Efficacy of sublingual immunotherapy with house dust mite extract in polyallergen sensitized patients with allergic rhinitis

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Background: It is suggested that polysensitized patients might not benefit from specific allergic rhinitis immunotherapy as much as monosensitized patients, although further research on this subject is needed.

Objective: To compare the efficacy of sublingual immunotherapy (SLIT) with standardized house dust mite extract in monosensitized and polysensitized patients with allergic rhinitis.

Methods: Patients who were sensitized to house dust mites and treated with SLIT for house dust mites for at least 1 year between November 2007 and March 2010 were studied. The monoallergen sensitized group was defined as patients who were sensitized to Dermatophagoides pteronyssinus and/or Dermatophagoides farinae (n = 70). The polyallergen sensitized group was defined as patients who were simultaneously sensitized to house dust mites and other allergens (n = 64). A standardized extract of house dust mites was used for immunotherapy. Antiallergic medication and the total nasal symptom score (TNSS), including rhinorrhea, sneezing, nasal obstruction, and itchy nose, were evaluated before and 1 year after SLIT.

Results: This study enrolled 134 patients. The TNSS improved significantly after SLIT in both groups, whereas the change in the TNSS did not differ significantly between the groups. The antiallergic medication scores also decreased significantly in both groups, but there was no significant difference between the groups.

Conclusions: In polysensitized allergic rhinitis patients, SLIT for D pteronyssinus and/or D farinae produced improvements in both nasal symptoms and rescue medication scores comparable to those in monosensitized patients, regardless of other positive allergens. SLIT for D pteronyssinus and/or D farinae should be considered in polysensitized allergic rhinitis patients.


INTRODUCTION

Recently, the sublingual administration of allergen extracts has become popular in many countries, and its efficacy in allergic rhinitis has been demonstrated.1 Sublingual immunotherapy (SLIT) reduces symptoms and the need for medication.2

Most randomized controlled studies demonstrating the efficacy of subcutaneous immunotherapy or SLIT have been conducted with single-allergen extracts. Recently, the administration of multiallergen extracts has been recommended. Some studies have shown that multiple allergen immunotherapy is effective when administered subcutaneously.3–5 However, the limited absorptive capacity of the sublingual mucosa may make treatment with multiallergen SLIT less effective.6

A recent study showed the effectiveness of monoallergen SLIT with grass pollen extract in polysensitized patients.7 However, to our knowledge, no reported study has compared the efficacy of SLIT with house dust mite extract between monosensitized and polysensitized patients with allergic rhinitis. Thus, we compared the efficacy of SLIT with standardized house dust mite extract in monosensitized and polysensitized allergic rhinitis patients.

METHODS

Study Design

This study was a prospective case series conducted at a tertiary referral center. Allergic rhinitis patients sensitized only to house dust mites were compared with patients simultaneously sensitized to house dust mites and other allergens after 1 year of SLIT with house dust mite extract. Antiallergic medication score (AMS) and total nasal symptom score (TNSS), including rhinorrhea, sneezing, nasal obstruction, and itchy nose, were evaluated before and 1 year after SLIT.

The institutional review board of the Clinical Research Institute at Seoul National University Hospital approved this study protocol. Written consent was obtained from the patients when they were enrolled. We have registered this study with a public trials registry (registration NCT01247259).
Patients
Between November 2007 and February 2010, patients who were sensitized to house dust mites and treated with SLIT for house dust mites for at least 1 year were consecutively enrolled. The inclusion criteria were as follows: (1) having more than 2 allergic rhinitis symptoms, including sneezing, itching, rhinorrhea, and nasal congestion with or without eye symptoms; (2) sensitization to Dermatophagoides pteronyssinus and/or Dermatophagoides farinae, defined as a serum specific IgE level for D pteronyssinus and/or D farinae of class 2 or higher on multiple allergen simultaneous tests (Immunosystems, Mountain View, California) or wheal diameters for D pteronyssinus and/or D farinae equal to or greater than that of positive control (histamine) on skin prick tests (ratio of the size of the allergen-induced wheal to the size of the wheal elicited by the histamine solution [A/H ratio], ≥1); and (3) SLIT with house dust mite for at least 1 year. The skin prick test included 55 inhalant allergens, which were divided into 5 groups: mites, molds, animals and insects, pollens (tree, grass, and weed), and others. The reactivity of skin prick test was graded according to the A/H ratio as follows: 1+, 25% to 9%, 2+, 50% to 99%, 3+, 100% to 199%; and 4+, 200% or higher. The reactivity of 3+ or higher (A/H ratio ≥1) was considered an indication of a clinically significant positive response. Patients who received immunotherapy in the preceding 3 years or who had systemic immunologic disorders were excluded.

A total of 182 patients were enrolled initially; however, 134 patients of 182 (73.6%) continued SLIT for 1 year after enrollment (Table 1). The monoallergen sensitized group was defined as the patients who were sensitized only to D pteronyssinus and/or D farinae (n = 70). The polyallergen sensitized group was defined as the patients who were simultaneously sensitized to house dust mites and other allergens (n = 64). The polyallergen sensitized group was divided into 5 subgroups according to other positive allergens, such as animals (n = 33), fungi (n = 24), tree (n = 17), house dust (n = 14), and grass (n = 11). The numbers are not mutually exclusive.

SLIT
Immunotherapy was performed using a standardized extract of house dust mites (50% D pteronyssinus and/or 50% D farinae; Pangramin SLIT; ALK-Abelló, Madrid, Spain). During a 4-week increasing-dose phase, the patients increased the daily dose from 1 to 5 drops of a 1,600-STU/mL solution from day 1 to 10, 1 to 5 drops of a 800-STU/mL solution from day 11 to 15, 1 to 5 drops of a 400-STU/mL solution from day 16 to 20, 1 to 5 drops of a 200-STU/mL solution from day 21 to 25, and 1 to 5 drops of a 1,000-STU/mL solution from day 26 to 30. After reaching the maintenance dose, 5 drops of a 1,000-STU/mL solution, the patients took the allergen 3 times per week during the maintenance phase. The patients had to keep the drops of allergen under the tongue for 2 to 3 minutes before swallowing. When the symptoms of allergic rhinitis were aggravated during immunotherapy, patients were allowed to use antihistamines or intranasal steroid.

Outcome Measures
All of the patients were asked to complete a symptom questionnaire before SLIT and 1 year after receiving SLIT. The questionnaire included questions on rhinorrhea, sneezing, nasal obstruction, itchy nose, and eye discomfort. The symptom score was recorded and averaged for 1 week using a 6-point scoring system (0 indicating no symptom; 1, very mild; 2, mild; 3, moderate; 4, severe; and 5, very severe). The TNSS was defined as the sum of the scores for 4 nasal symptoms: rhinorrhea, sneezing, nasal obstruction, and itchy nose (range, 0–20).

Rescue medication was recorded on diary cards. The patients were asked to record their uses of antiallergic medications, such as oral antihistamine and intranasal corticosteroid. The AMS could be calculated with frequency of use multiplied by each medication point. Oral antihistamine was scored as 1 point, and intranasal corticosteroid was scored as 2 points. The AMS was calculated every 2 months during the 1-year application of SLIT.

Statistical Analyses
Symptoms before and after SLIT were analyzed statistically using a paired t test. The t test was used to compare the changes in symptoms and antiallergic medications between the 2 groups. SPSS statistical software (version 12.0; SPSS Inc, Chicago, Illinois) was used for statistical analyses. P = .05 (2-sided) was considered the limit of significance in all analyses.

RESULTS
This study enrolled 134 patients with a mean age of 14.7 years (range, 4–53 years). The duration of allergic rhinitis symptom averaged 6.6 (range, 0.5–30) and 6.9 (range, 1–30) years in the monoallergen sensitized and polyallergen sensitized groups, respectively.

All allergic symptoms, including rhinorrhea, sneezing, nasal obstruction, itchy nose, and eye discomfort, improved significantly after 1-year application of SLIT in both the monoallergen sensitized group (Fig 1) and the polyallergen sensitized group (Fig 2).

The TNSS also improved significantly after SLIT in both groups, although the change in the TNSS did not differ significantly between the groups (TNSS change, 5.7 vs 5.6;
The AMSs were decreased significantly after SLIT in both the monoallergen sensitized and polyallergen sensitized groups but did not differ significantly between the 2 groups (54.1 vs 46.1, \( P = .56 \); Fig 3B).

In the 5 polyallergen sensitized subgroups, the changes in the TNSS did not differ significantly compared with that in the monoallergen sensitized group (Fig 4). The 5 subgroups did not differ significantly in the change in AMS compared with the monoallergen sensitized group (Fig 5).

The incidence of adverse events of SLIT was 22.9% during the 1-year follow-up period. Aggravation of allergic rhinitis symptoms was the most common adverse event (41.8%), followed by itching sense of the oral cavity (16.2%), itching sense or discomfort of the eye (13.5%), skin itching or rash (6.7%), breathing discomfort (4%), and wheezing (1.3%). However, these adverse events, including wheezing and breathing discomfort, were temporary and subsided spontaneously without medication. None of the patients needed
to visit an emergency department because of adverse events.

DISCUSSION

A double-blind, placebo-controlled study showed that SLIT with house dust mite extract in perennial allergic rhinitis was well tolerated, although it was reported that the improvement in the TNSS was not significant compared with the placebo group. Conversely, a meta-analysis found promising evidence of the efficacy of SLIT using house dust mite extract. Other retrospective studies of SLIT with house dust mite extracts in monosensitized patients claimed that SLIT was an effective treatment modality. Previously, we also reported a randomized study that showed that SLIT significantly improved the symptoms and medication scores in Korean patients with allergic rhinitis to house dust mites.

House dust mite is the most common allergen to provoke allergic rhinitis in Korea. It is known to be a perennial...
allergen that does not have seasonal variations, unlike pollen allergens. It is reported that the density of mite is lowest in May, but it is a sufficient amount to evoke the allergic symptoms. Thus, it is believed that there were no differences in exposure level to house dust mites throughout the year.

It is often suggested that polysensitized patients might not benefit from specific immunotherapy as much as monosensitized patients, although further research on this subject is needed, as indicated in a previous study. A randomized controlled trial of SLIT with timothy extract alone and multiple pollen extracts reported that SLIT with timothy extract alone was effective and showed significant improvements in immunologic outcomes, in contrast to SLIT with multiple pollen extracts. Therefore, it raised questions regarding the use of multiple allergen mixes for SLIT because multiple pollen extracts showed a limited response. Another study examined the efficacy of SLIT in polysensitized patients to grass and birch and reported that SLIT with birch only or grass only also conferred a measurable improvement. In our study, we used only house dust mite extract for polysensitized patients regardless of other positive allergens and found that the nasal symptoms and rescue medication scores improved significantly in all polyallergen sensitized group subgroups. It is assumed that because house dust mites play the main role as a dominant allergen in polysensitized group subgroups. It is assumed that because house dust mites play the main role as a dominant allergen in polysensitized patients, SLIT with house dust mite extract only in polysensitized patients might be as effective as that in monosensitized patients. These results are important clinically because most allergic rhinitis patients are polysensitized. On the basis of our results, SLIT can be recommended to more patients with allergic rhinitis due to house dust mites in countries where its use is currently restricted to monosensitized patients.

Previous studies showed that SLIT induces regulatory T-cell suppression via interleukin 10 and modulates the allergen-specific T-cell responses in a similar way to subcutaneous immunotherapy. Regulatory T cells contribute to the control of immune responses in 5 major ways: (1) suppression of antigen-presenting cells that support the generation of effector $T_{H2}$ and $T_{H1}$ cells; (2) suppression of $T_{H2}$ and $T_{H1}$ cells; (3) reduction of the production of allergen-specific IgE and induction of IgG4, IgA, or both; (4) reduced activity of mast cells, basophils, and eosinophils; and (5) interaction with resident tissue cells and remodeling.

A retrospective study showed that length of the effect of SLIT is strictly related to the length of treatment. Our previous study of SLIT with house dust mite extracts for 6 months showed significant improvements in all nasal symptoms. In addition, our 1-year follow-up results also demonstrated significant improvements. These studies support the evidence that a 6-month application of SLIT can improve nasal symptoms and the improvement persists for more than 1 year. During SLIT application, the use of rescue medications was also reduced significantly, so it is unlikely that rescue medications enhanced the efficacy.

One of the advantages of SLIT is improved safety. In our study, only minor adverse effects were reported, and no systemic allergic reaction, such as anaphylaxis, was seen. There was no significant difference in the number of adverse events between the 2 groups. SLIT induces fewer systemic adverse effects, and most adverse events have been local reactions in the nose, eye, and oral cavity. Three cases of anaphylaxis after SLIT were reported in the English literature. Two of these reports described anaphylaxis that was due to a mixture of multiple allergens, and the third case was due to...
to latex. However, no anaphylaxis occurred with commercially available allergens.20–22

In this study, we observed that subjective symptoms and antiallergic medication use decreased significantly with a 1-year application of SLIT with house dust mite extract in polysensitized patients with house dust mite allergic rhinitis. However, there are 2 limitations. First, there is no control group; thus, the placebo effect could not be fully evaluated. There was a review paper on SLIT for individual allergens in which SLIT with house dust mite appears to be more effective than treatment with other types of allergen and even more effective than treatment with placebo.1 In our study, we aimed to evaluate the efficacy of house dust mite SLIT in polyallergen sensitized patients with allergic rhinitis compared with that in the monosensitized group. Therefore, the monoallergen sensitized group could be considered as a control group to the polyallergen sensitized group. The second limitation is the small number of enrolled patient. Considering the limited number of patients with allergic rhinitis who are candidates for SLIT and 30% of the mean dropout rate,1 it was almost impossible to get a large sample size in our study. A further long-term study with a larger number of patients is needed to evaluate whether the reduced allergic symptoms persist and whether the symptom-free duration increased with the duration of SLIT application in polysensitized patients.

In summary, in polysensitized house dust mite allergic rhinitis patients, SLIT for *D pteronyssinus* and/or *D farinae* demonstrated comparable improvements in both nasal symptoms and rescue medication scores to those in monosensitized patients, regardless of other positive allergens. Thus, SLIT for *D pteronyssinus* and/or *D farinae* should be considered in polysensitized allergic rhinitis patients.

REFERENCES


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