

Clinical and immunologic effects of sublingual immunotherapy on patients with allergic rhinitis to house-dust mites: 1-Year follow-up results

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ABSTRACT

Background: There have been no data on sublingual immunotherapy (SLIT) in Asian patients with allergic rhinitis (AR) sensitized to house-dust mites (HDMs). This study aimed to investigate the efficacy and immunologic change after 12 months of SLIT in Korean patients.

Methods: Fifty-eight patients, who had AR caused by *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* and who completed 12 months of SLIT were included. Symptom scores were evaluated before and after 12 months of SLIT, and medication scores were assessed throughout the study. Peripheral blood eosinophil counts, eosinophil cationic protein (ECP), total IgE, and specific IgE were also evaluated.

Results: All of the symptoms of AR were significantly improved with reduced medication scores. In addition, there were significant decrements in peripheral blood eosinophil counts and ECP ($p = 0.025$ and $p = 0.048$, respectively). Specific IgE for *D. farinae* slightly increased ($p = 0.019$), whereas specific IgE for *D. pteronyssinus* and total IgE did not change significantly. Thirty-six (62%) of 58 patients were in the effective response group. Although not statistically significant, findings in the study showed that the effective response group had a tendency to have higher ECP levels before SLIT than the ineffective response group ($p = 0.056$).

Conclusion: SLIT improved the symptoms and medication scores in Korean patients with AR from HDM. Laboratory parameters including eosinophil counts, ECP, and specific IgE for *D. farinae* seemed to be modified after 1-year SLIT. A high ECP level may be a useful parameter to predict the effectiveness of SLIT and select the patient for the treatment.

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Key words: Allergic rhinitis, Asian, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, efficacy, eosinophil cationic protein, house dust mites, patient selection, sublingual immunotherapy

Specific immunotherapy is a method of reducing sensitivity to a given allergen by repeated administration of a dose of that allergen. During the past 100 years, subcutaneous immunotherapy (SCIT) has been a traditional and validated method for the treatment of allergic rhinitis (AR).^{1,2} However, this route of application is inconvenient and occasionally associated with severe systemic adverse effects.³ Sublingual immunotherapy (SLIT) has been used in the United States for >100 years and is being used in Europe with increased frequency for the last 20 years.⁴ This treatment has been gradually accepted as a viable alternative to SCIT. According to the World Health Organization Allergic Rhinitis and Its Impact on Asthma guidelines, SLIT could be effective for pollen or mite AR.⁵

A recent meta-analysis reported the efficacy of SLIT for house-dust mites (HDMs).⁶ There were significant reductions in symptoms and rescue medication use in the SLIT group compared with the placebo group. However, except for our previous report,⁷ there have been no data on Asian patients with AR sensitized to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. SLIT has been recently introduced in Korea, and we reported the first study on early compliance and short-term (>6 months) efficacy of SLIT. There were some reports about laboratory changes such as specific IgE, peripheral blood eosinophil counts, and eosinophil cationic protein (ECP) after SLIT. However, no predictive tests for the clinical response to SLIT are available. This study was performed to investigate the efficacy and immunologic changes after 12 months of SLIT in Korean patients with AR due to

HDM. In addition, laboratory parameters were analyzed to predict the response to SLIT.

MATERIALS AND METHODS

Patients

SLIT was performed on the patients who had rhinitis symptoms and a sensitization to HDM (*D. pteronyssinus* and *D. farinae*) without any sensitization to other allergens. The patients who started to receive SLIT between November 2007 and August 2008 were included in this study. Sensitization to *D. pteronyssinus* and *D. farinae* was defined as (1) a serum-specific IgE level for *D. pteronyssinus* and *D. farinae* of ≥ 0.7 UI/mL on multiple allergen simultaneous tests and/or (2) a mean wheal diameter for *D. pteronyssinus* and *D. farinae* that was greater or equal to that of histamine (positive control) in the absence of any reaction to the saline (negative control) on skin-prick test. Skin-prick test was performed using 55 common aeroallergens including HDM (*D. pteronyssinus* and *D. farinae*), animal danders (cat epithelia and dog epithelia), molds (*Aspergillus fumigatus* and *Alternaria alternata*), pollens (mugwort, ragweed, alder, hazel, birch, and oak), and cockroach (*Blattella germanica*). We included the patients who had a history of asthma, atopic dermatitis, or bronchial hyperresponsiveness, but none of them had asthmatic symptoms and needed regular medications such as oral steroids, steroid inhalers, or antihistamines. Pregnant or lactating women were excluded. The subjects who suffered from immunologic or hematological disorders were also excluded. In our study, 75 patients were initially recruited and 58 patients (mean age, 16.9 ± 12.2 years; range, 5–53 years) were treated for 12 months and completed symptom questionnaires. Forty-two patients were male subjects and 16 were female subjects. The Institutional Review Board of the Clinical Research Institute at Seoul National University Hospital approved the study protocol (H-0910-081-298).

Immunotherapy

SLIT was conducted as we previously described and reported.⁷ Standardized extracts of HDM (50% *D. pteronyssinus*/50% *D. farinae*;

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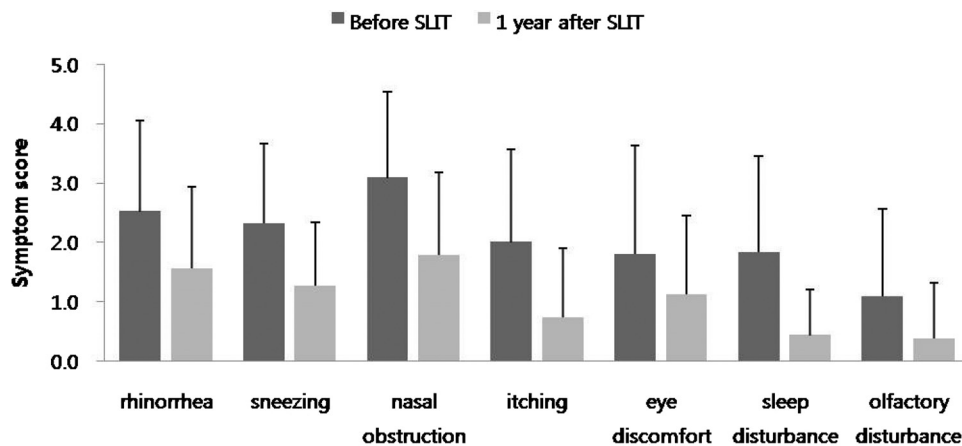


Figure 1. The symptom scores before and after 12 months of sublingual immunotherapy (SLIT). All of the symptoms were significantly improved after treatment ($p < 0.05$ by Wilcoxon signed-rank test).

Pangramin SLIT; ALK-Abelló, Madrid, Spain) were used for immunotherapy. The activities of the biologically standardized extracts were labeled in specific treatment units (STU). The extracts were used in the form of drops. During a 4-week up-dosing phase, the participants took daily increasing doses from 1 to 5 drops of 1.6 STU/mL solution from days 1 to 10, 1 to 5 drops of 8 STU/mL solution from days 11 to 15, 1 to 5 drops of 40 STU/mL solution from days 16 to 20, 1 to 5 drops of 200 STU/mL solution from days 21 to 25, and, finally, 1 to 5 drops of 1000 STU/mL solution from days 26 to 30. After reaching the maintenance dose, the participants took the allergen, 5 drops of 1000 STU/mL solution, 3 days/week during the maintenance phase. Drops had to be kept under the tongue for 2–3 minutes before being swallowed.

Symptom and Medication Scores

All of the patients were asked to complete the questionnaires before and 12 months after SLIT. The questionnaires covered symptoms including rhinorrhea, sneezing, nasal obstruction, itchy nose, eye discomfort, olfactory disturbance, and sleep discomfort as our previous study.⁷ Each symptom was graded from 0 to 5 (0 = no symptom, 1 = very mild symptom, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe). Total symptom scores (TSSs) were defined as the sum of the scores of rhinorrhea, sneezing, nasal obstruction, itchy nose, and eye discomfort. In addition, the patients were classified into two groups depending on whether they had a reduction of TSS of $\geq 30\%$ compared with their baseline (effective response group) or not (ineffective response group). This criteria was modified from a previous study, which had evaluated the allergen-specific immunotherapy as effective if the mean of the visual analog scale scores showed a 30% decrease with respect to the value of the visual analog scale score before the treatment.⁸

When necessary, patients were allowed to use the following symptomatic rescue medications: oral antihistamines, intranasal antihistamines, ocular antihistamines, and intranasal corticosteroids. The patients had to record on the diary card whenever they used medications. The daily medication points were assigned 0–5 points (1 point for antihistamine tablet, intranasal antihistamine, or ocular antihistamine; 2 points for intranasal corticosteroid) according to the statement of World Allergy Organization taskforce.⁹ Total medication scores were defined as the sum of the daily medication points patients accumulated while using symptomatic medications during each 2-month period of the 12-month study.

Adverse Effects

To evaluate adverse effects related to SLIT such as aggravation of AR symptoms, itchy mouth, gastrointestinal trouble, and breathing

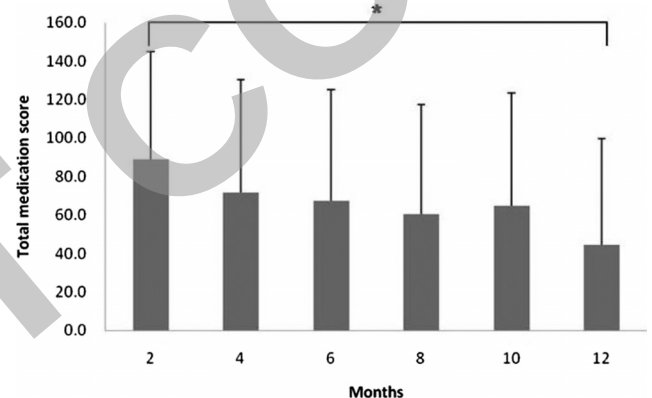


Figure 2. Total medication scores during the sublingual immunotherapy (SLIT). A significant reduction of symptomatic medication use was observed between the first and last 2 months ($*p = 0.001$ by Wilcoxon signed-rank test). The use of SLIT correlated with a reduction in rescue medication use over time.

discomfort, the participants recorded pertinent adverse effects every day on diary cards during the whole period.

Laboratory Parameters

Peripheral blood eosinophil counts, total IgE, ECP, and specific IgE for HDM (*D. pteronyssinus* and *D. farinae*) in serum were determined before and 12 months after treatment. The rates of change in each parameter after treatment were analyzed and compared between the effective and ineffective response groups. Peripheral blood eosinophils were measured with XE-2100 (Sysmex, Kobe, Japan). ECP, total IgE, and specific IgE for HDM (*D. pteronyssinus* and *D. farinae*) were determined by fluoroenzymeimmunoassay using the Unicap system (Phadia, Uppsala, Sweden), a solid-phase immunoradiometric assay (Siemens, Los Angeles, CA), and an allergosorbent test on paper discs (Bio-line, Brussels, Belgium), respectively.

Statistical Analysis

Statistical analyses were performed with SPSS (Version 17.0; SPSS, Inc., Chicago, IL). All data were expressed as mean $\pm$ SD. Symptom and medication scores before and 12 months after SLIT were analyzed by the Wilcoxon signed-rank test. Symptom scores before SLIT between effective and ineffective response groups were analyzed by the Wilcoxon rank sum test. The paired *t*-test

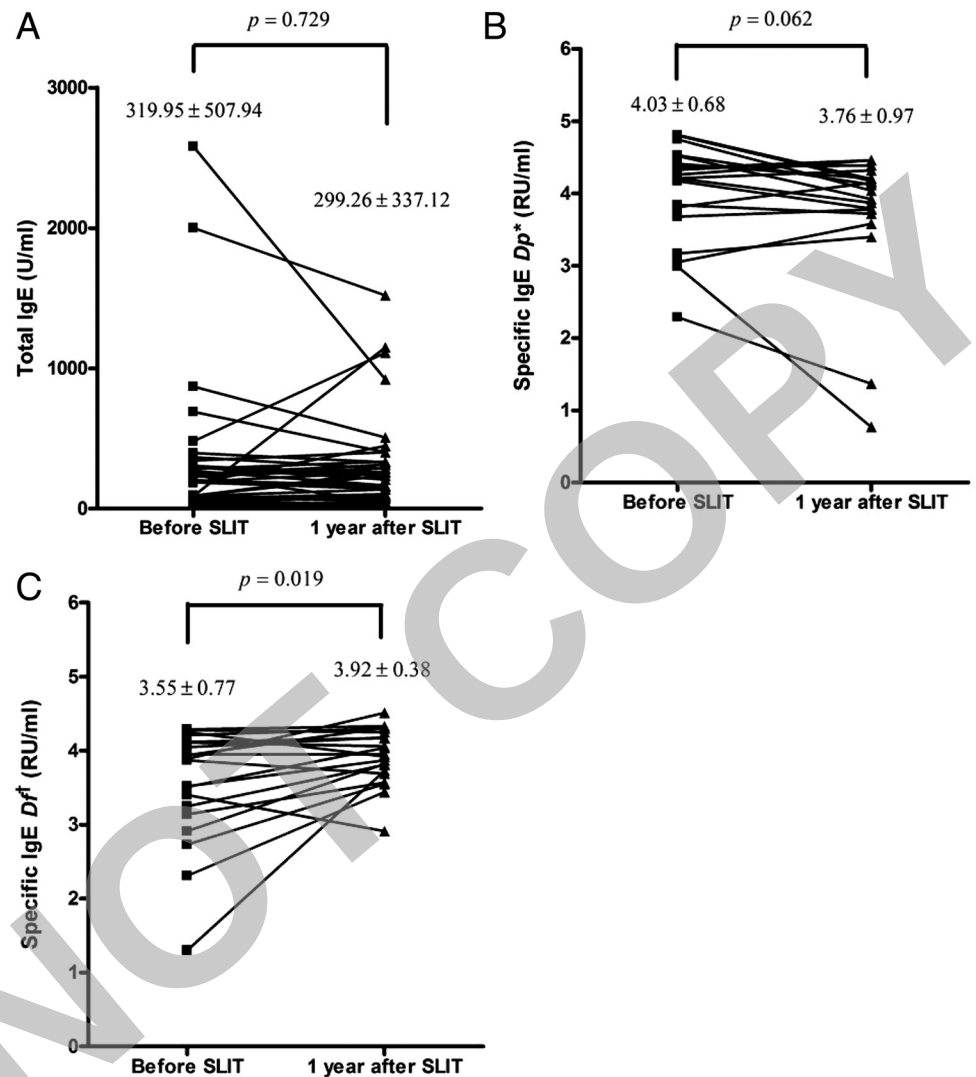


Figure 3. Level of (A) total IgE, (B) specific IgE for *D. pteronyssinus* and (C) specific IgE for *Dermatophagoides farinae*. Specific IgE for *Dermatophagoides farinae* was significantly increased after 12 months of sublingual immunotherapy (SLIT; $p = 0.019$ by paired t -test). **Dermatophagoides pteronyssinus*; †*Dermatophagoides farinae*.

was used to compare the change of laboratory parameters. All tests were two tailed, and the level of significance was set at 0.05.

RESULTS

Symptom Scores

TSS decreased significantly 12 months after starting SLIT (from 11.71 ± 5.23 to 6.43 ± 3.77 ; $p < 0.001$). All of the symptoms (rhinorrhea, sneezing, nasal obstruction, itchy nose, eye discomfort, olfactory disturbance, and sleep discomfort) were also significantly improved (all $p < 0.05$; Fig. 1). Thirty-six of the 58 patients belonged to the effective response group (62%) and 22 patients belonged to the ineffective response group (38%). The effective response group had a significantly higher TSS before SLIT than the ineffective response group (effective response group, 13.64 ± 4.98 , versus ineffective response group, 8.55 ± 4.01 ; $p < 0.001$).

Medication Scores

Total medication scores had a tendency to decrease over time during the 12 months of treatment (Fig. 2). A significant reduction in use of symptomatic medications was observed between the first and last 2 months ($p = 0.001$). There was also a significant difference between 2 and 4 months after starting treatment ($p = 0.001$).

Laboratory Parameters

The results of total IgE and specific IgE for HDM in serum are summarized in Fig. 3. Serum levels of specific IgE for *D. farinae* increased significantly after 12 months of SLIT (from 3.55 ± 0.77 to 3.92 ± 0.38 Rast unit (RU)/mL; $p = 0.019$), whereas no significant differences were observed in the level of total IgE and specific IgE for *D. pteronyssinus*. There were also significant reductions in the eosinophil counts (from 431.25 ± 276.17 to $337.67 \pm 249.47/13205$; $p = 0.025$) and ECP (from 21.47 ± 15.57 to 16.48 ± 13.53 ng/mL; $p = 0.048$; Fig. 4). To elucidate the relationship between symptom improvement and each parameter, we compared the level of parameters before SLIT and rates of change in each parameter after SLIT between the effective and ineffective response groups. In our study, the effective response group had a tendency to have a higher ECP level before SLIT than the ineffective response group (effective response group, 25.50 ± 16.75 , versus ineffective response group, 15.72 ± 12.05 ng/mL; $p = 0.056$). However, this result could not reach a statistically significant difference between the two groups (Table 1).

Safety

No serious adverse effects were reported. However, the incidence of adverse effects of SLIT was 56.9% (33 of 58 patients) during the up-dosing phase, in which aggravation of AR symptoms was the

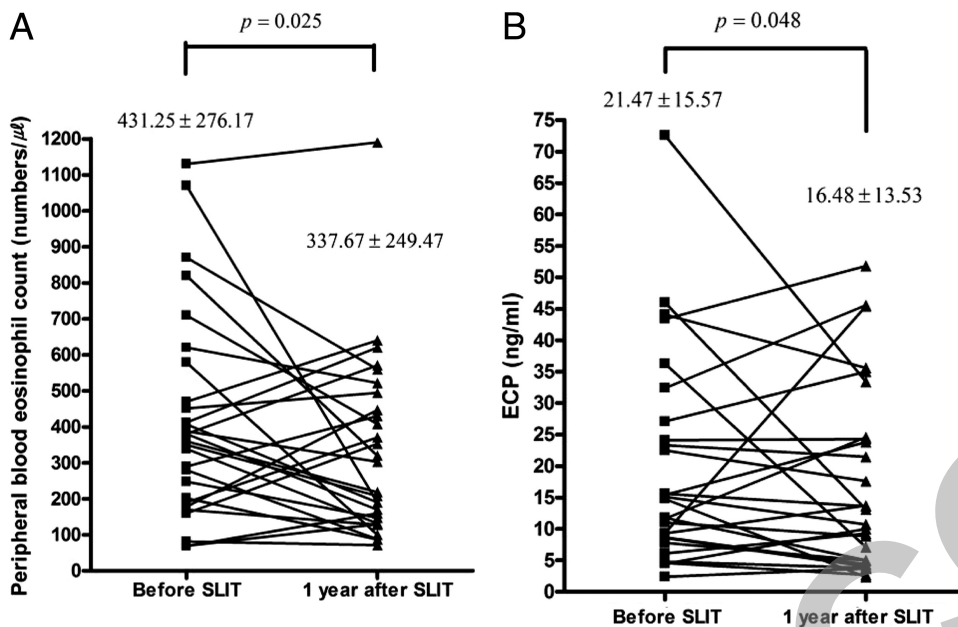


Figure 4. Comparison of (A) peripheral blood eosinophil counts and (B) eosinophil cationic protein (ECP) concentration before and after 12 months of sublingual immunotherapy (SLIT). Peripheral blood eosinophil counts and ECP significantly decreased after treatment ($p = 0.025$ and $p = 0.048$ by paired t-test).

Table 1 Comparison of laboratory parameters between the effective and ineffective response group

	Effective Response Group	Ineffective Response Group	<i>p</i>
Before sublingual immunotherapy			
Specific IgE for <i>D. pteronyssinus</i> (RU/mL)	4.01 $\pm$ 0.72	4.08 $\pm$ 0.62	0.840
Specific IgE for <i>D. farinae</i> (RU/mL)	3.64 $\pm$ 0.63	3.28 $\pm$ 1.16	0.536
Total IgE (U/mL)	383.0 $\pm$ 599.7	198.7 $\pm$ 227.9	0.183
ECP (ng/ml)	25.50 $\pm$ 16.75	15.72 $\pm$ 12.05	0.056
Peripheral blood eosinophil counts (μ L)	467.3 $\pm$ 306.1	374.6 $\pm$ 219.9	0.299
Rate of change after sublingual immunotherapy (%)			
Specific IgE for <i>D. pteronyssinus</i>	-4.1 $\pm$ 13.8	-18.2 $\pm$ 31.8	0.383
Specific IgE for <i>D. farinae</i>	10.5 $\pm$ 15.8	39.8 $\pm$ 83.0	0.475
Total IgE	62.3 $\pm$ 242.4	7.8 $\pm$ 33.3	0.280
ECP	-6.3 $\pm$ 101.7	-0.8 $\pm$ 64.9	0.849
Peripheral blood eosinophil counts	18.9 $\pm$ 59.5	15.0 $\pm$ 62.4	0.107

Bold type indicates that the effective response group had a tendency to have a higher eosinophilic chemotactic factor level before sublingual immunotherapy than the ineffective response group.

ECP = eosinophil cationic protein.

Table 2 Adverse effects of sublingual immunotherapy

Adverse Effects	Up-Dosing Phase	After 1-yr Treatment
Rate of adverse effects	33 (56.9%)	13 (22.4%)
Aggravation of symptoms	24 (41.4%)	9 (15.5%)
Eye discomfort	14 (24.1%)	6 (10.3%)
Skin rash or itching	12 (20.7%)	5 (8.6%)
Gastrointestinal trouble	11 (20.0%)	0
Itching of oral cavity or lip	8 (13.8%)	1 (1.7%)
Breathing discomfort	1 (1.7%)	3 (5.2%)
Wheezing	0	0

The numbers are not mutually exclusive.

most common adverse effect (Table 2). After 12 months, 13 patients (22.4%) still experienced intermittent symptom aggravation.

DISCUSSION

As in our previous study,⁸ this study also revealed that all of the symptoms of AR were improved after 12 months of SLIT. In addition,

the use of symptomatic medications decreased during the treatment. These results were similar to those of the earlier study, which reported that, in 68 patients with mild rhinitis, the drug intake score was significantly reduced at the 1st year after SLIT.¹⁰ However, there have been double-blind, placebo-controlled studies that have showed no statistically significant difference between the active treatment group and the placebo group for medication scores; instead, low medication consumption was observed in all patients.^{11,12} A limitation of the present study was the lack of the placebo group. Nevertheless, this study showed a $\geq 30\%$ reduction of TSS in 62% of patients with decreased medication scores during SLIT. Although symptoms of AR due to HDM are usually aggravated between late summer and early fall in Korea, this study showed a gradual reduction of symptomatic medication use regardless of the season after 1 year of SLIT. These results may suggest the effectiveness of SLIT on AR.

Results of a GA²LEN meta-analysis on SLIT for HDM showed that an increase from baseline in HDM-specific IgE level was observed in active groups in five studies, and none of this change was found in four studies.⁶ A double-blind, randomized, placebo-controlled study of SLIT in 20 asthmatic children reported that there were no changes in specific IgE for *D. pteronyssinus* and *D. farinae* after 6 months.¹³

There were some reports with longer follow-up data. A study on SLIT in 18 patients who had AR or asthma showed that specific IgE for *D. pteronyssinus* increased in the active treatment group and was different from the placebo group.¹⁴ Another study, in which 42 patients with AR completed 24 months of SLIT, reported that specific IgE for *D. pteronyssinus* and *D. farinae* increased significantly after 12 months in the active treatment group and specific IgE decreased slightly after 24 months.¹¹ Changes in specific IgE are variable, because the time of measurement is crucial.¹⁵ In our study, specific IgE for *D. farinae* increased at 12 months of SLIT, while specific IgE for *D. pteronyssinus* was not significantly modified. Additionally, we observed that peripheral eosinophil counts and ECP decreased at 12 months of treatment; these results are similar to previous studies.^{16,17} Reduction of eosinophil counts and ECP could be obtained earlier. A study that was conducted in asthmatic children receiving SLIT showed that eosinophil counts decreased at 24 weeks of SLIT.¹³ It was also found that ECP decreased significantly after 6 months of SLIT, but that study was performed in children allergic to grass pollen, not mites.¹⁸ As we mentioned in our previous study, the dropout rate was 31% and subjective ineffectiveness for SLIT was the second most common (22%) reason for discontinuation of SLIT. In addition, patients who receive SLIT should take an allergen for a long time. A report, which was conducted in 137 patients with AR due to HDM, suggested 3 years of SLIT for a long-term effect.¹⁹ A study was performed in 186 patients with seasonal AR; although no significant differences were found between the actively treated subjects and the placebo group after 1 year of SLIT, the subjects showed a reduction in symptoms after the 2nd year of therapy.²⁰ However, a recent report documented that 100 (49.3%) of 203 AR patients treated with 4 years of SLIT showed an ineffective clinical response.⁸ Therefore, laboratory parameters, which have been shown to predict the response to SLIT in early stages, are required to avoid unnecessary long-term treatment in nonresponders. In our study, the effective response group had a tendency to have higher ECP levels before SLIT than the ineffective response group. Although this result could not reach statistical significance, high ECP might be one of the predictive values. Therefore, this marker needs to be further investigated.

The safety of SLIT has been confirmed in many trials. Only six cases of anaphylaxis after SLIT have been reported in the English medical literature, some of which were with mixtures of multiple unrelated allergens using nonstandardized extracts, but two patients had a severe reaction after the first dose of a grass tablet.^{21–25} In our study, 56.9% of 58 patients had adverse effects, and the most common adverse effect was aggravation of the AR symptoms. As we mentioned in a previous report, the symptomatic aggravation of allergic rhinoconjunctivitis, which the participants reported as an adverse effect, involved not only the true adverse effect, but also disease aggravation due to environmental allergens.⁷ The most common side effect of SLIT has been known to be local irritation in the mouth and under the tongue; a clinical trial has shown that the rate of local irritation is between 47 and 52%.²⁶ We showed that there was no serious adverse effect in this study; local irritations in the oral cavity or lip occurred in 13.6% of patients. These symptoms subsided over time without any specific medication. After 12 months of treatment, local irritations in the oral cavity or lip disappeared in most patients, as did most adverse effects.

CONCLUSIONS

In conclusion, this study shows that subjective symptoms improved at 12 months after SLIT for HDM, and consumption of symptomatic medications decreased during the treatment. Laboratory parameters may be changed after SLIT. High ECP before SLIT may be a useful predictive marker for response to SLIT. However, further studies are required to evaluate the clinical efficacy of long-term SLIT and to elucidate the predicting markers for response to SLIT.

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