

Long-Term Efficacy of Sublingual Immunotherapy in Patients With Perennial Rhinitis

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Background: Sublingual immunotherapy has a documented clinical efficacy, but only a few long-term studies have been performed in people with perennial rhinitis.

Objectives: The purpose of this study was to evaluate the long-term efficacy of sublingual immunotherapy.

Methods: One hundred thirty-seven patients with allergies to house dust mites were treated with sublingual house dust-mite-specific immunotherapy for 2 or 3 years and were also observed for 3 years after discontinuation of the treatment. The patients were divided into 2 groups: group A (67 patients) received active treatment for 2 years and then 1 year for placebo, and group B (70 patients) received active treatment for 3 years. The success of the treatment was evaluated with the symptom score, skin prick test results, and the nasal allergen challenge score.

Results: According to our study results, we found a greater improvement in the 3 years of sublingual immunotherapy compared with the 2 years of sublingual immunotherapy when we looked at the comparative results of the total 6 years.

Conclusion: We suggest 3 years of sublingual immunotherapy for patients with perennial allergic rhinitis who require immunotherapy and do not accept the subcutaneous route of allergen administration.

Key Words: Sublingual immunotherapy, perennial allergic rhinitis, long-term follow-up.

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INTRODUCTION

House dust mites (HDM) (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) are a common source of allergens that cause perennial allergic rhinitis. The therapy for perennial rhinitis includes various preventive measures and pharmacological treatments with or

without specific immunotherapy (SIT). The key advantage of SIT, unlike conventional pharmacological treatment, is the potential for a long-term cure even after discontinuation of treatment. The subcutaneous form is the classic SIT procedure. Brief episodes of pollen allergy constitute the best indication for this treatment modality, but establishing its efficacy in perennial allergies, including those to house dust mites, has been more difficult.¹ Also, subcutaneous injections of allergen can provoke local or systemic reactions and even death from anaphylaxis²; therefore, new routes of administration for immunotherapy have been proposed. For this reason, and also to avoid repeated injections, sublingual administration of soluble allergen extracts, a more simple method, has been studied with both positive and disappointing results.³

Sublingual administration has been validated with extracts of pollen, including pediatric indications,⁴ but has been studied less extensively in people with allergy to house dust mites.

In this study, we compared long-term follow-up results of two different durations of sublingual immunotherapy (SLIT) by treating patients who have an allergy to HDM.

METHODS

Patient Selection

A double-blind, randomized trial of 2 or 3 years of SLIT and 3 years of observation was conducted. We chose 181 patients with allergy to HDM from subjects who were accepted into the SIT program.

In order to participate in the study, patients had to meet the following inclusion criteria:

1. Allergic complaints for ≥ 2 years.
2. Allergic symptoms and signs during the physical examination such as sneezing, runny nose, itchy nose, nasal crease, pale and swollen nasal mucosa, and watery discharge.
3. Positive skin test to extracts of *D pteronyssinus* and *D farinae* that is equal or greater than histamine reaction.
4. Detection of level II and above *D pteronyssinus* and *D farinae*-specific IgE (0.7 kU/liter and above). The Pharmacia diagnostic Immuno-CAP FEIA method was used (Pharmacia Diagnostics, Uppsala, Sweden).
5. No hypersensitivity to any other allergens.

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6. No prior immunotherapy.
7. No pharmacotherapy during the previous week.
8. No asthma or nasal polyposis.
6. No desire to take symptomatic treatment.
8. Dissatisfied with the results of previous pharmacotherapy.

However, pregnant women, patients with active systemic and immunological diseases as well as malignant growths of any system, and patients who had contraindications for SIT were not included in the study.

The patients were randomized into two groups, which were checked for homogeneity regarding demographics, symptom scores, and relevant clinical parameters. They were treated with immunotherapy for 2 or 3 years, and after the discontinuation of therapy, they were followed up for 3 years. Of 181 patients included in the study, 21 withdrew because of contraindications to therapy (pregnancy, comorbidity, newly prescribed drugs), 15 withdrew because of poor adherence, and 8 withdrew due to relocation. Of those completing the trial, 67 patients (36 females, 31 males, mean age 27.91 ± 9.73 , range, 12–51 years) were treated with 2 years of SLIT and 1 year of placebo (group A), and 70 patients (38 females, 32 males; mean age 25.87 ± 7.82 , range 10–49 years) were treated with 3 years of SLIT (group B).

This study was conducted with the permission of the medical research ethics committee of Istanbul University and with the informed consent of the subjects.

Study Design

The patients were selected from subjects with allergic rhinitis who had only *D pteronyssinus* and *D farinae* allergies and matched the criteria mentioned above. Sixty-seven patients were treated with 2 years of SLIT and 1 year of placebo, and 70 patients were treated with 3 years of SLIT. After discontinuation of the therapy, they were followed up for 3 years.

Skin prick tests, nasal allergen challenges, and symptom scores were performed six times during the study period (at the beginning, first, second, and third years of the treatment also at the first and third years of follow-up) to evaluate the effectiveness of the therapy.

Drug Usage

Patients used only antihistamines during the SIT period according to their needs. During follow-up, we permitted only antihistamine use (no other rescue medication such as nasal corticosteroids), but patients who used antihistamines more than two times in a week were excluded from the study. During the assessment periods, drug use was forbidden 1 month before assessment. By forbidding rescue medications, we aimed to see the actual long-term efficacies of immunotherapy. On the other hand, the medication score could not be evaluated for this reason.

Nasal Provocation Challenge Tests

Patients received nasal provocation at 5-minute intervals with control solution (ALK-Abelló), 100SQ-U/mL, 1000SQ-U/mL, 10000SQ-U/mL, and 100000SQ-U/mL of extracts of *D pteronyssinus* (ALK-Abelló). With each application, the response to provocation was recorded.

In the nasal provocation challenge test, we evaluated the following:

1. The alteration of the nasal airway resistance (NAR) and NAR score
2. Nasal secretion volume (mL) and score
3. Sneezing score
4. Total score

We graded the nasal provocation scores using a modified form of the end-point titration method described by Gerth van Wijk.⁵ The three criteria of the end-point titration method are 1) an increase of NAR 100%, 2) ≥ 0.5 mL nasal secretion, and 3) ≥ 5 sneezing. In our study, we scored these three criteria between 0 and 3 points for performing statistical analysis.

The nasal airway resistance was evaluated with rhinomanometry (Rhinometrics; Rhinostream, version 2.6, Ed. 1.1; Interacoustics A/S Denmark) before (NARb) and after (NARa) the nasal provocation and the alteration were recorded. The NAR score was assessed for an increase of 0% to 19% as zero points, 20 to 49% as 1 point, 50 to 99% as 2 points, and $\geq 100\%$ as 3 points.

Nasal secretion was collected with the method described by Borum et al.⁶ The nasal secretion score was assessed for less than 0.2 mL as 1 point, 0.2 to 0.49 mL as 2 points, and ≥ 0.5 mL as 3 points. If there was no secretion, the score was 0.

The sneezing scores were assessed as the following: for 0 to 1, sneezing = 1; for 2 to 4, sneezing = 2; and for ≥ 5 , sneezing = 3 points.

The NAR, nasal secretion, and sneezing scores comprise the total score. According to our assessment scale, patients with ≥ 4 points were considered provoked.

During all of our tests, patients were considered provoked according to the following criteria:

1. Matching one or more criteria of the end-point titration method
2. Total score of ≥ 4
3. Score of 4 to 6 points = positive (+)
4. Score of 7 to 9 points = strongly positive (+)

Symptom Score

All the patients were asked to complete diary cards of daily symptoms throughout the 1-month period before each clinical assessment. The diary cards covered nasal stuffiness, nasal discharge, sneezing, nasal itching, and eye symptoms. Each symptom was graded 0 to 3, where 0 = no symptoms, 1 = symptoms present but mild, 2 = moderate, and 3 = severe. The symptom score was calculated as the arithmetical mean of the sum of 5 symptoms.

Skin Prick Tests

A standardized panel (ALK-Abelló) was used to perform the skin prick tests. The panel included tree, weed, grass, cereal pollens, molds, *D pteronyssinus* and *D farinae*, histamine, and a control solution. The sensitivity of the skin test was estimated by the size of the wheal. The largest diameter of the wheal was evaluated as the size of the wheal. A wheal size <4 mm was evaluated as 1 point, 5 to 10 mm as 2 points, 11 to 15 mm as 3 points, and >15 mm as 4 points.

Immunotherapy

Allergen extracts from ALK-Abelló were used for SIT. The activities of the biologically standardized allergen extracts were labeled in STU (specific treatment units). *D pteronyssinus* and *D farinae* extracts were used in the form of drops (ALK-Abelló). The doses were increased for 30 days until the maintenance dose was reached. The initial dose was 1 drop of 1.6 STU/mL up to 5 drops on day 10; on days 11 to 15, 1 to 5 drops of 8 STU/mL; on days 16 to 20, 1 to 5 drops of 40 STU/mL; on days 21 to 25, 1 to 5 drops of 200 STU/mL; and on days 26 to 30, 1 to 5 drops of 1000 STU/mL. After the patient reached this dose or the maximum tolerated dose, the maintenance dose was administered three times per week. The total treatment period was 2 or 3 years. Placebo drops were physically identical to active medication.

TABLE I.
Mean Values $\pm$ SD of Parameters Within Group A.

Type of Score	Beginning of Treatment	End of 2nd Year	End of Treatment (3rd Year)	End of Observation (6th Year)
NAR	1.8806 $\pm$ 0.9927	1.4179 $\pm$ 1.0173	0.9701 $\pm$ 0.9995*	0.4925 $\pm$ 0.9272†‡
Secretion	1.4478 $\pm$ 1.1843	1.0388 $\pm$ 1.0458	0.5963 $\pm$ 0.7250*	0.9803 $\pm$ 0.8507†‡
Sneezing	2.1642 $\pm$ 0.9629	0.9009 $\pm$ 0.7694	0.6269 $\pm$ 0.6705*	1.1194 $\pm$ 0.8794†‡
Total	5.4925 $\pm$ 1.4603	3.8507 $\pm$ 1.9169	2.6582 $\pm$ 1.6760*	3.4522 $\pm$ 2.0097†‡
Symptom	2.3045 $\pm$ 0.2982	0.7015 $\pm$ 1.0194	0.5499 $\pm$ 0.7450*	0.8701 $\pm$ 0.8706†‡
Skin prick	3.4657 $\pm$ 0.6251	2.8569 $\pm$ 0.6237	2.6448 $\pm$ 0.8059*	3.0776 $\pm$ 0.8231†‡

*Significant changes from the beginning to the end of treatment ($P < .05$).

†Significant changes from the beginning to the end of the observational period ($P < .05$).

‡Significant changes from the end of treatment to the end of the observational period ($P < .05$).

NAR = nasal airway resistance; SD = standard deviation.

Statistical Analysis

Comparisons within the same group were analyzed by repeated measurements of ANOVA and LSD tests used as post hoc multiple comparisons. Values for groups A and B were compared statistically with the independent Student *t* test. Significance was accepted in either analyses when $P < .05$.

RESULTS

In our study, 67 patients (36 females, 31 males, mean age 27.91 ± 9.73 , range 12–51 years) were treated with 2 years of SLIT and 1 year of placebo (group A), 70 patients (38 females, 32 males; mean age 25.87 ± 7.82 , range 10–49 years) were treated with 3 years of SLIT (group B).

The mean values of the changing parameters during the study are shown for groups A and B in Tables I and II, respectively. The change of some important values between the groups is shown in Figures 1 and 2.

Nasal Airway Resistance

The NAR scores showed a regularly significant reduction in both groups from the baseline until the end of the trial even after discontinuation of the treatment. When the NAR scores of the baseline were compared with the scores at the end of the treatment, the group B showed a significant reduction compared with group A ($P = .000$, $t = -4.058$). When the baseline NAR scores were compared with the scores at the end of follow-up, group B showed a significant reduction compared with group A

($P = .001$, $t = -3.431$). During follow-up, the NAR scores were reduced significantly in both groups, but there was no significant difference between them according to the comparative results ($P = .375$, $t = 0.890$).

Secretion Score

During treatment, secretion scores diminished significantly in both groups, but after the end of therapy, a significant increase was observed. When we compared baseline scores with the scores at the end of the treatment, group B showed a significant reduction compared with group A ($P = .015$, $t = -2.471$). When the baseline secretion scores were compared with the scores at the end of the follow-up, group B showed a significant reduction compared with group A ($P = .045$, $t = -2.022$).

Sneezing Score

During the treatment, sneezing scores diminished significantly in both groups, but after the end of the therapy, a significant increase was observed. When we compared baseline scores with the scores at the end of the treatment, group B showed a significant reduction compared with group A ($P = .040$, $t = -2.069$). When the sneezing scores from the beginning of treatment were compared with the scores at the end of follow-up, group B showed a significant reduction compared with group A ($P = .049$, $t = -2.005$). During follow-up, there was no

TABLE II.
Mean Values $\pm$ SD of Parameters Within Group B.

Type of Score	Beginning of Treatment	End of 2nd Year	End of Treatment (3rd year)	End of Observation (6th year)
NAR	1.9515 $\pm$ 0.8586	1.3594 $\pm$ 1.1593	0.5106 $\pm$ 0.7862*	0.1702 $\pm$ 0.5982†‡
Secretion	1.4894 $\pm$ 1.1708	1.0468 $\pm$ 0.8844	0.4574 $\pm$ 0.5594*	0.8064 $\pm$ 0.7217†‡
Sneezing	2.2234 $\pm$ 0.7781	0.9362 $\pm$ 0.6848	0.3511 $\pm$ 0.5228*	0.8085 $\pm$ 0.7659†‡
Total	5.6926 $\pm$ 1.5621	3.9040 $\pm$ 2.1418	1.3021 $\pm$ 1.2749*	1.5851 $\pm$ 1.5754†
Symptom	2.3660 $\pm$ 0.3795	0.6809 $\pm$ 0.9299	0.2723 $\pm$ 0.5610*	0.3723 $\pm$ 0.5383†
Skin prick	3.3936 $\pm$ 0.5332	2.9681 $\pm$ 0.6792	2.3511 $\pm$ 0.7289*	2.6915 $\pm$ 0.8554†‡

*Significant changes from the beginning to the end of the treatment ($P < .05$).

†Significant changes from the beginning to the end of the observational period ($P < .05$).

‡Significant changes from the end of the treatment to the end of the observational period ($P < .05$).

NAR = nasal airway resistance; SD = standard deviation.

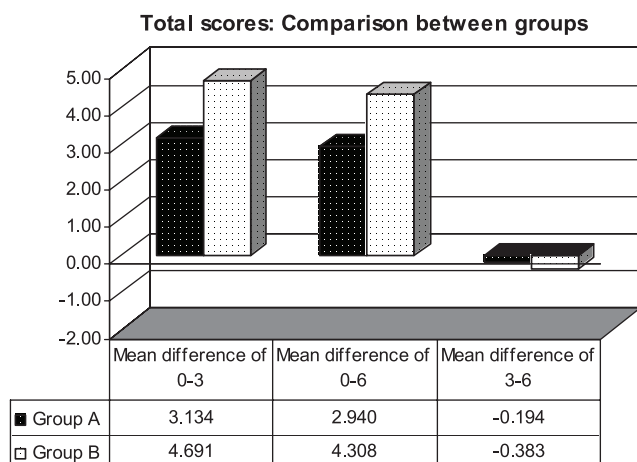


Fig. 1. Comparison of the mean differences of total scores between groups. Scores of 0 to 3 = treatment values; 0 to 6 = treatment and follow-up values; 3 to 6 = after treatment/follow-up values. Scores of 0 to 3 of group A versus group B: $P < .05$; 0 to 6 of group A versus group B: $P < .05$; 3 to 6 of group A versus group B: $P > .05$.

significant difference between the two groups according to the comparative results.

Total Score

During the first 3 years, while the therapy continued, the total score diminished significantly in both groups. When the total scores of the beginning were compared with the scores at the end of the treatment, group B showed a significant reduction compared with group A ($P = .000$, $t = -5.453$) (Fig. 1). When we compared the scores of year 3 with the scores of year 6 (the beginning and end of the observation period, respectively), there was a significant increase in group A, whereas there was a slight increase in group B. Also, we saw a significant reduction in both groups when the baseline total scores

were compared with the scores at the end of the study. However, when the scores from the beginning were compared with the scores at the end of follow-up, group B showed a significant reduction compared with group A ($P = .000$, $t = -4.266$) (Fig. 1).

Symptom Score

During treatment, a significant improvement in the symptom scores was observed in both groups, but group B showed a significant reduction when compared with group A ($P = .011$, $t = -2.557$) (Fig. 2). During the observation period, there was a significant increase in the symptom score in group A, whereas there was no statistically significant change in group B during the same time interval. When these scores were compared, group A showed a significantly higher increase compared with group B ($P = .000$, $t = -4.499$) (Fig. 2). We saw a significant reduction in both groups when the baseline symptom scores were compared with the scores at the end of the study, but group B showed a significant reduction compared with group A ($P = .000$, $t = -4.266$) (Fig. 2).

Skin Prick Test

The skin prick test scores were reduced significantly during the SIT and increased significantly during the observation period after the discontinuation of SIT. During treatment, group B showed a significant reduction compared with group A ($P = .041$, $t = -2.065$). We saw a significant reduction in both groups when the baseline skin prick scores were compared with the scores at the end of the study, but group B showed a significant reduction compared with group A ($P = .000$, $t = -5.903$).

Side Effects

No immediate systemic reactions or large local reactions were observed during either the induction or maintenance phase of the SLIT treatment. Oral pruritus (52%), rhinitis (37%), and gastrointestinal tract upset (14%) were mostly seen as minor side effects.

DISCUSSION

SLIT in clinical practice is controversial. Both positive^{7,8} and disappointing^{9,10} results have been reported. In the most studies, pollen extracts have been used sublingually.¹¹ Smith et al.¹² treated 186 patients with seasonal allergic rhinitis with SLIT for 1 or 2 years and compared them with a placebo group. After 1 year, no significant differences were found between actively treated subjects and the placebo group. After the second year of therapy, the subjects showed a reduction in symptoms. There are few studies concerning the efficiency of sublingual immunotherapy with mite extracts. Guez et al.¹⁰ assessed the efficiency and safety of sublingual immunotherapy in patients who were sensitive to HDM. A significant reduction in medication and total symptom scores was observed after 12 and 24 months of treatment, but there was no significant difference between the active and placebo groups. Tonnel et al.¹³ evaluated the efficacy of SLIT in HDM-sensitive patients and concluded that the improvement by therapy was obtained by using high doses and mainly concerned the rhinitis symptom scores, while

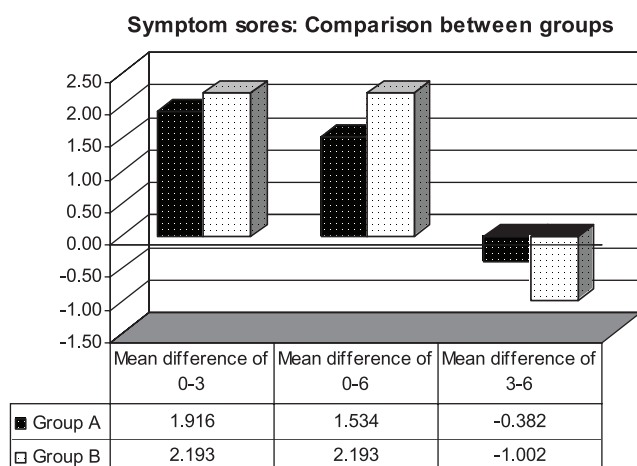


Fig. 2. Comparison of the mean differences of symptom scores between groups. Scores of 0 to 3 = treatment values; 0 to 6 = treatment and follow-up; 3 to 6 = after the treatment/follow-up values. Scores of 0 to 3 of group A versus group B: $P < .05$; 0 to 6 of group A versus group B: $P < .05$; 3 to 6 of group A versus group B: $P < .05$.

medication consumption remained unchanged. However, the long-term efficacy of SLIT for perennial allergic rhinitis has yet to be investigated.

SLIT in our patients was clinically effective. The NAR, sneezing, total, symptom, and prick test scores were significantly reduced at the end of the first year; the secretion scores were reduced significantly at the end of the second year of the treatment in both groups. In addition, all of these parameters continued to decrease significantly during the treatment period. While the NAR scores continued to decrease during follow-up, the sneezing, and prick test scores increased significantly in both groups. The symptom scores and total scores increased slightly during the observation period at 3 years of SLIT, while there was a significant increase at 2 years of SLIT. Continuation of the NAR score decreasing during follow-up (with the other scores increasing) demonstrates that using only the NAR scores for evaluation of the nasal provocation challenge, as the authors^{14,15} indicate, can reduce the reliability of the results. Furthermore, the other supporting evidence is that the total score, which includes the NAR and other evaluation scores, continues to increase during follow-up. However, when we compared the entire baseline scores with the scores at the end of the study (the end of 6 years), we saw a more significant reduction at 3 years of SLIT compared with 2 years of SLIT.

SLIT is a simpler and safer method because it requires fewer physician office visits and is suitable for people who are afraid of receiving injections. It is now accepted by the World Health Organization as a valid alternative to the subcutaneous route and should be used in all patients who require immunotherapy and do not accept the subcutaneous route of allergen administration.

CONCLUSION

Three years of SLIT confers clinical benefits in patients with perennial allergic rhinitis whose HDM allergy is resistant to conventional drug treatment.

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