND METHODS

Subjects

All data were collected retrospectively. Children ages 6–15 years with a documented history of bronchial asthma and seasonal/perennial AR were recruited from our Asthma and Allergy Center at Inje University Sanggye Paik Hospital in Seoul, Korea. These subjects were selected based on a positive skin prick test (wheal size > 3 mm) to 36 aeroallergens (Allergopharma GmbH & Co. KG, Reinbek, Germany) common in Korea. The skin reaction test was performed with the skin prick test and classified as 1+ to 4+, according to wheal (W) size: 1+, 1≤W<3 mm, flare<21 mm; 2+, 1≤W<3 mm, flare>21 mm; 3+, 3≤W<5 mm, flare>21 mm; 4+, W> 5 mm, flare>21 mm [14]. Recruited patients were sensitive to no more than 4 aeroallergens. In addition, selected patients were screened for all inclusion and exclusion criteria (see below). Subjects were then randomly selected to 1 of 2 groups:

Group 1 – SCIT add-on therapy group, referred to hereafter as the "immunotherapy group": inhaled corticosteroids (ICS) and short-acting beta$_2$-agonist (SABA) + subcutaneous injection of standardized extracts of up to 4 allergens (n = 53).

Group 2 – A standard Global Initiative for Asthma [15] pharmacotherapy group, referred to hereafter as the "drug only group": ICS and SABA (n = 19).

Patients in both groups visited our clinic every 2 months for the entire study period of 3 years for specimen collections (nasal, sputum, and blood) and doctor consultations.

This study was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (2019-05-005).

Nasal swab

A sterile swab was inserted into the nostril and gently rotated until resistance was met at the level of the turbinates (less than 2.5 cm into the nostril). The swab was then rotated a few times against the nasal wall, withdrawn, then placed back into the container, sealed and taken to lab within 1 hour.

Sputum induction

All subjects were premedicated with 2 puffs of albuterol (total dose of 180 μg) via spacer tube. Sputum induction was performed with aerosolized 3% hypertonic saline solution and generated by a DeVilbiss Ultra-Neb 99 ultrasonic nebulizer (DeVilbiss Co., Somerset, PA, USA). Every 2 minutes for up to 12 minutes subjects were instructed to cough, in order to produce sputum, which was then collected in a sterile container.

Nasal lavage fluid collection

Nasal lavage fluid specimens were collected from every subject during each clinic visit, as described in Kim et al. [16].

Specific immunotherapy

Standardized extracts of up to 4 allergens {house dust mites [*Dermatophagoides pteronyssinus* (D.p.), *D. farinae* (D.f.)], animal dander [cat, dog], molds [*Aspergillus, Alternaria*], and pollens [oak, alder, rye grass, ragweed, mugwort]} (Allerpha International, Seoul, Korea) were administered following an 'updosing' schedule. For the first 4 months, patients were given a weekly injection beginning with a 0.1 mL, which was doubled in strength each subsequent injection (i.e., 0.2 mL, 0.4 mL, 0.8 mL). After 4 months, a 'maintenance' schedule was followed, involving monthly injections for the remainder of the treatment period (i.e., total treatment period was approximately 3 years).

Inclusion and exclusion criteria

The subject must have both AR and AA; the asthma must be mild or moderate in severity; and the asthma must be considered stable at time of enrollment.

Exclusion criteria included: (1) any clinically significant nasal disease other than AR; (2) any acute or inflammatory disease other than bronchial asthma, including allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis; (3) any severe psychiatric disturbance or medical condition that would impair the ability to survive an allergic reaction;

(4) any autoimmune disease; any nasal structural abnormality (e.g., nasal polyps or marked septal deviation); or (5) any use of β-blockers.

Sputum processing

Collected sputum was processed, as described by Pizzichini et al. [17], with modifications. Sputum was processed within a time limit of 2 hours. Sputum specimens were used for eosinophil counts and eosinophil-derived neurotoxin levels.

Measurement of BHR

BHR was evaluated by methacholine bronchial challenge, as previously described by Chai et al. [18] but modified. Inhaled short-acting β_2-agonists were withheld for at least 8 hours, and other medications were withheld for 3 days before each challenge. Fresh solutions of methacholine were prepared in buffered saline solution at concentrations of 0.075, 0.15, 0.3, 0.625, 1.25, 2.5, 10, and 25 mg/mL. The procedure was terminated when FEV_1 decreased by more than 20% of its postsaline value or when the highest methacholine (25 mg/mL) concentration was reached. The percentage decline of FEV_1 from the postsaline value was then plotted against the log concentrations of the inhaled methacholine. Methacholine provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) was calculated by interpolating between 2 adjacent data points when the FEV_1 decreased by more than 20% after inhalation of up to 25 mg/mL. If the maximal dose of methacholine failed to produce a 20% drop or greater in FEV_1, a dose of 50 mg/mL was used for calculation.

Symptom scoring

Symptoms related to nose, eye, and breathing were recorded using the following scoring system: score 0, no symptoms; score 1, slight symptoms, occasional; score 2, moderate symptoms, frequent; score 3, severe symptoms, very frequent [19].

Statistical analysis

Symptoms and medication scores were summed up each year and expressed as the area under the curve (AUC). AUC data and nasal and sputum counts (eosinophils), all of which were not normally distributed, were expressed as medians (interquartile ranges). PC_{20} values were logarithmically transformed to normalize their distribution and expressed as geometric mean (range).

For all nonparametric data (AUC values and nasal/sputum eosinophil counts), differences between groups were compared using Kruskal-Wallis 1-way analysis of variance (ANOVA) followed by Mann-Whitney *U*-test. Within group comparisons were analyzed using Friedman test followed by Wilcoxon matched pairs signed-rank test where appropriate. PC_{20} was analyzed using 2-way ANOVA followed by the paired Student *t*-test. A p-value < 0.05 was considered as statistically significant.

RESULTS

Demographic and FEV data

All demographic data are presented in **Table 1**. There were no significant differences between the 2 treatment groups.

Referring to **Table 1**, FEV_1, % of predicted increased more in the immunotherapy group over the 3-year treatment period when compared to the increase in the drug only group (p =

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Table 1. Demographics and lung function

Variable	Immunotherapy group (n = 53)	Drug only group (n = 19)	*p*-value
Age (yr), median (range)	8 (6–15)	9 (6–15)	0.100
Sex, female:male	15:38	9:10	0.130†
FEV_1 (% of predicted)			0.011*,#
Baseline			
Mean±SD	82.1±13.1	86.4±13.3	
95% CI	78.1–86.0	79.6–93.3	
After 3 years			
Mean±SD	91.5±10.7	88.3±12.0	
95% CI	88.5–94.5	82.4–94.3	
FEV_1/FVC%			0.001*,#
Baseline			
Mean±SD	82.5±10.6	86.8±7.3	
95% CI	79.2–85.8	82.9–90.6	
After 3 years			
Mean±SD	89.5±5.9	87.5±6.6	
95% CI	87.8–91.2	84.0–91.0	

FEV_1, forced expiratory volume in 1 second; SD, standard deviation; CI, confidence interval; FVC, forced vital capacity.
*$p < 0.05$, significance level for between-group differences. †Chi-square test. #Mann-Whitney test.

0.0113). FEV_1/FVC% also increased more in the immunotherapy group over the same period when compared to the drug only group ($p = 0.0004$).

Nasal and sputum eosinophilia reduction

Nasal and sputum results are displayed in **Table 2**. Comparing the 2 treatment groups, the immunotherapy group showed a significantly ($p = 0.0058$) greater reduction in nasal eosinophilia over the 3-year treatment period (**Fig. 1**). And within the immunotherapy group, there was significant reduction in nasal eosinophilia ($p < 0.0001$) from baseline to after 3 years of immunotherapy. Within the drug only group, there was no significant change in nasal eosinophilia ($p = 0.8785$).

Referring to **Fig. 2**, there was no significant difference in reduction of sputum eosinophilia between the 2 groups ($p = 0.2756$). However, within the immunotherapy group, there was a significant reduction of sputum eosinophilia from baseline to after 3 years of immunotherapy ($p = 0.0030$). Within the drug only group, there was no significant change in sputum eosinophilia over the same treatment period ($p = 0.4531$).

Table 2. Nasal and sputum eosinophilia reduction

Variable	Immunotherapy group (n = 53)			Drug only group (n = 19)			*p*-value†
	No.	Mean±SD	Median (range)	No.	Mean±SD	Median (range)	
Nasal eosinophilia							
Baseline	51	13.27±16.09	7 (0–74)	17	8.06±20.45	2 (0–86)	
After 3 years	51	3.12±5.70	1 (0–36)	17	4.24±6.08	2 (0–24)	
Difference	49	−10.69±16.76	−6 (−74 to 16)	16	−4.25±22.55	0.5 (−86 to 18)	0.006
p-value‡			0.001			0.879	
Sputum eosinophilia							
Baseline	50	7.18±12.74	2 (0–70)	17	5.29±10.74	1 (0–42)	
After 3 years	51	2.75±5.30	1 (0–25)	18	2.94±5.30	2.5 (0–9)	
Difference	50	−4.38±12.99	−1 (−70 to 19)	17	−2.53±9.35	0 (−34 to 9)	0.276
p-value‡			0.003			0.453	

SD, standard deviation.
†Wilcoxon rank-sum test comparing change in immunotherapy group to drug only group. ‡Wilcoxon signed-rank test comparing change within each group.

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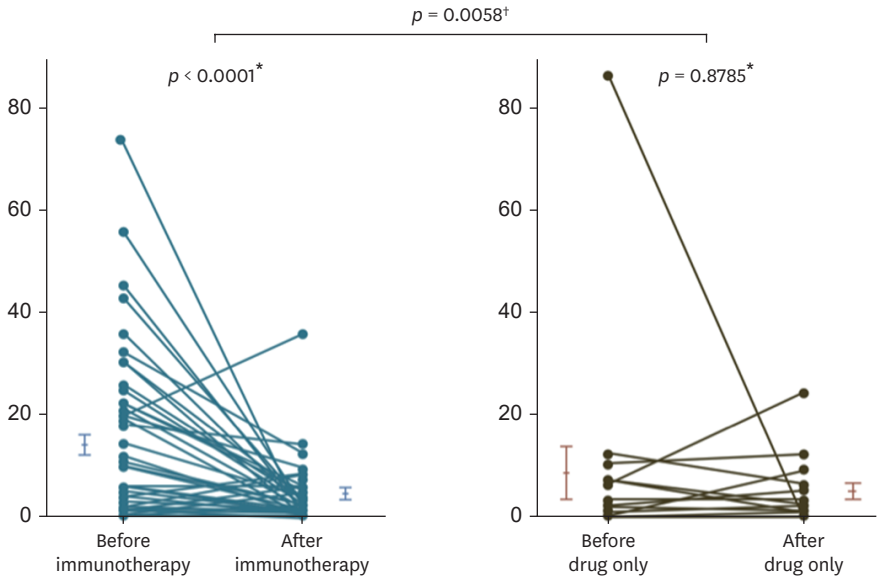

Fig. 1. Nasal eosinophil count in the immunotherapy group (left) and drug only group (right). Bars on graph show mean±standard deviation.

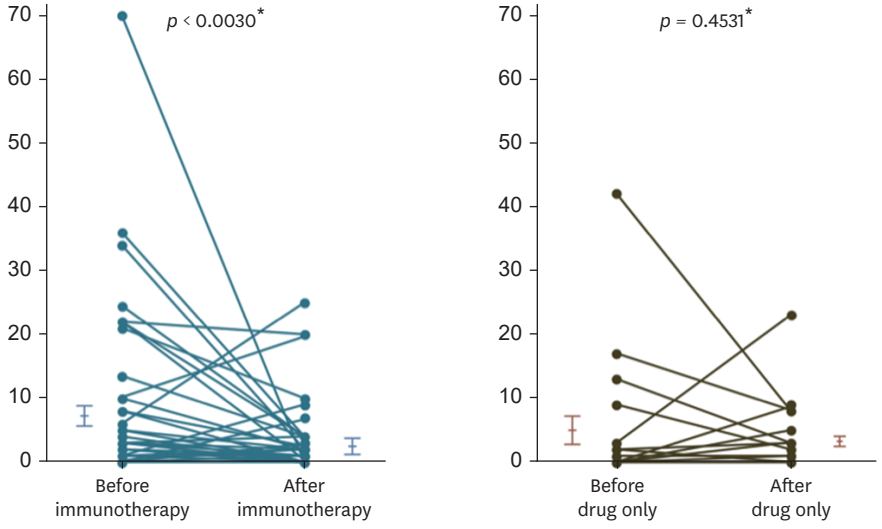

Fig. 2. Sputum eosinophil count in immunotherapy group (left) and drug only group (right). Bars on graph show mean±standard deviation.

Methacholine challenge test

Results for change in BHR, as measured by the Methacholine Challenge Test (MCT; PC20-Mch), were as follows: (1) immunotherapy group (n; mean ± standard deviation [SD]; median [range]) at baseline (47; 6.45 ± 8.47; 1.88 [0.31–25]) vs. after 3 years of treatment (53; 17.10 ± 10.27; 25 [0.32–25]) for a significant improvement over the treatment period ($p < 0.0001$); (2) drug only group (17; 7.19 ± 9.34; 3.75 [0.32–25]) vs. after 3 years of treatment (18; 4.24 ± 6.08; 5.63 [0.94–25]) for a significant improvement over the treatment period ($p = 0.0029$). When comparing the 2 treatments, there was a significantly greater improvement in the immunotherapy group compared to the drug only group ($p = 0.020$).

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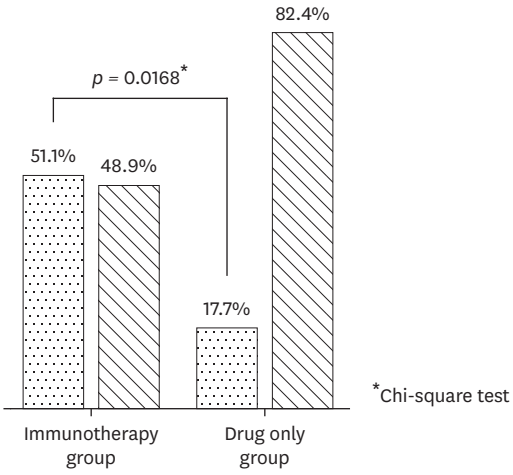

Fig. 3. Bronchial hypersensitivity negative conversion. Dotted bars on left in each group are proportion of patients with negative conversion after treatment. Cross-hatched bars on right in each group are proportion of patients with no significant improvement after treatment.

Results for the MCT negative conversion rate are in **Fig. 3**. Nearly 3 times (51.1% vs. 17.7%) the proportion of patients in the immunotherapy group significantly improved compared to the drug only group ($p = 0.0168$).

Symptom scores

Symptom scores for patients according to condition are presented in **Table 3**. For patients with bronchial asthma, there was greater improvement in symptom scores in the immunotherapy group when compared to the drug only group ($p < 0.0001$), with most patients (82.35%) feeling "a good deal better." In patients with AR, there was also a greater symptom score improvement in the immunotherapy group when compared to the drug only group ($p = 0.0009$), with 78.44% of patients feeling either "a good deal better" or "slightly better." Patients with upper respiratory tract infection also significantly benefitted from immunotherapy when compared to the drug only group ($p < 0.0001$). Thirty-eight of patients (74.51%) receiving immunotherapy felt "a good deal better."

Changes in wheal size as measured by skin prick test

Changes in wheal size can be found in **Fig. 4** (D.p.) and **Fig. 5** (D.f.) (n = 42). Comparing the 2 treatment groups according to change in wheal size (D.p.) (**Fig. 4**), there was a reduction in the immunotherapy group (mean ± SD: -1.40 ± 1.53) over the 3-year treatment period (baseline: 3.52 ± 1.06 vs. after 3 years: 2.12 ± 1.19), while in the drug only group wheal size actually increased (0.92 ± 1.73) (baseline: 2.75 ± 1.60 vs. after 3 years: 3.67 ± 0.98) ($p < 0.0001$). Comparing the 2 treatment groups according to change in wheal size (D.f.) (**Fig. 5**), there was also a reduction in wheal size (-1.14 ± 1.53) in the immunotherapy group with no change in the drug only group (0 ± 1.34) over the same 3-year treatment period ($p = 0.035$).

For all other allergens tested [birch (n = 8), cat (n = 5), dog (n = 7), *Alternaria* (n = 3), hazel (n = 5), mugwort (n = 5), oak (n = 9), peach (n = 2), ragweed (n = 2), asp (n = 0), timothy (n = 1), pine (n = 1)], there were no significant changes in allergen reactivity when comparing the 2 groups to each other (data not shown).

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Table 3. Symptom score changes by condition

Symptom score by condition	Immunotherapy group	Drug only group	*p*-value†
Bronchial asthma	n = 51	n = 17	
−3	0 (0)	0 (0)	
−2	0 (0)	0 (0)	
−1	0 (0)	3 (17.65)	
0	1 (1.96)	5 (29.41)	
1	8 (15.69)	5 (29.41)	
2	42 (82.35)	4 (23.53)	
3	0 (0)	0 (0)	
Mean±SD	1.88±0.45	0.59±1.06	<0.001
Median (range)	2 (0–2)	1 (−1 to 2)	
Allergic rhinitis	n = 51	n = 17	
−3	0 (0)	0 (0)	
−2	0 (0)	1 (5.88)	
−1	0 (0)	2 (11.76)	
0	11 (21.57)	8 (47.06)	
1	20 (39.22)	4 (23.53)	
2	20 (39.22)	2 (23.53)	
3	0 (0)	0 (0)	
Mean±SD	1.18±0.45	0.24±1.06	0.001
Median (range)	2 (0–2)	0 (−2 to 2)	
Upper respiratory tract infection	n = 51	n = 17	
−3	0 (0)	0 (0)	
−2	0 (0)	0 (0)	
−1	0 (0)	0 (0)	
0	2/51 (3.92)	8 (47.06)	
1	10 (19.61)	6 (35.29)	
2	38 (74.51)	3 (0)	
3	1 (1.96)	0 (0)	
Mean±SD	1.75±0.56	0.71±0.77	<0.001
Median (range)	2 (0–3)	1 (0–2)	

SD, standard deviation.
†Wilcoxon rank-sum test comparing change in immunotherapy group to drug only group.
Score: −3, much worse; −2, a good deal worse; −1, slightly worse; 0, more or less the same; +1, slightly better; +2, a good deal better; +3, much better.

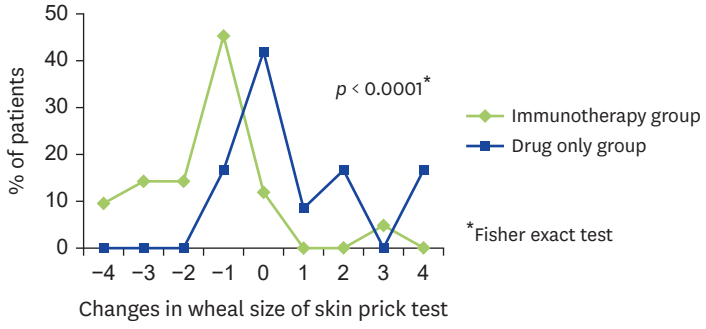

Fig. 4. Changes in wheal size (*Dermatophagoides pteronyssinus*) in immunotherapy group and drug only group.

Development of new sensitizations

In the immunotherapy group, 71.74% of patients did not develop new sensitizations to allergens, while only 53.85% of patients in the drug only group did not development new sensitizations over the same 3-year period. There was no significant difference between these 2 proportions ($p = 0.3143$).

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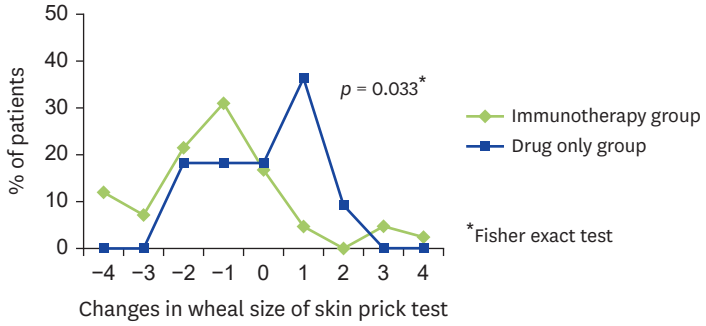

Fig. 5. Changes in wheal size (*Dermatophagoides farinae*) in immunotherapy group and drug only group.

DISCUSSION

Overall, the immunotherapy group demonstrated an excellent response to SCIT. When compared to the drug only group, there were greater improvements in lung function and BHR and reductions in nasal and sputum eosinophilia and allergen reactivity to house dust mites. Changes in symptom scores were also much greater in patients receiving SCIT when compared to those who did not receive it.

Though it is considered evidence-based therapy for both AR and AA, real-life efficacy of SCIT treatment is severely limited by perceived low patient compliance [20] and substantial delay in effect after initiation of therapy [2]. Some estimates put the delay at 7 or 8 months [4, 21]. SIT benefits can, however, be demonstrated after only a short-period but it is generally considered that these benefits may actually increase over several allergy seasons. It is also thought that the benefits from a short course of SIT may be quickly lost, whereas longer courses may result in longer lasting benefits [2]. Therefore, many allergists recommend at least 2 years of SIT to reap statistically significant benefits (e.g., symptom and IgE decreases), which is backed up by empirical studies [2]. Because of this, we chose a treatment study period of 3 years.

AR is the most common immunologic disorder and is characterized by an IgE-mediated inflammation induced by allergen exposure. T cells, eosinophils, mast cells, and basophils infiltrate the airways releasing several mediators, consequently causing symptoms and cytokines that promote and amplify the inflammatory cascade. This infiltration and release result in both a local and systemic response. There is strong evidence the respiratory airways function as a single anatomic unit, the 'one airway, one disease' hypothesis [22]. It is believed rhinitis and asthma are 2 manifestations of a single syndrome, the chronic allergic respiratory syndrome, and it has been shown that one therapy can treat both diseases simultaneously [23, 24]. Evidence clearly supports a link between upper and lower airway disease. Most patients with AA have concurrent AR, and 10%–40% of those with AR have AA [25]. All patients in our immunotherapy group had diagnosed AA and AR. When these patients' symptom scores were subdivided into AA symptoms and AR symptoms, both sets of symptom scores showed vast improvement after SCIT. 82.35% of patients felt their AA symptoms were "a good deal better," while 78.44% felt their AR symptoms were "a good deal better" or "slightly better." SIT is the only allergy treatment that modifies the underlying pathophysiology of the disease [26].

A primary endpoint of this study was change in nasal and sputum eosinophilia. Eosinophils are major effector cells in allergic disease and eosinophil activation and recruitment to target

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organs can be reduced during immunotherapy, which may affect the late-phase response to the allergen [4, 27]. In our immunotherapy group, there were significantly greater reductions in nasal and sputum eosinophilia when compared to the drug only group. Demarche et al. [28] found decreases in sputum eosinophilia predicted improvements in asthma control. And a meta-analysis of several studies [29] found treatment based on sputum eosinophil counts is more efficacious (i.e., reduces the frequency and severity of exacerbations) than treatment based on clinical symptoms and other traditional objective measures of lung function, such as peak expiratory flow and spirometry. Knowing both the inflammatory profile and the clinical categorization of the patient develops a clearer phenotype of the asthma patient and appears to contribute improved asthma care [30].

Changes in allergen reactivity to house dust mites, as measured by skin prick test, are easy to clinically evaluate and considered a reliable measure of immunotherapy efficacy. Many studies on immunotherapy efficacy have demonstrated reductions in allergen reactivity [31-33]. We experienced similar results in our patients with house dust mite (D.p. and D.f.) allergies, considered to be the most common of all allergies. Compared to patients receiving standard pharmacotherapy, those that received SCIT showed statistically significant improvements in allergen reactivity (i.e., wheal size). Looking at reactivity to allergens other than house dust mites—such as animal dander, molds, and pollens—there were no significant improvements in allergen reactivity over the 3-year SCIT period. However, because these allergies are far less common, the number of patients receiving SCIT for them was much lower than patients receiving SCIT for house dust mites ($n < 10$ for animal dander, molds, and pollens vs. $n = 42$ for house dust mites). Low numbers of patients with the much less common allergies may make it difficult to demonstrate statistically significant improvements in allergen reactivity.

The major limitation of our study was the possible increase in nasal or sputum eosinophils in cases of seasonal AR. However, it is unlikely that there will be a significant effect on the difference between the 2 treatment groups because all patients were sampled under the same conditions. The strength of our study is the fact that there are not many published papers describing the therapeutic effect of SCIT in childhood asthma. In particular, there are not many studies that have produced good results like in our study.

Though there has been some success treating both diseases with the same treatment (e.g., inhaled steroids), there are few studies on the effects of proper treatment and management of AR on asthma control. A number of studies have resulted in recommendations made to minimize the side effects; however, the safety and efficacy of multiallergen SCIT for allergic disease is unknown. Furthermore, more knowledge is needed as to the therapeutic mechanisms underlying SCIT's efficacy. With substantial increases in allergic disease prevalence over the last 30 years, and the understanding that AR and AA are often comorbidities, this study is both prudent and timely. Pediatric patients with concomitant AR and AA may respond very well to SCIT in terms of nasal and sputum eosinophilia, lung function, symptom scores, and allergen reactivity to house dust mites.

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