INTRODUCTION

The treatment of allergic rhinitis (AR) includes avoidance, pharmacologic treatment and immunotherapy. Contrary to other treatment modalities, immunotherapy is the only therapeutic option that modifies the basic allergic mechanism by inducing desensitization and an anergy state for the allergen. Immunotherapy by subcutaneous allergen injection (subcutaneous immunotherapy, SCIT) has been used since Noon’s first report in 1911 and it has been demonstrated to be a clinically effective treatment for allergic disorders such as rhinoconjunctivitis or asthma. However, due to the inconvenience, invasiveness and severe systemic adverse effects of SCIT, other methods of administering allergen have been developed such as the oral, sublingual, nasal or bronchial routes (1, 2). Among them, the sublingual route is now widely used to replace the subcutaneous route and it was acknowledged by the WHO Allergic Rhinitis and Its Impact on Asthma (ARIA) group that sublingual immunotherapy (SLIT) could be effective for pollen or mite AR (3). However, there have been no studies on Asian patients sensitized to \textit{Dermatophagoides pteronyssinus} (\textit{Dp}) and \textit{Dermatophagoides farinae} (\textit{Df}).

SLIT has recently been introduced and it is available for treating AR in Korea. This study was conducted to investigate the short-term efficacy, the adverse effects and the patient satisfac-
tion with SLIT for Korean patients with AR that is caused by house dust mites.

MATERIALS AND METHODS

Patient selection
The patients who were diagnosed with AR at Seoul National University Hospital or Seoul National University Bundang Hospital and who were sensitized to Dp and Df were indicated for SLIT. The patients who started to receive SLIT between November 2007 and July 2008 were included in this study. The patients who had a history of asthma, atopic dermatitis or bronchial hyper-responsiveness, but who didn’t need regular medication were enrolled, while the patients with symptomatic asthma, atopic dermatitis or bronchial hyper-responsiveness that required regular medication such as oral steroid, steroid inhaler or anti-histamine were excluded. The subjects who suffered from immunologic or hematologic disorder were also excluded. Sensitization to Dp and Df was defined as 1) a serum specific IgE level for Dp and Df ≥0.7 UI/mL on multiple allergen simultaneous tests (MAST) or 2) the wheal diameters for Dp and Df were equal to or greater than that of the positive control (histamine) on skin prick tests. The Institutional Review Board of the Clinical Research Institute at Seoul National University Hospital approved the study protocol (H-0811-034-262).

Immunotherapy
Standardized extract of house dust mites (50% Dp/50% Df; Pangramin® SLIT, ALK-Abello, Madrid, Spain) was used for the immunotherapy. 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 day 1 to 10, 1 to 5 drops of 8 STU/mL solution from day 11 to day 15, 1 to 5 drops of 40 STU/mL solution from day 16 to day 20, 1 to 5 drops of 200 STU/mL solution from day 21 to day 25 and 1 to 5 drops of 1,000 STU/mL solution from day 26 to day 30. After reaching the maintenance dose (5 drops of 1,000 STU/mL solution), the participants took the allergen 3 times a week during the maintenance phase. The patients had to keep the drops of allergen under their tongue for 2-3 min before swallowing. When the symptoms of AR were aggravated during immunotherapy, the patients were allowed to use antihistamine and/or intranasal steroid.

Symptom score and satisfaction
All the patients were asked to complete the questionnaires before SLIT and 6 months after receiving SLIT without medication. The questionnaire included items on rhinorrhea, sneezing, nasal obstruction, itchy nose, olfactory disturbance, eye discomfort and sleep discomfort. Each symptom was graded from 0 to 5 (0=no symptom, 1=very mild symptom, 2=mild, 3=moderate, 4=severe, 5=very severe). The total nasal symptom score (TNSS) was defined as the sum of the scores of five nasal symptoms, to, rhinorrhea, sneezing, nasal obstruction, itchy nose and olfactory disturbance. The patients were also asked to assess their use of anti-allergic medications such as anti-histamine, anti-leukotriene, and intranasal steroid according to 3 categories of, “increased”, “similar”, and “decreased”, comparing months after SLIT to before SLIT. Patient satisfaction was evaluated by 3 categories of “satisfied”, “fair”, and “unsatisfied” simultaneously with the symptom evaluation after SLIT. If the participants had discontinued SLIT, the reason of cessation was ascertained by telephone interview.

Adverse effects
To evaluate the adverse effects, the participants recorded the adverse effects related to SLIT everyday on diary cards during the whole period.

Statistical analysis
The symptoms before and after SLIT were statistically analyzed by paired t-tests. Student’s t-test, paired t-tests and the Wilcoxon signed rank test were used to compare the symptomatic changes. SPSS ver. 12.0 was used for all the statistical analysis. All of the tests were 2-tailed and the criterion for statistical significance was set at $P<0.05$.

RESULTS

One hundred forty-two patients (mean age, 16.3 yr; range, 5 to 71 yr) were enrolled in this study. Ninety-one of the patients were male and 51 were female. Ninety-eight of 142 patients continued SLIT and 44 discontinued. Ninety-two of the 98 patients who continued SLIT were considered in this study and the other six were excluded due to the lack of data. The mean age of the 92 patients under consideration was 15.8 yr (range, 5 to 53 yr) and the duration of allergic rhinitis was a mean of 7.0 yr (range,
1 to 30 yr). The mean duration of receiving SLIT was 9.8 months (range, 6 to 13 months). All the symptoms, including the nasal symptoms, the eye discomfort and the sleep disturbance, were significantly improved after SLIT (Fig. 1). For the questionnaire about the use of anti-allergic medication, 63 patients responded “decreased use”, 24 patients responded “similar use”, and 6 patients responded “decreased use”.

When the patient satisfaction was assessed, forty-two patients (45.7%) answered as “satisfied”, 39 patients (42.4%) answered as “fairly satisfied” and 11 patients (12%) answered as “unsatisfied”. When the TNSS was compared before and after SLIT according to the satisfaction, respectively, the patients who were “satisfied” or “fairly satisfied” had significant improvement of their TNSS. However, the TNSS was not significantly changed for the unsatisfied patients (Fig. 2). When comparing symptoms between the patients who were “satisfied” and “fairly satisfied”, the latter had more severe symptoms before and after SLIT. However, the degree of changes of the TNSS was not different for each group (Fig. 3).

The incidence of adverse effects of SLIT was 52.1% (48 of 92 patients) during first 30 days, which is the up-dosing phase. Aggravation of the AR symptoms was the most common adverse effect during the up-dosing phase (Table 1). After 6 months or more, 13 patients (14.1%) had experienced temporary adverse effects (Table 1). However, these adverse effects, including wheezing and breathing discomfort, were temporary and they subsided spontaneously without medication. None of the patients needed to visit an emergency room due to adverse effects.

Forty-four patients (30.1%) with mean age of 17.3 yr (range, 5 to 71 yr) discontinued SLIT. The male to female ratio was 26:18. Among these patients, 36 patients responded to our telephone interview. Twenty-one of 36 patients ceased SLIT after 3 months and 8 patients ceased SLIT after 4-6 months and 7 patients ceased SLIT after 7 months. The reasons for discontinuation of SLIT were inability to take medication according to schedule (n=10, 27.8%), ineffectiveness (n=8, 22.2%), the discomfort of regularly visiting the hospital regularly (n=6, 16.7%) and adverse effects (n=5, 13.9%). The adverse effects causing discontinuance included aggravation of the symptoms of AR (n=2), fever (n=1), gastrointestinal trouble (n=1) and skin rash (n=1). High cost (n=2), the problem of storing the allergen (n=1) and pregnancy (n=1) were also reported. Three patients answered that they thought SLIT was not useful any more due to the improvement of symptoms.

**DISCUSSION**

Clinical trials for evaluating the safety and efficacy of SLIT were initiated in 1980s and in 2001, and the WHO ARIA group reported that SLIT could be effective for treating AR (3). A meta analy-
sis involving 21 trials and 959 SLIT subjects indicated that SLIT had efficacy against allergic symptoms (4). As the evidence has accumulated, SLIT has received much attention as a valid treatment for AR around the world.

This study revealed that all the symptoms were changed for the better after SLIT in patients with house dust mites AR underwent SLIT. It was not easy to say that house dust mites SLIT had efficacy against AR in our series because the duration of the follow-up was short and our study was not a double-blind, placebo controlled trial. However, placebo-control studies about SLIT have been published since 1990 around the world and many of them reported that SLIT was an effective treatment for pollen-induced allergic airway diseases, and especially seasonal AR (5-10). The effectiveness of SLIT for patients with house dust mites AR has recently been revealed (2, 11). Based on others studies, we anticipate the good long-term results of our series.

Forty six percent of the patients were satisfied with receiving SLIT and 12% were unsatisfied. Forty two percent of the patients went SLIT. It was not easy to say that house dust mites SLIT had efficacy after SLIT in patients with house dust mites AR under SLIT, 12% were unsatisfied. Forty six percent of the patients were satisfied with receiving SLIT and 12% were unsatisfied. Considering the relationship between the satisfaction and the symptoms, the degree of improvement of symptoms affected the patient satisfaction involving 21 trials and 959 SLIT subjects indicated that SLIT had efficacy against allergic symptoms (4). As the evidence has accumulated, SLIT has received much attention as a valid treatment for AR around the world.

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6-13 months of immunotherapy and 45.7% of the patients were satisfied with SLIT. The adverse effects were mostly local reactions and these subsided without other treatment. The incidence of adverse effects was high in the up-dosing phase and this was lowered after continuing immunotherapy. Therefore, we should be alert for adverse effects during the up-dosing phase. The drop out rate was 31%, which is relatively high compared to other studies. Further long-term studies are required to evaluate if the reduced allergic symptoms persist, which was observed during short-term SLIT, and if the symptoms get better in the patients who didn’t show symptom improvement with short-term SLIT. Proper and prudent management of the patients is needed to reduce the drop out rate.

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