

Efficacy and safety of a once-daily sublingual immunotherapy without escalation regimen in house dust mite-induced allergic rhinitis

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Background: The conventional escalation regimen for sublingual immunotherapy (SLIT) in patients with allergic rhinitis has been proven to be safe and successful in reducing allergic symptoms. However, few studies compared the efficacy and safety between a conventional escalation regimen for SLIT and once-daily SLIT. The aim of the present study was to compare the efficacy and safety of once-daily SLIT without escalation (SLITsE) to conventional escalation therapy (SLITwE).

Methods: This study was a nonrandomized open label observational study. In total, 153 patients suffering from allergic rhinitis symptoms and sensitized to the perennial house dust mite allergens *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, were enrolled in this study from July 2008 to December 2009. The patients were divided into 2 groups, SLITwE and SLITsE. Each patient was followed with a diary card on which a symptom score, a rescue medication score, and adverse events were recorded.

Results: All of the nasal symptoms, including rhinorrhea, sneezing, nasal obstruction, itching, and olfactory symp-

toms, defined as a total nasal symptom score, were reduced after 6 months in both groups ($p < 0.05$). The rescue medication score, defined as the sum of all of the allergy medications used, also decreased in both groups. Adverse events were similar in both groups, and no major adverse events, such as anaphylaxis, were reported.

Conclusion: Once-daily SLITsE was well tolerated and showed safe and comparable efficacy compared with a conventional SLITwE regimen. © 2012 ARS-AAOA, LLC.

Key Words:

administration; sublingual; immunotherapy; allergic rhinitis; house dust mites

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Allergic rhinitis is the most frequent disease among allergic disease entities and shows an increasing prevalence

worldwide.^{1,2} As the prevalence of allergic rhinitis has increased worldwide, the economic burden has also increased.³ To treat allergic rhinitis, many drugs that reduce allergic symptoms have been developed. However, to eradicate and modify the natural course of allergic rhinitis, the only treatment option is immune therapy.

As a method of administering immune therapy, subcutaneous immunotherapy (SCIT) is used in many countries, but there are some reports on the risk of life-threatening anaphylactic events.^{4,5} In SCIT, an escalating regimen, which includes progressively increasing doses of allergen extract, is used as conventional therapy. However, rush and ultra-rush regimens with a buildup phase of several weeks to 2 hours have also been attempted with *Hymenoptera* venom allergen and have been reported to be as successful as traditional SCIT.^{6,7} However, the safety of these methods is still controversial because of a potentially higher frequency of severe systemic reactions. The evolution from SCIT into sublingual immunotherapy (SLIT), in which the

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allergen is administered under the tongue, is providing the treatment opportunities for many patients with allergic rhinitis because it has been proven to be a safe method of reducing the sensitivity to given allergens.^{8–13}

Like SCIT, there are different administration methods for SLIT, including a conventional escalation regimen with 1 month of a buildup phase followed by a maintenance regimen, a rush escalation regimen with an initial 3-day buildup phase followed by a maintenance regimen, an ultra-rush escalation regimen with an initial 2 hours of a buildup phase followed by a maintenance regimen, and once-daily SLIT without escalation.^{14–19} All of these different administration methods have been developed for the convenience of patients by reducing the buildup phase and maintaining the efficacy and safety of SLIT. Each therapy has been proven to be effective in reducing allergic symptoms. SLIT without escalation has been reported to reduce allergic symptoms and rescue medication scores in grass- and olive-sensitized patients.¹⁵ However, there have been few studies comparing the efficacy and safety between the different administration methods. This study was designed to compare the initial efficacy and safety of once-daily SLIT without escalation (SLITsE) with conventional SLIT with escalation (SLITwE) in house dust mite (HDM) allergy. The primary outcome is to compare the adverse events in the first month, and the secondary outcome is to compare treatment efficacy and compliance 6 months later.

Patients and methods

Patients

SLIT was applied to the patients who had rhinitis symptoms and a sensitization to HDM including *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df). Patients with bronchial hyperresponsiveness who did not require regular medication therapy were included. By contrast, pregnant or lactating women and subjects who suffered from immunologic or hematological disorders were excluded.

This study was an open label, nonrandomized, observational study. The patients were treated with SLIT for Dp/Df with either Pangramin SLIT® (50% Dp, 50% Df; ALK-Abello, Madrid, Spain), which included an escalation period of 1 month, from July 2008 to December 2008, or SLITone® (50% Dp, 50% Df; ALK-Abello), which is a once-daily dosage without escalation, from July 2009 to December 2009.

Sensitization to Dp/Df was defined as a mean wheal diameter for Dp/Df that was greater than or equal to that of histamine (positive control) in the absence of any reaction to saline (negative control) in a skin-prick test and/or a serum Dp/Df-specific immunoglobulin E (IgE) level greater than 0.7 UI/mL in multiple-allergen simultaneous tests.

TABLE 1. Demographics of patients with house dust mite-induced allergic rhinitis who were treated with SLIT

Group	SLITwE (n = 75)	SLITsE (n = 78)	p ^a
Sex (% males)	65.3	61.5	0.629
Age (years), mean ± SEM	18.6 ± 1.67	22.6 ± 1.64	0.086
Allergic symptom frequency more than 4 days per week (%)	80	84.6	0.457
Allergic symptom duration more than 1 month (%)	70.7	73.1	0.742
Mean allergic symptom duration (years)	7.06	7.92	0.420
Atopy (%)	32	20.5	0.107
Asthma (%)	10.7	10.3	0.934
Family history of allergic rhinitis (%)	46.7	64.1	0.030

^aIndependent t test.

SEM = standard error of the mean; SLIT = sublingual immunotherapy; SLITsE = SLIT without an escalation regimen; SLITwE = SLIT with a conventional escalation regimen.

A total of 75 patients were treated with SLITwE and 78 patients were treated with SLITsE. The demographic data are presented in Table 1.

Consensus and ethics committee approval

Informed consent was obtained from all patients or patients' parents. The Institutional Review Board of the Clinical Research Institute at Seoul National University Hospital approved the study protocol.

Immunotherapy

SLITwE was conducted as we previously described and reported.^{20,21} Standardized HDM extracts 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 escalation phase in the initial treatment, the patients took daily increasing doses of 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 1 to 5 drops of 1000 STU/mL solution from days 26 to 30. After reaching the maintenance dose, the patients took the allergen (5 drops of 1000 STU/mL solution) 3 days/week during the maintenance phase. The drops had to be maintained under the tongue for 2 to 3 minutes before being swallowed.

By contrast, for SLITsE users, immunotherapy was directly initiated by the administration of single-dose containers directly under the tongue, which were maintained for at least 2 minutes before swallowing. Each single-dose container contains 0.2 mL of extractable volume, which

corresponds to 5 drops of 1000 STU/mL solution for SLITwE. The allergen quantity of 5 drops of Pangramin SLIT® is similar to the allergen extract quantity in 1 single-dose container of SLITone®. Thus, at the final dose, the droppers were identical in both groups.

To assess symptom changes and adverse events (AEs), each patient was followed with a diary card on which a symptom score, a rescue medication score (RMS), and AEs were recorded.

Efficacy: total nasal symptom score and rescue medication score

All of the patients were asked to complete questionnaires for the symptoms before and 6 months after SLIT. A total of 5 nasal symptoms were measured including rhinorrhea, sneezing, nasal obstruction, itching, olfactory disturbance, and eye discomfort, as reported in our previous study. Symptoms were scored using a scale ranging from 0 to 3 points: 0 points for no symptoms; 1 point for mild symptoms; 2 points for moderate symptoms; and 3 points for severe symptoms.

The total nasal symptom score (TNSS) was defined as the sum of all the allergic nasal symptom scores including rhinorrhea, sneezing, nasal obstruction, itching, and olfactory symptoms. TNSS differences were defined by subtracting the TNSS after 6 months of SLIT from the TNSS before treatment.

Rescue medication was prescribed and administered to the patients to control their allergic symptoms if needed. The rescue medications consisted of nasal and oral antihistamines, nasal corticosteroids, and ocular antihistamines. The patients were asked to record the medication use and each of the medications was scored and used to calculate the RMS. The RMS was defined as the sum of all medication use for 6 months. Each daily medication score was assigned 1 to 3 points: 1 point for oral antihistamine, ocular antihistamine, or intranasal antihistamine; 2 points for intranasal corticosteroid; 3 points for oral corticosteroid. RMS differences were defined by subtracting the RMS after 6 months of SLIT from the RMS before treatment.

Safety: adverse events

To evaluate AEs related to SLIT, every AE during the whole period of SLIT administration was recorded by patients. AEs were divided into major and minor by consensus among all the investigators. Major AEs were defined as respiratory symptoms, including dyspnea and stridor, that may have been the initial sign of an anaphylactic event. Minor AEs include 4 symptom groups: aggravation of allergic symptoms, which include rhinorrhea, sneezing, nasal obstruction, itchy nose or eyes, and epiphora; local irritation symptoms, including tongue itching, lip itching, mouth itching, lip bulla, lip pain, and dry lip; gastrointestinal symptoms, including abdominal discomfort, and diarrhea; and other minor symptoms for which the event frequency was lower. These included epistaxis, sore throat, dizziness,

and sputum. Although all of the AEs were recorded by the patients and their parents, only the AEs in the first month were regarded as suitable for comparison between the SLITwE and SLITsE groups because the major difference in the groups was the dose escalation during the first month.

Satisfaction

The participants' subjective satisfaction was evaluated by 3 categories of satisfaction 6 months after completion of SLIT: "satisfied," "fair," and "dissatisfied."

Dropout rate

Dropout rate was defined as the number of patients who discontinued SLIT, either due to follow-up loss or giving up for other reasons, such as AEs, lack of efficacy/symptom improvement, and a difficult SLIT schedule, compared to the number of patients who enrolled in SLIT.

Statistical analysis

Statistical analyses were performed with SPSS (Version 18.0; SPSS, Inc., Chicago, IL). All of the data were expressed as the mean $\pm$ standard error of the mean (SEM). Values of $p < 0.05$ were considered to be statistically significant and independent t tests and paired tests were used.

Results

Efficacy: total nasal symptom score and rescue medication score

All of the nasal symptoms, including rhinorrhea, sneezing, nasal obstruction, itching, and olfactory symptoms, but not eye symptoms, were significantly decreased in the SLITwE group ($p < 0.05$), whereas all nasal and eye symptoms improved in the SLITsE group ($p < 0.05$) (Fig. 1).

In the SLITwE group, the initial TNSS was 8.7, and it decreased to 3.7 after 6 months of follow up. In the SLITsE group, the initial score was 10.1, and it decreased to 3.6 after the same follow-up period. The SLITsE group showed a significant improvement in TNSS, which suggested that the level of symptom improvement was higher in the SLITsE group ($p = 0.0001$) (Fig. 2).

The RMS score decreased from 116.2 to 74.1 in the SLITwE group and from 123.3 to 53.1 in the SLITsE group. The resulting difference in the RMS was 42.1 in the SLITwE group and 70.1 in the SLITsE group, and medication use was significantly decreased in the SLITsE group ($p = 0.037$) (Fig. 3).

Safety: adverse events

AEs were reported in multiple-answer form. Among the 75 patients in the SLITwE group, 29 reported AEs; 29 (38.7%) complained of the aggravation of the allergic symptoms, 7 (9.3%) patients reported local irritation symptoms, and 8 (10.6%) patients had gastrointestinal symptoms. Other

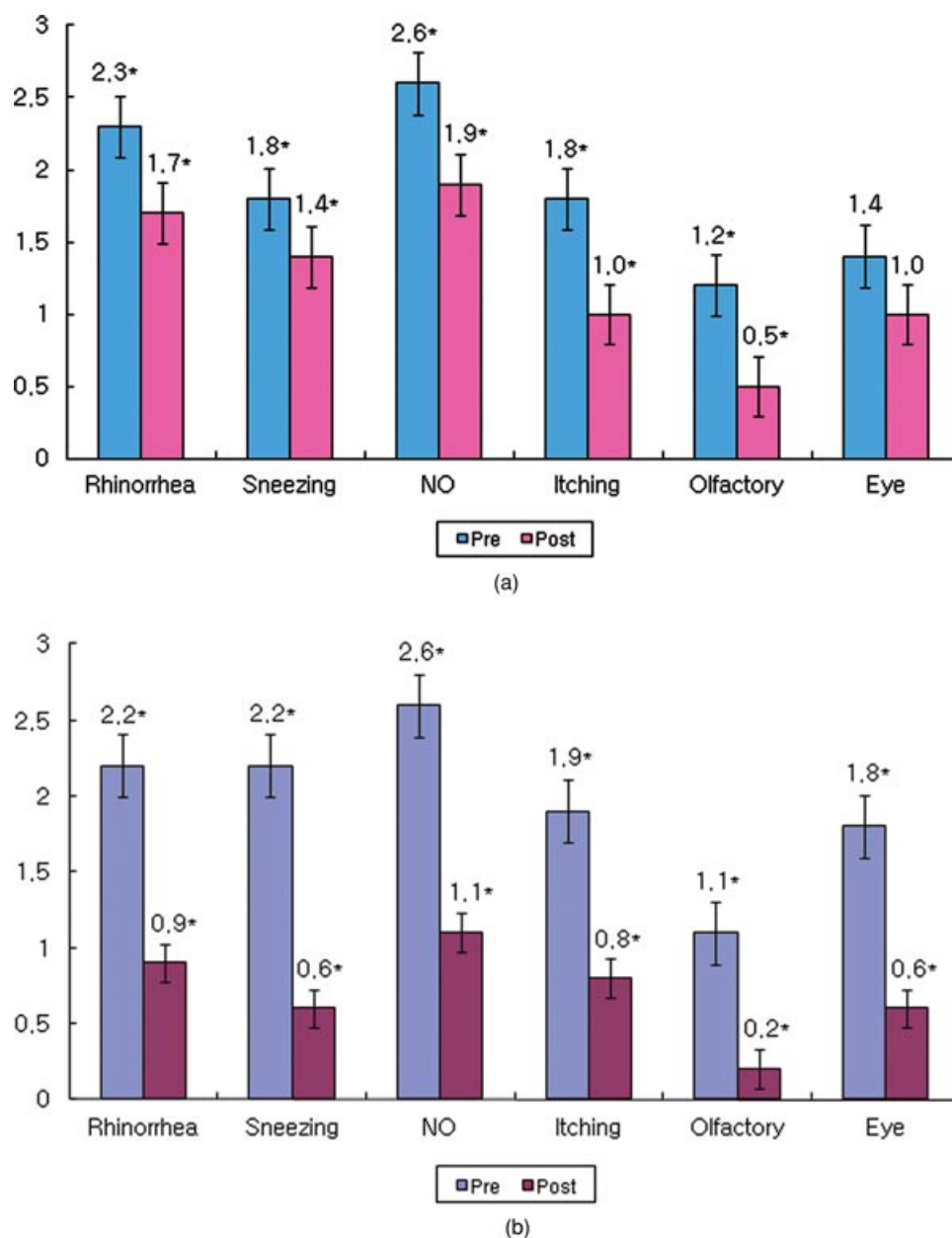


FIGURE 1. The TNSSs in the sublingual immunotherapy groups with or without escalation. (A) The TNSS in SLIT with escalation. (B) The TNSS in SLIT without escalation. All of the nasal symptoms, including rhinorrhea, sneezing, nasal obstruction, itching, and olfactory symptoms, were significantly decreased. *Significantly different between pre- and post-SLIT ($p < 0.05$). Paired t test. Eye = eye symptoms; NO = nasal obstruction; Olfactory = olfactory symptoms; Post = post-SLIT; Pre = pre-SLIT; SLIT = sublingual immunotherapy; TNSS = total nasal symptom score.

minor AEs were reported in 9 (12.0%) patients. Respiratory symptoms including dyspnea or stridor were reported in 4 patients, accounting for 5.3% in the SLITwE group. In the SLITsE group, 28 experienced AEs. Among them, 25 (32.1%) complained of an aggravation of symptoms, 9 (11.5%) reported local irritation symptoms, 4 (5.1%) experienced gastrointestinal symptoms, and other minor symptoms were found in 10 patients. Major AEs were reported in 3 patients (3.8%) in the SLITsE group. In the patients who reported dyspnea or stridor, all the symptoms improved within a few minutes without any medication,

and there were no anaphylactic events that required further treatment (Table 2).

Satisfaction

The patients' subjective satisfaction was ascertained by questionnaires after at least 6 months of SLIT use. In the SLITwE group, 47.6% of patients were satisfied with SLIT, 45.2% selected fair, and 7.1% were dissatisfied with SLIT. In the SLITsE group, 73.5% were satisfied, 23.5% selected fair, and 2.9% were dissatisfied with SLIT.

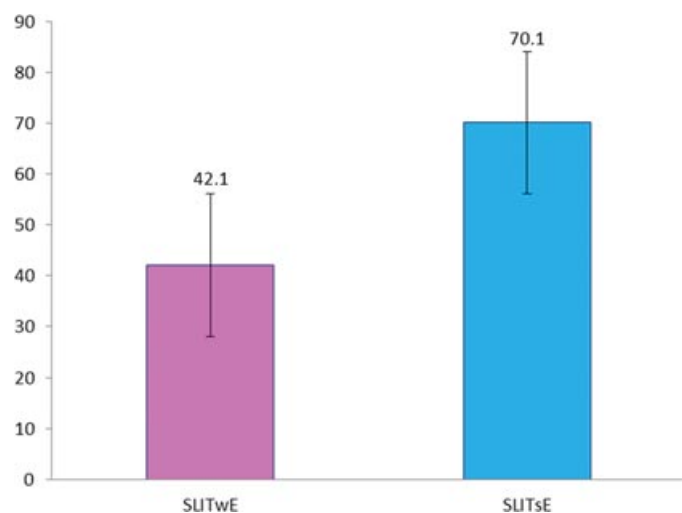


FIGURE 2. The difference in the TNSS between sublingual immunotherapy groups with or without escalation. The SLITsE group showed a higher score, suggesting that the level of symptom improvement was better in the SLITsE group. $T = -3.36$, $p = 0.0001$. Independent t test. SLIT = sublingual immunotherapy; SLITsE = SLIT without escalation; SLITwE = SLIT with a conventional escalation regimen; TNSS = total nasal symptom score.

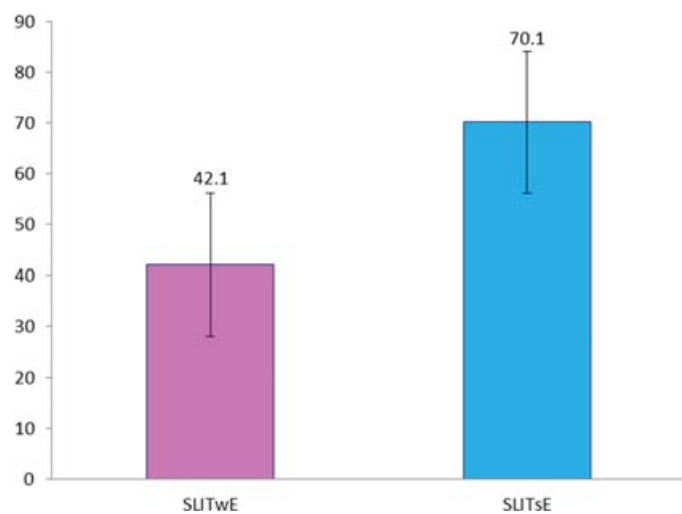


FIGURE 3. The difference in the RMS between sublingual immunotherapy groups with or without escalation. The SLITsE group showed a higher score, suggesting that the level of medication use was markedly decreased in the SLITsE group. $T = -2.13$, $p = 0.037$. Independent t -test. SLIT = sublingual immunotherapy; SLITsE = SLIT without escalation; SLITwE = SLIT with a conventional escalation regimen; RMS = rescue medication score.

Dropout rate

The dropout rate was calculated and substituted for compliance in this study. In the SLITwE group, among the 75 enrolled patients, 21 dropped out, resulting in a dropout rate of 28.0%. The reasons for quitting SLIT were determined by a telephone survey. The most frequent answer was the inability to take medication according to the schedule. A lack of efficacy/symptom improvement, AEs, the cost, and the discomfort of regularly visiting a hospital were also provided as reasons for quitting. In the SLITsE group, the dropout rate was 26.9% (21 dropped out among the 78 patients enrolled). An inability to take medication accord-

TABLE 2. Adverse events in 1 month of SLIT by patients with house dust mite-induced allergic rhinitis*

Group	SLITwE (n = 75)	SLITsE (n = 78)
Major adverse events ^a		
Respiratory symptom	4 (5.3%)	3 (3.8%)
Minor adverse events		
Aggravation of allergic symptom	29 (38.7%)	25 (32.1%)
Local irritation symptom	7 (9.3%)	9 (11.5%)
Gastrointestinal symptom	8 (10.6%)	4 (5.1%)
Other minor symptom	9 (12.0%)	10 (12.8%)
The number of patients with adverse events	29	28

*Numbers are not mutually exclusive.

^aMajor adverse symptoms subside in minutes without specific treatment. SLIT = sublingual immunotherapy; SLITsE = SLIT without an escalation regimen; SLITwE = SLIT with a conventional escalation regimen.

TABLE 3. The causes for the discontinuation of SLIT by patients with house dust mite-induced allergic rhinitis

Group	SLITwE (n = 75)	SLITsE (n = 78)
Inability to take medication according to schedule	6	6
Adverse events (aggravation of symptom, edema, urticaria)	3	4
Lack of efficacy/symptom improvement	3	3
Cost	2	3
Discomfort in regularly visiting a hospital	2	2
Others	5	3
Total	21	21

SLIT = sublingual immunotherapy; SLITsE = SLIT without an escalation regimen; SLITwE = SLIT with a conventional escalation regimen.

ing to the schedule was the most frequently given reason (6 patients), followed by AEs, a lack of efficacy/symptom improvement, and the cost and discomfort of regularly visiting a hospital (Table 3).

Discussion

The authors performed a short-term observational study between a once-daily SLITsE group and a conventional SLITwE group. The patients were recruited and treated with SLIT from July 2008 to December 2008 in the SLITwE group and from July 2009 to December 2009 in the SLITsE group. Although there was a time difference between the 2 groups, to exclude the seasonal variance of allergen, the season was adjusted to July to December because symptoms are more severe and more common in the late summer and early autumn in Korea (a high concentration of HDM

allergens in the environment), although HDM allergens are perennial.

All of the nasal symptom scores were significantly decreased in both groups but eye symptoms did not decrease in the SLITwE group. The RMS also significantly decreased in both groups. SLITsE appeared to show the same efficacy as SLITwE in early observations. According to a study on individual seasonal symptoms of eye and nose and grass allergen tablet immunotherapy, eye and nose symptoms were shown to decrease at a 2-month follow-up after allergen tablet immunotherapy.²² Because our study was a short-term observational study, eye symptoms may have shown a significant decrease in the SLITwE group in a longer follow-up.

In our present study, the incidence of AEs was 38.7% and 35.9% in the SLITwE and SLITsE group, respectively, which was comparable to the 48% in our previous study.²¹ The most frequently reported AE was the aggravation of allergic symptoms. There was no difference between the SLITwE and SLITsE groups in terms of the frequency or percentage of the AEs. Although suspected major respiratory symptoms subsided spontaneously, dyspnea and stridor occurred in 5.3% of patients in the SLITwE group and 3.8% of patients in the SLITsE group. AEs, such as aggravation of allergic symptoms, local irritation, edema, and urticaria, were the second most common reason for discontinuing SLIT in our study. While this is primarily a safety study, it is underpowered to meaningfully determine if there is a difference in anaphylaxis between the 2 groups as anaphylaxis is uncommonly reported in SLIT. Long-term studies are required to identify predictive factors of AEs.

The satisfaction rate for each group was 47.6% in the SLITwE group and 73.5% in the SLITsE group. The results of the SLITwE group were similar to 46% of satisfaction rate obtained in our previous study.²¹ In a further survey to identify why a patient rated their experience as satisfied, both symptoms and allergic tendency improved in 24% of patients, whereas only symptoms improved in 76%. Among the patients who chose fair or dissatisfied, 22.5% reported that there was no symptom improvement, 68% reported that their symptoms improved, but the allergic tendency still remained higher than their expectations, 9.5% answered that their symptoms improved, but it was too uncomfortable to perform SLIT. Accordingly, patient satisfaction will increase if the allergic tendency decreases following symptom improvement. A previous study reported that the proportion of satisfied patients is becoming higher in 3-year immunotherapy groups than in 1- or

2-year groups, which may suggest that better satisfaction can be obtained with the long-term use of SLIT.²³ The reason that patient satisfaction in the SLITsE group was higher is not clear; however, we speculate that better efficacy and the ease of use without schedule changes during the buildup period may underlie the greater patient satisfaction in the SLITsE group.

The compliance rates were 28.0% and 26.8% ($p = 0.231$) in the SLITwE and SLITsE groups, respectively. The results were similar to our previous study, which showed a compliance rate of 31.0%. We had hypothesized that the dropout rate would be lower in the SLITsE group due to the convenience of administration compared with SLITwE group. However, there was no statistical difference in our study. It is possible that compliance is not only influenced by convenience but also by socioeconomic and cultural reasons, which were reported as reasons for dropping out. According to our study, even if the administration methods were changed to a more convenient form, there might still be a fixed dropout rate in Korea.

It is unclear why the SLITsE group showed better improvements in TNSS and RMS than the SLITwE group. However, we can speculate that the high concentration of allergen extracts applied every day for SLITsE treatment may facilitate its clinical effects.

Although several reports have suggested the effectiveness of once-daily SLITsE in grass pollen allergic rhinitis, this study may be the first to evaluate the efficacy and safety of once-daily SLITsE in HDM-induced allergic rhinitis.²⁴ Although this study investigated the short-term results, once-daily SLITsE appeared to be more effective and satisfactory to the patient with HDM-induced allergic rhinitis in Korea than SLITwE. Long-term studies, however, will be needed.

Conclusion

Once-daily SLITsE was proven to be a safe and well-tolerated method and could be an alternative administration method for HDM-sensitized allergic rhinitis patients. However, future studies are required to evaluate the long-term clinical efficacy of SLITsE and to elucidate the predicting markers for responsiveness to SLIT. ④

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