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Sublingual Immunotherapy in Asian Children: 2-Year Follow-Up Results

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Backgrounds: House-dust mites are the main cause of allergic rhinitis in Asia, for which immunotherapy (SLIT) is a currently accepted treatment. However, few studies have evaluated the efficiency of SLIT on Asian children with allergic rhinitis for a period longer than one year. The aim of this study was to investigate the efficacy and safety of SLIT for Asian children with allergic rhinitis due to house-dust mites over a 2-year period.

Materials and Method: This study included 65 patients who had allergic rhinitis due to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. All patients were treated with SLIT (Staloral®). Symptom scores and quality of life were evaluated by using questionnaires over two years. The medication score was assessed monthly by a diary medication card and serologic tests were evaluated before and two years after the start of treatment. Adverse effects and dropout rates were also investigated.

Results: All nasal and non-nasal symptoms and quality of life were significantly improved after two years of treatment. Furthermore, the total medication score decreased significantly and the serologic tests showed a significant change two years after the start of SLIT. Although minor adverse effects were reported, no systemic reactions were observed. The dropout rate was 40%.

Conclusion: SLIT is an efficient and safe therapeutic tool for a period of two years in Asian children with allergic rhinitis to house-dust mites.

KEY WORDS: Sublingual immunotherapy · Allergic rhinitis · House-dust mite · Quality of life · Children.

INTRODUCTION

Allergic rhinitis is one of the most prevalent problems in the developed world. Recent studies suggest that approximately 20% of children in South Korea live with allergic rhinitis and the prevalence might be as high as 32%.[1)] Kong et al. reported a prevalence of 10.8% of allergic rhinitis in children in central China.[2)] Similarly, in Singaporean and Vietnamese preschoolers, the cumulative prevalence of allergic rhinitis was 25.3% and 34.9%, respectively.[3)] Because of its increasing prevalence and impact on quality of life, allergic rhinitis is associated with a substantial medical care cost for both individuals and the society as a whole.[4)]

To our knowledge, the treatments for allergic rhinitis are classified as education, allergen avoidance, symptomatic medication, and immunotherapy. Among these treatments, specific immunotherapy is the only one that modifies the immune reaction. Specific immunotherapy involves the administration of increasing doses of the causal allergen extract in order to induce clinical tolerance toward the causal allergen in a gradual manner. Since the introduction of specific immunotherapy 100 years ago, specific immunotherapy has been administered through subcutaneous immunotherapy (SCIT). SCIT is known as an effective method for

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changing the natural course of allergic rhinitis and it has long-term effects.[5)6)] However, because SCIT is associated with some risks that may cause systemic or even fatal reactions, alternative administration route methods are required.[7)]

While sublingual immunotherapy (SLIT) has been used safely and effectively in Europe since 2005,[8)] the effect of SLIT on children has been evaluated in only a few clinical trials. Instead, it is presumed that the results of adult trials are applicable to children, however, this is not always true. A safer and simpler approach is particularly important for pediatric patients. Some of the clinical trials that assessed SLIT for house-dust mites were conducted in European children with allergic rhinitis to confirm the efficacy of SLIT in children. This trial demonstrated significantly improved symptoms, decreased symptomatic medication use, and generally good tolerability, which are similar to the results of the adult trials.[9)] However, it is not known whether the therapeutic results of SLIT from clinical trials in European children can be extrapolated to Asian children because sensitization patterns and environmental factors might differ.

We previously reported the efficiency and safety of SLIT for Asian children during 1 year.[6)] However, few studies have been performed in Asian children with allergic rhinitis sensitized to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* for a longer period, such as 2 years. Thus, the aim of this study was to investigate the efficacy and safety of SLIT for Asian children with allergic rhinitis to the house-dust mite for 2 years.

MATERIALS AND METHODS

Subjects

The study was performed at the Department of Otorhinolaryngology of the Korea University Guro Hospital in Seoul, Korea. Patients who started SLIT between January 2009 and January 2011 were recruited in this study. The study population comprised 65 subjects (39 boys and 26 girls) ranging in age from 6 to 15 years. The indications of SLIT were moderate to severe or persistent symptoms, insufficient control by conventional pharmacotherapy, poor compliance to medication, and refusal of injections. House-dust mite allergic rhinitis was diagnosed by clinical history and positive allergen-specific skin tests (wheal diameter $\geq$10 mm) to house-dust mite extract or Immuno CAP test (Phadia AB, Uppsala, Sweden) to house-dust mites (*D. pteronyssinus* or *D. farinae*). Exclusion criteria were as follows: multiple skin sensitization, previous immunotherapy courses, irreversible airway obstruction, systemic or immunologic problems, malignancies, psychiatric disorders, and pregnancy. The study protocol was approved by the Institutional Review Board of the Korea University College of Medicine (KUGH11132), and informed written consent was obtained from the subjects.

Sublingual immunotherapy

SLIT was prescribed to patients with allergic rhinitis sensitized to *D. pteronyssinus* and *D. farinae*. A standardized house-dust mite extract (Staloral®, Stallergenes, France) was used for immunotherapy. The medication was administered according to the manufacturer's instructions. The patient received the vaccine sublingually, kept it for 2 minutes without retention reagent, and then swallowed it. The procedure was repeated with each vial. The dose is measured in full presses, not in drops. SLIT consisted of a build-up phase of 11 days and a maintenance phase. SLIT was started at the lowest concentration (1 dose, 10 IR/mL), and gradually increased to 10 daily doses of 10 IR/mL solution for the first 6 days. During the following 5 days of the build-up phase, patients increased their daily intake from 1 to 8 doses of 300 IR/mL. Once the build-up phase was achieved, the patients began the maintenance phase in which they took 4 doses of the medicine every day. Follow-up was performed monthly during the first 3 months, and the patients were subsequently asked to visit the hospital every 3 months.

Symptom and medication scoring

The patients or their parents were instructed to keep a diary during the treatment period for a daily evaluation of symptoms according to the following 4-point scoring system for each nasal symptom: 0 (no symptoms), 1 (symptoms present, not bothering the patient), 2 (symptoms present, bothering the patient), and 3 (severe symptoms impairing daily activities). The symptoms included rhinorrhea, nasal obstruction, nasal itching, and sneezing. The sum of all 4 nasal symptoms was termed the total nasal score. Non-nasal symptoms such as eye itching, epiphora, itching palate, and eye redness were evaluated by the same methods. The sum of all 4 non-nasal symptoms was termed the total non-nasal score. The patients were allowed to use medications if needed, and they were asked to record use of medication on the diary card. Medication was recorded based on drug characteristics using a code of 1 for anti-histamines and 2

for topical nasal steroids.[8] The individual daily symptom and medication scores were recorded on a daily basis for the entire study period and the mean of the 1 monthly score was calculated.

Quality of life

Quality of life measure was based on the quality of life questionnaire, which consists of 7 items: sleep disturbances, nonrhinitis symptoms, generalized symptoms, practical problems, nasal symptoms, ocular symptoms and emotional disturbances. Responses were scored on a 5-point symptom scale: not affected 0), mildly bothered 1), modestly bothered 2), moderately bothered 3), and severely bothered 4). When evaluating the effects of SLIT on quality of life, clinical improvement was defined as reduction of at least 1 point after treatment.

Serologic tests

Blood was collected from the patients' venous plexus before treatment and 2 years after SLIT. Serum levels of *D. pteronyssinus*- and *D. farinae*-specific IgG4, IgE, and eosinophil cationic protein (ECP) were determined by enzyme immunoassay following the CAP System RAST FEIA method (Phadia, Uppsala, Sweden). Measurements were made at the end of the study by using the same assay for each evaluated parameter.

Adverse events

The participants recorded adverse events, including aggravation of symptoms, skin itching or rash, a sense of itching of the oral cavity or lip, eye discomfort, gastrointestinal problems, or anaphylactic shock, on the symptom-medication diary cards every day.

Dropout rate

The dropout rate was assessed, and the patients were asked to specify the reasons that they dropped out at the end of the treatment.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). The results are expressed as the mean±SE. The Wilcoxon signed rank test was used to analyze symptom scores, total medication scores, and quality of life (before and 2 year after SLIT). $P<0.05$ was defined as statistical significance.

RESULTS

A total of 140 patients initially enrolled in this prospective study, but 28 patients refused to participate. Therefore, 112 patients were started on SLIT and 65 patients (39 boys and 26 girls; age range, 6−15 years; mean±SE, 11.3±0.43 years) were treated for 2 years and completed questionnaires (Fig. 1).

Symptom and medication score

All nasal symptom scores including sneezing, rhinorrhea, nasal obstruction, and itchy nose decreased significantly after SLIT. The total nasal symptom score also decreased significantly after SLIT (Fig. 2). Scores for non-nasal symptoms including itchy eyes, epiphora, and red eyes and the total non-nasal symptom score were decreased after SLIT. However, the score for itching palate as non-nasal symptoms was not significantly decreased after SLIT (Fig. 3). The total medication score gradually decreased with time (Fig. 4).

Quality of life

Assessment of quality of life revealed that sleep disturbances, nonrhinitis symptoms, practical problems, nose

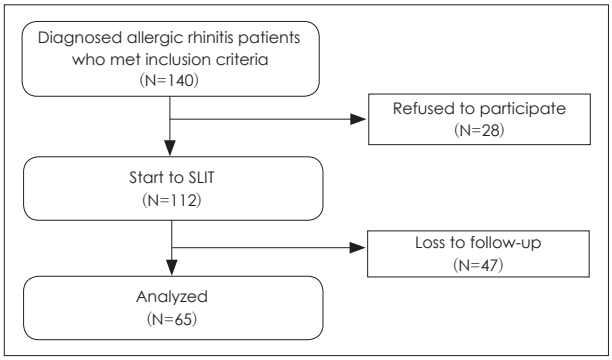

Fig. 1. Demographics of the study

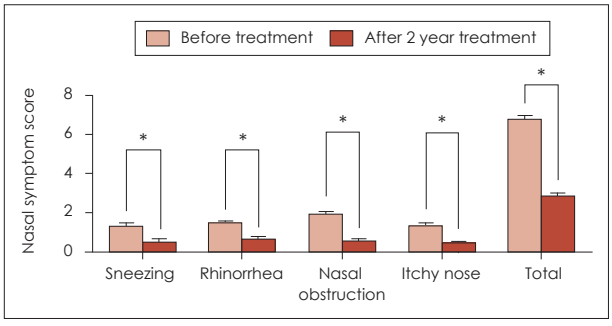

Fig. 2. Nasal symptom score before treatment and 2 years after sublingual immunotherapy. All nasal symptom scores and total symptom scores were decreased significantly after sublingual immunotherapy. *: $p<0.05$.

symptoms, eye symptoms, and emotional disturbances were improved after SLIT. Of the items related quality of life, the scores for practical problem and nose symptoms showed a definite decrease 2 years after SLIT. However, generalized symptoms related to quality of life were not improved after SLIT (Fig. 5).

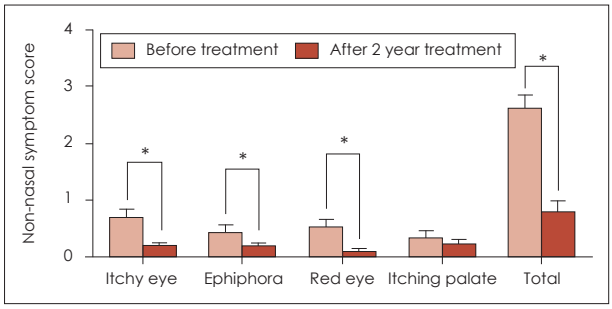

Fig. 3. Non-nasal symptom score before treatment and 2 years after sublingual immunotherapy. The symptom scores of itchy eye, epiphora, and red eye and the total symptom score were decreased significantly after sublingual immunotherapy. *: $p<0.05$.

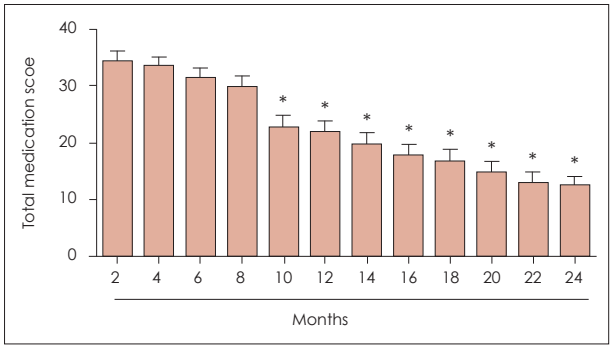

Fig. 4. Change in the total medication score during sublingual immunotherapy. The medication score gradually decreased with time after sublingual immunotherapy, with a statistically significant decrease of the total medication score observed 10 months after sublingual immunotherapy. *: $p<0.05$.

Serologic tests

Total IgE, IgG4, and ECP levels were evaluated. The total IgE and the IgE/IgG4 ratio were significantly decreased at 2 years. Furthermore, the ECP level was decreased (Fig. 6).

Adverse events

Adverse events were reported by 43 patients (58.9%), including aggravation of symptoms in 21 patients (48.8%), an itching sensation of the oral cavity or lip in 11 patients (25.5%), gastrointestinal problems in 6 patients (13.9%), skin itching or rash in 3 patients (4.5%), and eye discomfort in 2 patients (3.5%). Life-threatening adverse effects did not occur (Table 1).

Dropout rate

The dropout rate was 40% (48 patients) in our study. The most common reason for dropout was adverse effects (43.7%), followed by lack of efficacy (29.2%), inconve-

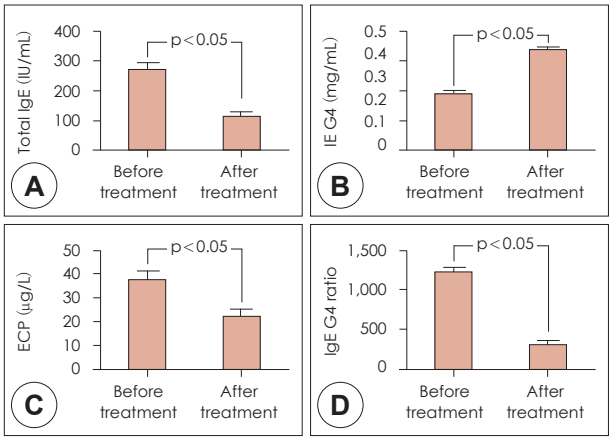

Fig. 6. Total IgE was significantly decreased at 2 years (A). IgG4 was significantly increased at 2 years (B). In addition, the level of ECP was decreased at 2 years (C). The IgE/IgG4 ratio showed a similar significant reduction (D). *: $p<0.05$ vs. before treatment.

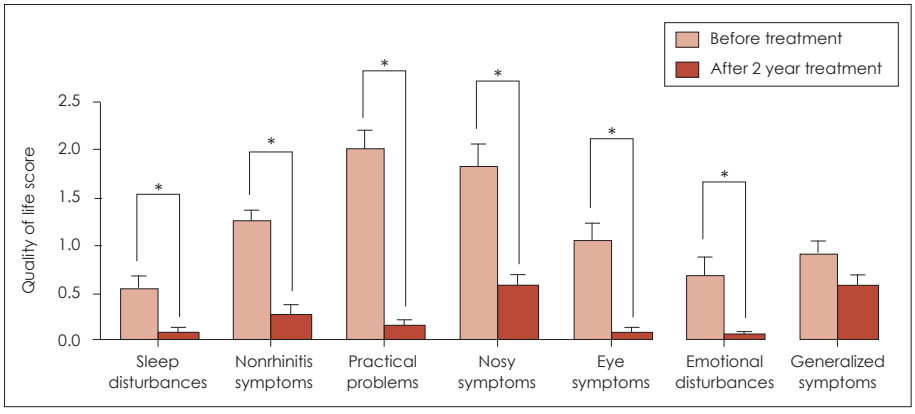

Fig. 5. Quality of life score before treatment and 2 years after sublingual immunotherapy. Sleep disturbances, nonrhinitis symptoms, practical problems, nose symptoms, eye symptoms and emotional disturbances were improved after sublingual immunotherapy. *: $p<0.05$.

Table 1. Adverse effects reported by patients in this study

Adverse effects	Number (%)
Aggravation of symptoms	21 (48.8)
Itching sensation in the oral cavity or of the lip	11 (25.5)
Gastrointestinal trouble	6 (13.9)
Eye discomfort	3 (4.5)
Skin itching or rash	2 (4.5)
Anaphylactic shock	0 (0.0)

Table 2. Reasons for dropout

Reasons for dropout	Number (%)
Adverse effects	21 (43.7)
Lack of efficacy	14 (29.2)
Inconvenient application	8 (16.6)
No time to visit the office	5 (10.4)

nient application (16.6%), and no time to visit the office (10.4%) (Table 2).

DISCUSSION

The house-dust mite is one of the common allergen in pediatric patients with allergic rhinitis.[9-11] Natural remission of the disease is rare in childhood and the condition carries over to adulthood in most patients. Allergen-specific SCIT is the current therapy that can alter the natural course of this condition. However, the treatment has practical inconveniences.[12-14] SLIT has been proposed as an effective alternative, but recent reviews indicate that the efficacy of SLIT in pediatric house-dust mite allergic rhinitis has not yet been shown.[6-8] Furthermore, few studies have investigated the effect of SLIT in Asian children with allergic rhinitis sensitized to the house-dust mite. The recommended duration of SLIT is reliant on empiric data and is not well documented. In our opinion, an adequate SLIT should guarantee clinical efficacy with significant reduction of the symptoms and medication needs and should have a good safety profile without unpredictable systemic reactions. To date, few studies have attempted to identify the proper duration of SLIT required to fulfill these requirements for Asian children. To our knowledge, this is the first trial that prospectively explored the currently recommended duration and efficiency of SLIT for Asian children with allergic rhinitis sensitized to the house-dust mite.

According to the change in the nasal symptom scores, sneezing, rhinorrhea, nasal obstruction, and itchy nose were significantly improved after SLIT. The change in the score was marked at 1 year after SLIT, although each of the nasal symptom scores decreased between 1 and 2 years after SLIT. Non-nasal symptom scores such as itchy eye, epiphora, and red eye were also improved after SLIT. However, itching palate was not improved after SLIT. Both total nasal and total non-nasal scores were significantly decreased at 2 years after SLIT.

In the last few years, the patient's point of view has become more important both in clinical practice and in therapeutic evaluation.[15-17] Accordingly, quality of life questionnaires were included as primary endpoint. However, few studies have been performed concerning the long-term quality of life after SLIT in Asian children with allergic rhinitis. In this study, quality of life was evaluated with a questionnaire. Improvements in quality of life were shown in terms of sleep disturbances, non-rhinitis symptoms, practical problems, nose symptoms, eye symptoms, and emotional disturbances, but not for generalized symptoms. Ciprandi *et al*.[18] reported similar results for Western children. Although no systemic side effects were reported in this study, 43 patients (56.3%) reported adverse effects. Aggravation of symptoms was reported most commonly (48.8%), followed by a sense of itching of the oral cavity or lip (25.5%). The dropout rate is a cornerstone for the efficacy of any medical treatment. We excluded patients who had discontinued SLIT as well as those whose cumulative doses were too low and could potentially compromise the efficacy of SLIT. We observed a dropout rate of 40% at 2 years in this study, whereas the dropout rate was 21% in our previous report for 1-year follow-up after SLIT. Vita *et al*. pointed out that the dropout rate is higher in patients who attend fewer clinical visits per year.[19] In the present study, a caregiver performed close check-up and consultation with the patient and their parents, and the patients were asked to visit the hospital every 3 months thereafter. This suggested that regular check-ups are required in order to decrease the dropout rate. Our rate is consistent with the wide range of compliance rates reported among subjects following SLIT, which vary from 16% to 80%.[20] The reasons for dropout were adverse effects (43.7%), followed by lack of efficacy (29.2%), inconvenient application (16.6%), and no time to visit the office (10.4%). Although the effects of SLIT on immunoglobulin isotypes have been studied, the changes in allergen-specific IgE or IgG do not appear to be reproducible.[21] However, previous results indicated that SLIT does not increase the levels of allergen-specific IgG1 and IgG4 antibodies,

which are consistently upregulated during SCIT.[22] Further, the serum level of total IgE antibodies was shown to be significantly reduced after therapy, whereas eosinophil counts and ECP are decreased significantly after 1 year of follow-up.[23] From this point of view, our results were similar to those of previous studies. Based on our previous findings after 1 year of SLIT, we expected that the dropout rate would increase in a study that proceeded for longer than 1 year and that the results of serologic tests would change significantly. The findings of this study are consistent with our expectations, and a study with a larger number of patients and a longer follow-up period is ongoing. The most obvious limitation of this study is its design, per-protocol analysis. Per-protocol analysis includes subject who completed the study without any major protocol violations. Thus, study the efficacy of sublingual immunotherapy are likely to overestimate in actual clinical results. However, we analyzed the reasons for drop out and observed no significant life-threatening adverse effects.

This study demonstrated the safety and effectiveness of Staloral® in Asian children with allergic rhinitis sensitized to house-dust mites for a period of 2 years, supporting the effect of SLIT in this population. To investigate the long-term effect of SLIT in Asian children, more long-term follow-up results are required. Our next study will focus on the persistence of the effect of SLIT.

Acknowledgments

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