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Efficacy and safety of sublingual immunotherapy in Asian children

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ABSTRACT

Objective: Sublingual immunotherapy is currently accepted as a suitable alternative to subcutaneous immunotherapy because of its easy and painless administration and improved safety. Many clinical trials have demonstrated that sublingual immunotherapy is an effective and safe treatment for pollen or mite allergic rhinitis. However, there have been very few studies overall on children with allergic rhinitis who are sensitized to house-dust mites in Asia. The purpose of the present study was to investigate the efficacy and safety of sublingual immunotherapy in children with allergic rhinitis to house-dust mites. **Methods:** A total of 112 patients under the age of 15 who had allergic rhinitis to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were included. All patients were treated with sublingual immunotherapy (Staloral[®]). Symptom scores and quality of life were evaluated by questionnaires until one year after sublingual immunotherapy. The medication score was assessed monthly using a diary medication card and serologic tests were evaluated before and 6 and 12 months after treatment. Adverse effects and compliance were also investigated.

Results: All nasal and non-nasal symptoms and quality of life were significantly improved after treatment. The total medication score was decreased significantly after sublingual immunotherapy. There was no significant change in serologic tests. Some minor adverse effects were reported, however there were no systemic reactions. The drop-out rate was 21%.

Conclusions: Sublingual immunotherapy is a valuable therapy for the treatment of allergic rhinitis in Asian children sensitized to house-dust mites.

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1. Introduction

Allergic rhinitis is a very common condition, with a high and increasing worldwide prevalence. The age of onset of allergic rhinitis is also decreasing, and the influence of the disease in younger patients is becoming an important issue [1]. Although allergic rhinitis is not a life-threatening disease, it impairs school performance and is not easy to treat in children [2].

The management of allergic rhinitis includes patient education, pharmacotherapy, and allergen-specific immunotherapy. Among these, allergen-specific immunotherapy is the only treatment that modifies the immune response [3]. Allergen-specific immunotherapy is the practice of administering allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure to the causative allergen.

Subcutaneous immunotherapy (SCIT) has been demonstrated to change the immune response in allergic rhinitis [4,5]. However,

it has certain risks including systemic reactions that may be life threatening [6]. Compliance is another problem associated with SCIT [7]. These problems become even more important when considering treatment for children.

Sublingual immunotherapy (SLIT) is currently accepted as a suitable alternative to SCIT. Compared with SCIT, SLIT is an easy and painless treatment method for allergic rhinitis, with the added benefit of improved safety. Many clinical trials have demonstrated that SLIT is an effective and safe treatment for allergic rhinitis induced by pollen or mites [8–10]. However, there have been few studies in children with allergic rhinitis who are sensitized to house-dust mites and only one study in Asia, which was not specifically related to children. The purpose of the present study was to investigate the efficacy and safety of SLIT in Asian children with allergic rhinitis induced by house-dust mites.

2. Materials and methods

2.1. Subjects

This study was performed at the Department of Otorhinolaryngology of Korea University Guro Hospital in Seoul, Korea.

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Patients who started SLIT between January 2009 and January 2011 were recruited into this study. Inclusion criteria were patient age more than 6 and less than 15 years, and a history of allergic symptoms and sensitization to house-dust mites (*Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*) as assessed by a skin prick test or multiple allergen simultaneous test (Optigen[®], Hitachi, Japan). Exclusion criteria were included 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 written informed consent was obtained from all participants.

2.2. Sublingual immunotherapy

SLIT was prescribed to patients with allergic rhinitis who were sensitized to *D. pteronyssinus* and/or *D. farinae*. A standardized house-dust mite extract (Staloral[®], Stallergenes, France) was used for immunotherapy. Administration of the medication was performed according to the manufacturer's instructions. Immunotherapy consisted of 11 days of a build-up phase followed by a maintenance phase. SLIT was started at the lowest daily dosage (one dose, 10 IR/ml), and was gradually increased to ten doses of 10 IR/ml over the first 6 days. During the next five days of the build-up phase, patients took increasing doses daily, from one to eight doses of 300 IR/ml. Once the build-up phase was completed, the patients took four doses every day during the maintenance phase. Follow-up was performed monthly during the first three months. After that time, the patients were asked to visit the hospital every three months.

2.3. Scoring of symptoms and medications

Patients (or their parents) were instructed to keep a diary during the treatment period for daily evaluation of nasal symptoms (rhinorrhea, nasal obstruction, nasal itching, and sneezing) according to a four-point scoring system from 0 (no symptoms) to 3 (severe symptoms) for each symptom. The sum of all four nasal symptoms was defined as the total nasal score. Non-nasal symptoms (itching or redness of the eyes, tearing, and itching of the palate) were evaluated by the same method and the sum of all four non-nasal symptoms was defined as the total non-nasal

score. The patients were allowed to use medications if needed and were asked to record on the diary card whenever they used medications. The medication score was 1 for antihistamines, 2 for intranasal steroids, and 3 for oral corticosteroids. The individual symptom and medication scores were recorded on a daily basis over the entire study period and the mean of the monthly score was calculated.

2.4. Quality of life

Measurement of quality of life was based on a quality of life questionnaire, which consisted of seven items: sleep problems, generalized symptoms, practical problems, nasal symptoms, ocular symptoms, activities, and emotions. Responses were scored on a five-point scale: 0, not affected; 1, mildly affected; 2, modestly affected; 3, moderately affected; and 4, severely affected.

2.5. Serologic tests

Total IgE, IgG, IgG1, IgG4, WBC differential counts, and level of eosinophil cationic protein (ECP) were measured before treatment, and after 6 and 12 months. Each parameter was analyzed to evaluate the immunologic changes after SLIT.

2.6. Adverse events

Participants recorded adverse events, including aggravation of symptoms, skin itching or rash, itching sensation in the oral cavity or of the lip, eye discomfort, gastrointestinal trouble, or anaphylactic shock, on the symptom-medication diary cards every day.

2.7. Compliance

The drop-out rate was assessed, and the patients were asked to explain why they dropped out.

2.8. Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). The results are expressed as the mean $\pm$ SE. The Wilcoxon signed-rank test was used to analyze symptom scores, total medication scores, and quality of life (before,

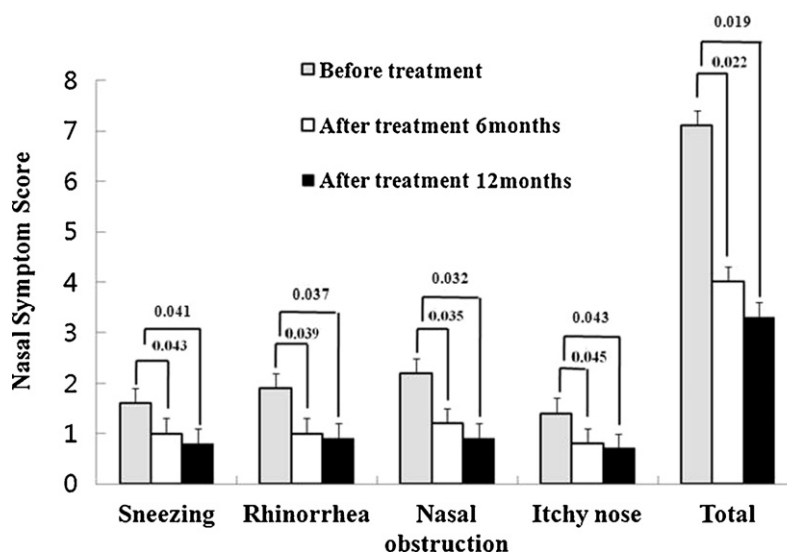


Fig. 1. Nasal symptom scores before treatment and 6 and 12 months after sublingual immunotherapy. All individual nasal symptom scores and the total symptom score decreased significantly after sublingual immunotherapy.

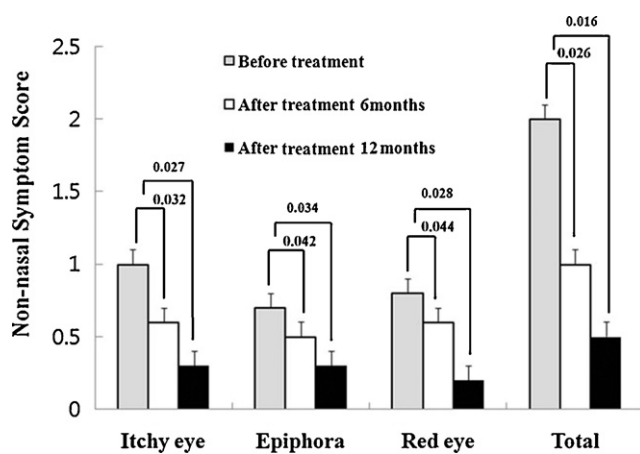


Fig. 2. Non-nasal symptom score before treatment and 6 and 12 months after sublingual immunotherapy. The scores for symptoms of itchy eyes, epiphora, and red eyes and the total symptom score decreased significantly after sublingual immunotherapy.

and 6 and 12 months after SLIT). p -Values <0.05 were considered statistically significant.

3. Results

3.1. Demographics and baseline characteristics

A total of 140 patients under the age of fifteen met the inclusion criteria in this prospective study, and 28 of these refused to participate. Thus, 112 patients were started on SLIT and 88 patients (49 males and 39 females aged 5–15 years, with a mean age of 9.6 years) were treated for 12 months and completed the questionnaires.

3.2. Symptom and medication scoring

All nasal symptom scores including sneezing, rhinorrhea, nasal obstruction, and itchy nose decreased significantly after SLIT. The

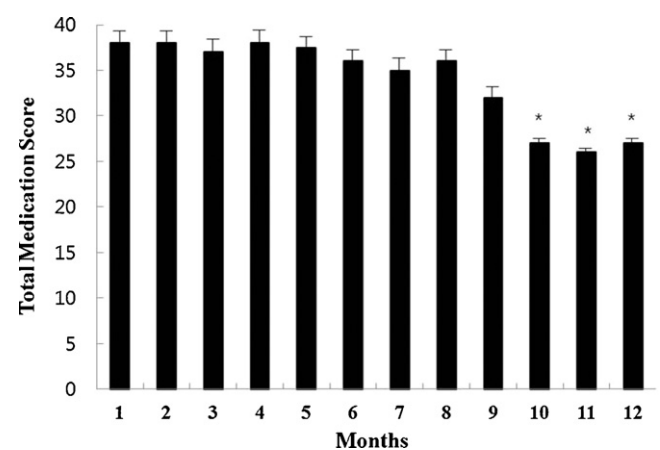


Fig. 3. Change in the total medication score during sublingual immunotherapy. After initiation of sublingual immunotherapy, the medication score gradually decreased over time. From ten months after sublingual immunotherapy onwards, a statistically significant decrease in the total medication score was observed (* $p < 0.05$).

total nasal symptom score also decreased significantly after SLIT. There was no significant change in nasal symptom scores between 6 months and 12 months after SLIT (Fig. 1). Scores for non-nasal symptoms including itchy eyes, epiphora, and red eyes, were also decreased after SLIT, and the total non-nasal symptom score was significantly decreased after SLIT. There was no significant changes in any of the non-nasal symptom scores between 6 months and 12 months after SLIT (Fig. 2). The total medication score gradually decreased with time (Fig. 3).

3.3. Quality of life

Based on responses to the quality of life questionnaire, sleep, non-rhinitis symptoms, practical problems, nose symptoms, eye symptoms, and emotions all improved after SLIT (Fig. 4). There were marked changes in nasal and non-nasal symptoms and quality of life at six months after treatment.

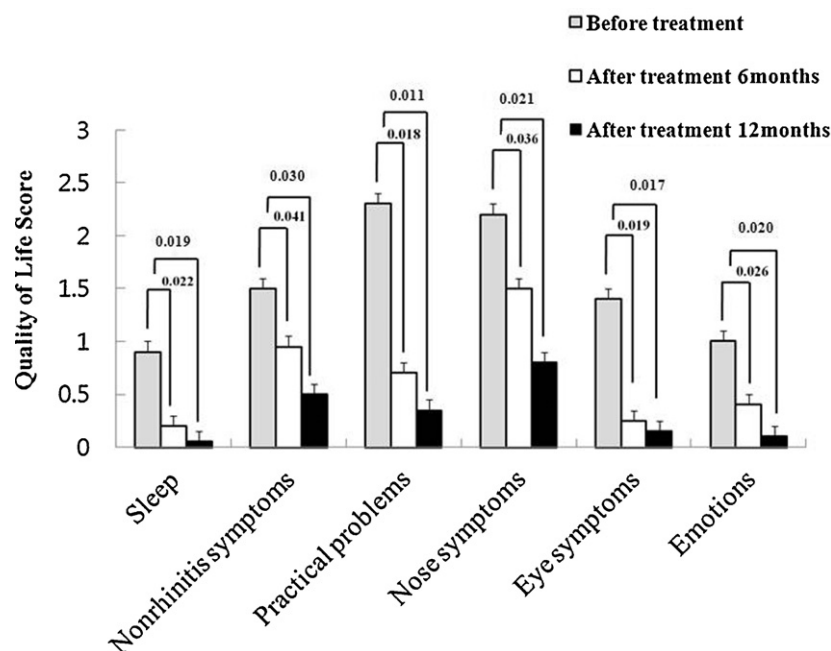


Fig. 4. Quality of life score before treatment and 6 and 12 months after sublingual immunotherapy. Sleep, non-rhinitis symptoms, practical problems, nose symptoms, eye symptoms, and emotions all improved after sublingual immunotherapy.

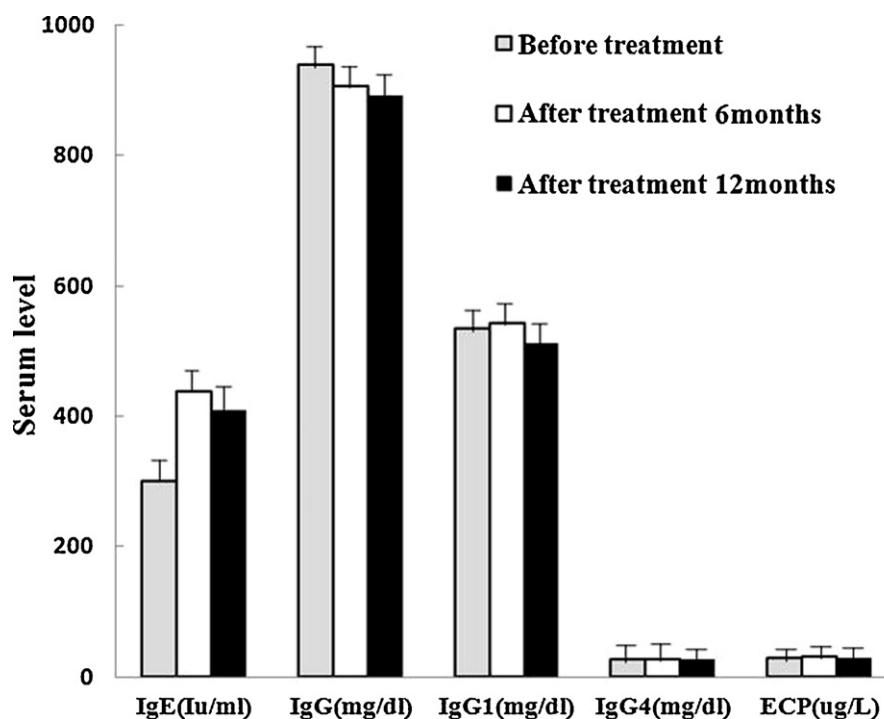


Fig. 5. Serologic test score before treatment and 6 and 12 months after sublingual immunotherapy. Total IgE, IgG, IgG1, IgG4, and eosinophil cationic protein levels did not change significantly after sublingual immunotherapy (* $p < 0.05$).

3.4. Serologic tests

Total IgE, IgG, IgG1, IgG4, WBC differential counts, and ECP level did not change significantly after SLIT (Fig. 5).

3.5. Adverse events

Thirty patients (34.1%) reported 48 adverse effects including symptom aggravation in 16 patients (18.1%), itching sensation in the oral cavity or of the lip in 13 (14.8%), gastrointestinal trouble in 11 (12.6%), eye discomfort in 4 (4.5%), and skin itching or rash in 4 (4.5%) (Table 1). There were no life-threatening adverse effects.

3.6. Compliance

The drop-out rate was (24 of 112 patients) 21%. The most common reason for drop-out was adverse effects (33.4%), followed

by lack of efficacy (33.4%), inconvenient application (20.8%), and no time to visit the office (12.5%) (Table 2).

4. Discussion

The purpose of this study was to determine the efficacy and safety of SLIT in Asian children with allergic rhinitis induced by house-dust mites. According to the change in the nasal symptom scores, sneezing, rhinorrhea, nasal obstruction, and itchy nose significantly improved after SLIT. The change in the scores was marked at six months after SLIT. Between 6 months and 12 months after SLIT, each nasal symptom score further decreased, but the difference was not statistically significant. Scores for non-nasal symptoms including itchy eyes, epiphora, and red eyes were also improved. Both the total nasal and total non-nasal scores decreased significantly after SLIT. Quality of life was improved in terms of sleep, non-rhinitis symptoms, practical problems, nose symptoms, eye symptoms, and emotions. These results support the effectiveness of SLIT in children with allergic rhinitis triggered by house-dust mites (Fig. 6).

The results of the present study agree well with those of earlier studies reporting that SLIT significantly alleviates symptoms of allergic rhinitis. In 2010, Yonekura et al. demonstrated that SLIT with house-dust extract administered for more than 30 weeks is a safe and effective treatment for house-dust mite allergic rhinitis in children [11]. Olaguibel and Alvarez Puebla similarly suggested that sublingual delivery of allergen vaccination is safe and effective in children [12]. Penagos et al. documented that SLIT with standardized extracts is effective in pediatric patients with allergic rhinitis compared with placebo [13].

SLIT has an effect on maturation of the immunity system. During SLIT, Langerhans-like local dendritic cells play a critical role by capturing the allergen, and the dendritic cells then mature and migrate to the proximal draining lymph nodes. These local lymph nodes produce blocking IgG antibodies and induce T lymphocytes with suppressive function. At last, SLIT induces systemic immunity and mucosal immunity with Th1-driven immune response [14].

Table 1
Patient-reported adverse effects.

Adverse effects	Number (%)
Aggravation of symptoms	16 (18.1)
Itching sensation in the oral cavity or of the lip	13 (14.8)
Gastrointestinal trouble	11 (12.6)
Eye discomfort	4 (4.5)
Skin itching or rash	4 (4.5)
Anaphylactic shock	0 (0.0)

Table 2
Reasons for patient drop-out during sublingual immunotherapy treatment.

Reasons for drop-out	Number (%)
Adverse effects	8 (33.4)
Lack of efficacy	8 (33.4)
Inconvenient application	5 (20.8)
No time to visit office	3 (12.5)

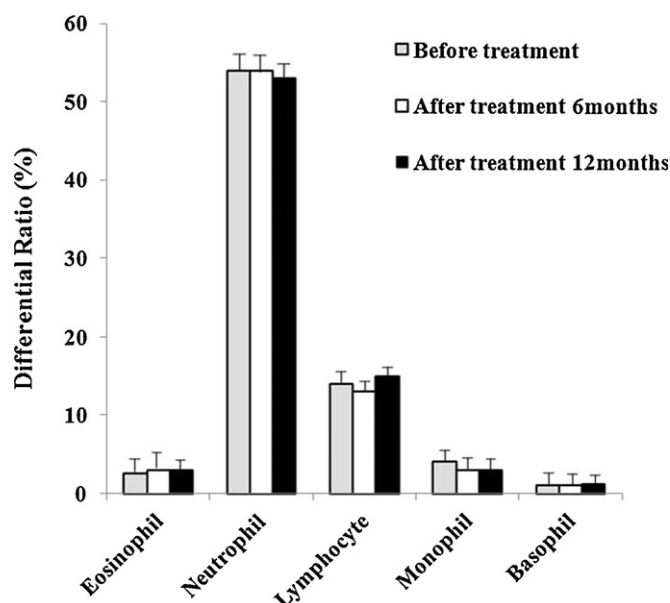


Fig. 6. WBC differential counts before treatment and 6 and 12 months after sublingual immunotherapy. percentages of eosinophils, neutrophils, lymphocytes, monophils and basophils did not change significantly after sublingual immunotherapy (* $p < 0.05$).

Piconi et al. reported that SLIT resulted in increases in the production of IL-10, expression of programmed cell death ligand 1, and concentration of allergen-specific IgG4, as well as a reduction in CD80 and CD86 expression and IL-4 production [15]. The effects of SLIT on immunoglobulin isotypes have been studied, but the changes in allergen-specific IgE or IgG do not seem to be reproducible [16–18]. However, previous results indicated that SLIT does not increase levels of allergen-specific IgG1 and IgG4 Abs, which are consistently up-regulated during SCIT [17–19]. Previous results also indicate that the serum level of allergen-specific IgE Abs is significantly reduced after 12 months of therapy [20] and eosinophil counts and ECP are decreased significantly after one year of follow-up [21]. In this regard, our results differ from those of previous studies. In the present study, there were no significant changes in serologic data.

There were no life-threatening adverse effects in this study. The safety of SLIT in children has been proven in many studies. Fiocchi et al. showed that high-dose immunotherapy in children younger than five years does not cause more adverse reactions than in children aged five to seven years [22]. Rienzo et al. also reported that SLIT is safe in children under the age of five years [23]. Considering the fact that SCIT is contraindicated in children under five years of age, SLIT is an important treatment option for young children.

The drop-out rate in our study was 21%. This percentage is consistent with those of the earlier studies, which reported SLIT compliance rates ranging from 60% to 90% even when long-term surveillance was performed [24,25]. Vita et al. pointed out that the drop-out rate is higher in patients with fewer clinical visits per year. They suggested that patients must be instructed to carefully follow the schedules of administration and to visit the clinic at least every three months [26]. In the present study, follow-up was performed monthly during the first three months, after which patients were asked to visit the hospital every three months.

There are some limitations to the present study. First, the sample size was small. Second, the follow-up period was too short given the fact that the typical treatment period with SLIT is three to five years. We expect that the number of patients who drop-out might increase as our study proceeds for longer than a year, and the results of serologic tests might change significantly. This is a preliminary study and further study with a larger number of

patients and a longer period of follow-up is ongoing. In conclusion, SLIT is a valuable therapy for the treatment of allergic rhinitis in Asian children who are sensitized to house-dust mites.

Conflicts of interest

None.

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