Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy

Ayfer Yukselen,¹ Seval Güneser Kendirli,² Mustafa Yılmaz,² Derya Ufuk Altintas² and Gulbin Bingol Karakoc²

Summary

Background: Both SCIT (subcutaneous immunotherapy) and SLIT (sublingual immunotherapy) have clinical and immunologic efficacy in children with rhinitis and asthma but comparative studies are scarce.

Objective: To investigate the clinical and immunological efficacy of mite-specific SLIT and SCIT in children with rhinitis and asthma.

Method: Thirty children monosensitized to house dust mite were randomized to receive either active SCIT or SLIT or placebo for 1 yr in a double-blind double-dummy placebo controlled design (Yukselen A et al., Int Arch Allergy Immunol 2012; 157:288-298). Thereafter, the placebo group was randomized to receive SCIT or SLIT, and for 1 yr all patients received active treatment with SCIT or SLIT. Symptom scores, drug usage, titrated skin prick tests, nasal and bronchial allergen provocation doses, serum house dust mite-specific immunoglobulin E, sIgG4, IL-10 and IFN-γ levels were evaluated.

Results: The reduction of clinical scores with SLIT was more evident after 2 years of treatment in comparison to both the baseline and DBPC phase of the study. The change in titrated skin prick tests and nasal provocative doses was more prominent with both SCIT and SLIT at the end of the open phase. Although the increase in bronchial provocative doses was not significant at the end of the first year of treatment with SLIT, it reached a statistically significant difference after two years of treatment.

Conclusion: The clinical efficacy of SLIT is more prominent at the end of the second year, although this improvement is observed from the first year of treatment with SCIT in mite-sensitive children. (Asian Pac J Allergy Immunol 2013;31:233-41)

Key words: children, clinical efficacy, subcutaneous immunotherapy, sublingual immunotherapy

Abbreviations

NP = Nasal provocation
TU = Therapeutic units

Introduction

Specific allergen immunotherapy is the only treatment modality with the capacity of changing the natural course of allergic diseases.¹,² Subcutaneous immunotherapy (SCIT) in children is effective for the treatment of allergic rhinitis, allergic asthma, and venom allergy.³,⁶ SCIT has been validated for the treatment of both asthma and rhinitis.⁴,⁵ Sublingual immunotherapy (SLIT) appears to be associated with a lower incidence of systemic reactions and as a long-term treatment as an adjunct to pharmacotherapy results in the reduction of both the duration and the dose of inhaled corticosteroids and successful discontinuation of therapy, along with an improvement of lung function.⁷-¹⁴ SLIT has been reported to have promising evidence of efficacy in mite allergy¹⁵ and has been validated with pollen extracts, including pediatric indications.¹²,¹⁴,¹⁶

In a randomized, double-blind, double dummy study which evaluated the efficacy of SCIT and SLIT in children with allergic rhinitis and asthma
monosensitized to house dust mites,\textsuperscript{17} we showed that both SCIT and SLIT had more clinical efficacy on symptoms of both rhinitis and asthma compared to the baseline year. In comparison to the placebo arm, only SCIT was found to have a superior effect to placebo on reduction of rhinitis and asthma symptoms after one-year of treatment. The same cohort was then followed for the one subsequent year in an open scheme and the placebo group was randomized to receive SCIT or SLIT. Here, we report the extended analysis of the clinical and some immunologic effects of SCIT and SLIT after two years immunotherapy in this cohort.

**Methods**

**Patients**

The patients were selected from those who were referred to the Pediatric Allergy and Immunology Clinic on the basis of perennial nasal and bronchial symptoms. Recruitment criteria included a clinical history at least 1 year of rhinitis with asthma related to symptoms with house dust mites and no previous treatment with specific immunotherapy. Thirty two children presenting with persistent rhinitis and asthma, and monosensitized to house dust mites were included. Patients fulfilled the criteria for persistent mild asthma according to GINA guidelines \textsuperscript{18}, and the diagnosis of persistent allergic rhinitis was based on criteria in ARIA consensus statement.\textsuperscript{19}

The study was approved by the ethical committee of the University Hospital and each patient and their caregivers gave written informed consent.

**Study design**

The study design was shown in Figure 1. The immunotherapy duration was planned to be a three year period.

The first year of the study (run-in period) consisted of the follow up of patients to evaluate their baseline symptom scores and to optimize medication scores related to asthma and rhinitis. The patients were treated with inhaled budesonide 100 to 800 mcg/day and inhaled salbutamol as required for the control of their asthma. Intranasal mometasone and antihistamines were given as needed to alleviate the symptoms of rhinitis. None of the patients were treated with oral corticosteroids or leukotriene antagonists.

The design of the the second year was a randomized, placebo-controlled, double-blind, double-dummy study. All study personnel and participants were blinded to treatment assignment for the first year of the immunotherapy. Based on

![Figure 1. The design of the study](image-url)
computer-generated randomization, the patients were allocated into three groups: the SCIT-group (10 patients) received active subcutaneous immunotherapy (injections) and placebo sublingual drops; the SLIT-group (11 patients) received active sublingual immunotherapy (drops) and placebo subcutaneous injections; and the Placebo-group (10 patients) received placebo sublingual drops and placebo subcutaneous injections.

After the 1 yr double-blind, double-dummy, placebo controlled immunotherapy period, codes were broken and placebo-treated subjects were switched to active treatment with SCIT or SLIT, according to a computer-generated code. Immunotherapy was administered for one further year to all subjects. Therefore, children initially assigned to placebo had SCIT or SLIT for 1 yr whereas those initially assigned to active treatment had SCIT or SLIT for two years.

Physical examination, titrated skin prick tests, pulmonary function tests, allergen-specific nasal and bronchial challenges were performed at the beginning, at the end of DBPC phase and at the end of open phase of the study.

**Immunotherapy**

Allergen extracts from Allergopharma were used for specific immunotherapy (SIT). Active treatment involved a standardized *D. pteronyssinus* and *D. farinae* (50/50) mite extract for sublingual use (NovoHelisen Oral, Allergopharma, Reinbeck, Germany) and for subcutaneous administration (NovoHelisen Depot, Allergopharma, Reinbeck, Germany).

SLIT was self administered at home. The initial dose was 1 drop of 10 TU/ml up to 28 drops on day 28; on days 29-56, 1-28 drops of 100 TU/ml; on days 57-84 1-28 drops of 1000 TU/ml. After the patient reached this dose or the maximum tolerated dose, the maintenance dose was administered 3 times per week as 28 drops of 1000 TU/ml. The cumulative 2-years dose for SLIT was approximately 347466 TU (173733 TU *D. pteronyssinus* and 173733 TU *D. farinae*).

SCIT was administered in the clinic and included a 12-week induction phase (weekly injections) starting with a dose of 0.2-0.8 ml of 50 TU/ml (week 1-3), 0.2-0.8 ml of 500 TU/ml (week 4-8) and 0.2-0.8 ml of 5000 TU/ml (week 9-12). The maximum tolerated dose achieved during the induction phase was the maintenance dose, and it was repeated every 4th week. The cumulative 2-years dose for SCIT was approximately 87540 TU (43770 TU *D. pteronyssinus* and 43770 TU *D. farinae*).

The ratio of dosages during maintenance therapy for SLIT and SCIT (SLIT/SCIT) was 4.2.

**Symptom and medication scores of subjective rhinitis and asthma**

Parents completed a self-assessment diary each day, scoring the symptoms of rhinitis (rhinorrhea, sneezing, nasal itching, blocked nose) and asthma (cough, wheezing, dyspnea and chest tightness) The symptoms were rated as: 0= no symptoms, 1=mild, 2=moderate, and 3=severe symptoms.

Prophylactic and rescue drug intake was recorded daily on the same diary card. One point was given if a beta-2 agonist rescue drug was taken on that day, and 0, if not. The daily dose of inhaled budesonide and intranasal mometasone was scored as published in our previous study.17

**Nasal Provocation test**

Nasal provocation (NP) was performed according to the EAACI guidelines using a Rhinospir 165 rhinomanometer (Sibelmed, Barcelona, Spain). The response was evaluated by measuring nasal resistance at 150 Pa with active rhinomanometry and by scoring the clinical symptoms. Total symptom scores represented the sum of the scores for: sneezing (0–2 sneezes: 0 points; 3–5: 1 point; >5: 2 points); rhinorrhea (moderate: 1 point; severe: 2 points); tearing, itching (eyes, throat); 1 point; conjunctivitis, cough, urticaria and/or dyspnea: 2 points. Positive clinical nasal challenge was defined as >3 points.21

After spraying 0.2 ml of the diluent, increasing concentrations of allergen extract (50, 500, 5000 BU/ml, Allergopharma, Reinbeck, Germany) were sprayed into the same nostril every 15 min until symptoms appeared and resistances doubled those induced by diluent.

**Nasal eosinophils**

Nasal cytologic specimens were obtained by using the same technique as described previously in another paper.17 Nasal eosinophil counts were determined from cytospins (Cytospin 4; Shandon Corp., Pittsburgh, PA, USA) and expressed as percentages of total cells.

Pulmonary function and allergen-specific bronchial provocation tests

Lung function was assessed at each visit using a Zan 100 Spiromed (Germany).

Bronchial challenge tests were performed according to the general guidelines for
standardization of bronchial challenge tests with allergens using standardized allergen solutions (Allergopharma, Reinbeck, Germany). The solution is inhaled with continuous nebulization (PARI, Proneb Compressor Nebulizer, Midlothian, VA, USA) over 60 seconds during tidal breathing. After 15 minutes, FEV\textsubscript{1} value was obtained by spirometry and it was accepted as a reference value. Challenge continued with administration of the lowest allergen dose (5 BU/ml). After 15 minutes, a new FEV\textsubscript{1} value was obtained by spirometry and then increasing allergen concentrations were administered as 50 BU/ml. The test was stopped after a fall in FEV\textsubscript{1} of 20% or greater had occurred, or when the maximum concentration of 5000 BU/ml had been administered.

**Sputum eosinophils**

Sputum induction, processing and analysis were performed as described previously\cite{17}. Cytospin preparations (Cytospin 4; Shandon Corp.) were made at 220 g for 6 min and stained with May-Grunwald-Giemsa for an overall differential cell count of 400 nonsquamous cells. The eosinophil counts are expressed as percentage of total nonsquamous cells.

**Serum HDM sIgE, sIgG4, IL-10 and IFN-γ levels**

Serum HDM sIgE and sIgG4 levels were determined using the CAP System (Pharmacia, Uppsala, Sweden) according to the manufacturer’s instructions.

Serum IL-10 and IFN-γ concentrations were measured by means of ELISA (AssayPro, MO, USA). The minimum detectable doses of IFN-γ and IL-10 are 30 pg/mL and < 100 pg/mL, respectively.

**Assessment of clinical efficacy**

Clinical efficacy was assessed separately for both symptom and medication scores; and was calculated by the comparing immunotherapy period with the run-in year in order to take advantage of the monitoring in the first year.

**Exposure to house dust mite allergens**

Dust samples were taken from mattresses with a vacuum cleaner equipped with a nozzle (Indoor biotechnologies, UK) containing a collector with a filter paper. A semi-quantitative test (Acarex\textsuperscript{®}) was carried out on the dust samples to assess the guanine dosage at the beginning and at the end of first and second year of immunotherapy. Exposure was assessed as follows: ‘none’ (0), ‘mild’ (1), ‘moderate’ (2), and ‘heavy’ (3).

**Statistics**

All the analyses were performed using computer software (SPSS version 11.0; SPSS; Chicago, Illinois, USA). Data were presented as medians and min-max or mean ± SD, as indicated. The Wilcoxon signed-rank test for intra group analysis, and if there were two samples, Mann-Whitney-U test for between group analysis were performed.

**Results**

**Patients**

The demographic characteristics of the patients are shown in Table 1.

Of the 32 randomized patients, only 30 were evaluable (1 patients withdrew their consent at the end of the run-in period and 1 patient randomized to active SLIT refused to take the drops after 3 months of the first immunotherapy year and was excluded) for efficacy at the end of first year of immunotherapy. Thus, 10 patients (6 male, 4 female) received active SCIT, 10 patients (5 male, 5 female) active SLIT and 10 patients (6 male, 4 female) placebo in the double blind period. In the open phase, after the placebo treated children were randomized to take active SCIT or SLIT, 15 patients (aged 11.5 ± 3.0 yrs) received active SCIT and 15 patients (aged 11.8 ± 2.5 yrs) received active SLIT during the second year of immunotherapy.

There were no significant differences between groups in terms of age (p =0.58) or gender (p =0.95).

**Mite exposure**

The level of exposure to house dust mites was not found to be significantly different between groups of the patients, at the beginning (p =0.75), at the end of one year (p =0.72) and at the of second year (p =0.77) of immunotherapy.

**Table 1.** The demographic data for patients included in the study.

<table>
<thead>
<tr>
<th></th>
<th>SCIT</th>
<th>SLIT</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>N (Male/Female)</td>
<td>15</td>
<td>15</td>
<td>0.95</td>
</tr>
<tr>
<td>(9/6)</td>
<td>(8/7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years (mean±SD)</td>
<td>11.5±3.0</td>
<td>11.8±2.5</td>
<td>0.58</td>
</tr>
<tr>
<td>(36-144)</td>
<td>(12-144)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of rhinitis, months†</td>
<td>72</td>
<td>54</td>
<td>0.62</td>
</tr>
<tr>
<td>(36-144)</td>
<td>(12-144)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of asthma, months†</td>
<td>60</td>
<td>48</td>
<td>0.25</td>
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<tr>
<td>(24-120)</td>
<td>(12-120)</td>
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Symptom and medication scores

The symptom and medication scores for both rhinitis and asthma were recorded daily during both the baseline year and the SIT period and calculated as monthly median values.

The reduction of symptoms related to rhinitis and asthma was maintained both in SCIT ($p=0.005$, for both) and SLIT ($p=0.005$, for both) groups in comparison to the baseline year.

We found that the decrease in symptoms related with rhinitis and asthma was more prominent at the end of second year in comparison to the first year with SLIT ($p=0.005$ for rhinitis and and $p=0.008$ for asthma) (Figure 2). Similarly, reduction of symptoms related to rhinitis and asthma was observed after 1 yr immunotherapy (SCIT or SLIT) in the placebo group (Figure 2).

When compared with the baseline data, the median percentage improvement of symptom scores at the end of first and second year of treatment was 31% and 64.5% for rhinitis, and 100% for asthma with SCIT. Similarly, the median percentage improvement of symptom scores at the end of first and second year of treatment was 6.6% and 28% for rhinitis, and 3.3% and 27.8% for asthma with SLIT.

The patients who received placebo during the DBPC phase of the study showed an improvement in their rhinitis symptoms of 22% and in asthma symptoms of 29.9%, after turning to active treatment.

The reduction in medication scores of rhinitis and asthma was maintained at 2 yr of treatment with SCIT ($p=0.005$, for both).

Although the reduction in medication scores for rhinitis and asthma with SLIT was not statistically significant ($p=0.18$ for rhinitis, and $p=0.16$ for asthma) at the end of 1 yr, it reached a statistical significance at the end of second year of treatment ($p=0.012$, for both) (Figure 2).

No statistically significant difference between SCIT and SLIT was observed in terms of the reduction in symptoms of rhinitis ($p=0.25$), and in medication scores related with rhinitis ($p=0.19$) at the end of second year of immunotherapy. However, symptoms and medication usage related to asthma decreased significantly in the SCIT group ($p=0.03$ and $p=0.04$, respectively) when compared with the SLIT group (Figure 2).

Pulmonary function tests

The mean FEV1 values of the SCIT and SLIT groups after 2-yr of immunotherapy period were

![Figure 2](image.png)

Figure 2. Symptom and medication scores for rhinitis and asthma, in the run-in, DBPC phase and open phase of the study (1), $p=0.03$, between SCIT and SLIT at the end of second year (2), $p=0.04$, between SCIT and SLIT at the end of second year.
105.2 ± 13.0 and 101.9 ± 6.6, respectively. FEV1 values showed an average increase of 11.4% in after SCIT and 10.7% in the SLIT group.

When compared with the baseline year, FEV1 values increased significantly with SCIT and SLIT ($p = 0.007$, for both).

Patients who received placebo in the DBPC phase of the study showed significant increase in FEV1 values in comparison to the baseline year after switching to active treatment ($p = 0.02$).

**Skin prick tests**

The wheal diameter of $D_p$ and $D_f$ extracts significantly decreased in both the SCIT ($p = 0.007$ and $p = 0.006$, respectively) and the SLIT group ($p = 0.01$, for both) at the end of second year of immunotherapy. However, the patients receiving placebo did not show a significant decrease in wheal diameter for either $D_p$ or $D_f$ ($p = 0.24$ and $p = 0.35$, respectively) although they received active treatment for 1 year.

**HDM-specific nasal provocation**

Titrated nasal provocation HDM-doses increased significantly after 2 years of IT in both the SCIT ($p = 0.01$) and SLIT groups ($p = 0.02$, for both) (Figure 3). No significant difference was observed between SCIT and SLIT regarding titrated nasal provocation HDM-doses ($p = 0.53$).

Nasal eosinophil increment after NP was significantly decreased in both the SCIT ($p = 0.005$) and SLIT ($p = 0.02$) groups, when compared with the baseline values, after 2 yr of treatment.

At the end of second year of immunotherapy, no difference was observed between SCIT and SLIT in terms of reduction in nasal eosinophil increment after NP ($p = 0.14$).

**HDM-specific bronchial provocation**

The patients treated with SCIT ($p = 0.05$) showed significant increases in HDM-specific bronchial provocation doses after 2 years (Figure 3). When SLIT did not show an increase in HDM-specific bronchial provocation doses at the end of first year ($p = 0.56$), a significant increase was detected after 2 years of immunotherapy ($p = 0.02$) (Figure 3).

Sputum eosinophil increments after BP showed significant decreases in comparison to the baseline year in the SCIT group ($p = 0.02$). Although this decrease was not observed in patients receiving SLIT ($p = 0.51$) at the end of first year, a statistically significant difference ($p = 0.01$) was detected at the end of second year of SLIT in the sputum eosinophil increment after BP.

The reduction in sputum eosinophil increment was found to be significantly different between SCIT and SLIT ($p = 0.02$); SCIT had a more prominent effect than SLIT on this reduction.

**Serum HDM-specific IgE, sIgG4, IL-10, and IFN-γ levels**

A significant decrease in HDM-sIgE levels was observed in SCIT ($p = 0.009$) and SLIT ($p = 0.01$) patients after 2 years of treatment. The patients receiving placebo in the DBPC phase of the study did not show a significant decrease in HDM-sIgE levels although they had switched to active treatment ($p = 0.45$).

Serum IL-10 levels increased significantly in patients treated with SCIT ($p = 0.005$) and SLIT ($p = 0.005$) after 2 years of treatment (Figure 4). Patients who received placebo showed a significant increase in serum IL-10 levels after switching to active treatment.

**Figure 3.** HDM-specific NP and BP doses, in the run-in, DBPC phase and the open phase of the study
Clinical efficacy of SCIT and SLIT vs placebo

Figure 4. Serum IL-10 levels, in the run-in, DBPC phase and the open phase of the study.

Figure 5. Serum D.pt. specific IgG4 levels in the run-in, DBPC phase and the open phase of the study.

Serum D.pt. and D.f. sIgG4 levels increased significantly only in the SCIT group \( (p = 0.007) \) after 1 yr of treatment. They showed statistically significant increases both in SCIT and SLIT groups after two years of immunotherapy \( (p = 0.005, \text{ for both}) \) (Figure 5).

We did not detect a significant change in IFN-\( \gamma \) levels after 2 years of both treatment modes \( (p = 0.28 \text{ for SCIT and } p = 0.42 \text{ for SLIT}) \).

No significant difference was observed in terms of HDM-sIgE, IL-10 and IFN-\( \gamma \) levels between the SCIT and SLIT groups. Serum D.pt. and D.f. sIgG4 levels increased significantly in the SCIT group in comparison to the SLIT group \( (p = 0.02) \) after 2 years of treatment (Figure 5).

Discussion

We have reported the clinical and some immunologic results of a study which was initiated as a DBPC and double-dummy course of SCIT and SLIT for one year in children with rhinitis and asthma monosensitized to mites previously. The study was then continued in an open setting for another one year and immunotherapy was extended to all children. The main results of this paper show that clinical and some immunologic parameters were down modulated since the first year of SCIT and SLIT, and this effect was consolidated in the second year. Additionally, the effect of SLIT on symptoms and drug usage related to asthma was less prominent than SCIT in the first year, but it increased in the second year of SLIT.

SIT has a central importance because of its ability to modify the natural history of the disease when administered for an adequate dosage and duration. The subcutaneous route has been for decades the traditional route of administration, but in recent years the sublingual route has emerged as an alternative treatment option. The clinical efficacy of SCIT is well established for both rhinitis and asthma. SLIT has also been validated in this respect. Two recent metaanalyses in children showed that sublingual delivery of allergen vaccination constitutes a safe and effective alternative to the injectable route to reduce allergy respiratory symptoms and drug intake. In our study, SCIT reduced significantly symptom and medication scores related to both rhinitis and asthma from the first year of treatment. However, we found that in the first year of SLIT neither symptom nor drug scores were overall reduced in actively treated vs. placebo patients. In the open phase of the study, patients previously treated with active SLIT had reduced symptom and drug scores related to both rhinitis and asthma in the second year of treatment vs. the first one. For symptoms of rhinitis, the median percentage of improvement with SLIT was 6.6 % in the first year, whereas it was 28 % in the second year. Similarly, the efficacy of SLIT on asthma symptoms reached a statistical significance after the second year of treatment (3.3 % and 27.8 % in the first and second year, respectively). Although reduction in medication scores for rhinitis and asthma with SLIT was not statistically significant \( (p = 0.18 \text{ for rhinitis, and } p =0.16 \text{ for asthma}) \) at the
end of the first year, it reached a statistical significance at the end of second year of treatment ($p=0.012$, for both).

Placebo treated patients in the DBPC phase had a favorable trend in terms of symptoms in the open phase of the study.

Successful SIT was also shown to reduce responses to local allergen challenge in the skin and nasal mucosa in patients with rhinitis and non-specific airway hyper-reactivity and bronchial response to inhaled allergen challenge in patients with asthma.23-24 Our results confirm the effects of SIT, whereby both treatment modes decreased the specific allergen reactivity in the skin and increased the threshold dose to induce nasal hyper-reactivity. Similarly, nasal eosinophil increments after NP were significantly decreased in both the SCIT and SLIT groups in comparison to baseline. Nevertheless, reduction of nasal eosinophil increments after NP was more prominent in the SCIT group than the SLIT group ($p=0.02$), although they all received two years active treatment.

In the DBPC phase of the study, we did not observe an increase in bronchial provocation doses of HDM and a reduction in sputum eosinophil increment after BP with SLIT, although these improvements were seen in patients who received SCIT. However, at the end of the second year of active SLIT, we also detected a significant increase in BP doses of HDM as well as a significant reduction in sputum eosinophil increments after BP. With regard to the nasal allergen provocation doses or the nasal eosinophilic response to NP, the efficacy of SCIT was more pronounced than SLIT on the bronchial allergen hyperreactivity and sputum eosinophilic increment after BP.

Although there have been some studies performed to compare the clinical efficacy of SCIT and SLIT,25-30 there are conflicting results in the literature about efficacy of these two treatment modes on immunologic parameters. Our findings show significant down-regulation of allergen specific IgE as well as increases in IL-10 production, both with SCIT and SLIT after two years of treatment. A significant increase was also observed in allergen-specific IgG4 levels with both SCIT and SLIT at the end of the second year of active treatment, though this finding was shown only in SCIT group at the end of first year.

Taken together these results indicate that longer treatment with SLIT is needed in children sensitized to mites to achieve clinically relevant results. Our observations are consistent with previous studies which in more favorable outcomes were obtained with treatment lasting more than 18 months by SLIT.

The number of patients is small in this study. A potential reason for this is the fact that both the placebo arm and the double-dummy design of the first year of the study led to difficulties regarding the enrollment of children.

The current study is an extension of our first study and it was carried out using an open protocol. Although the gold standard method for comparing the efficacy of these two routes of immunotherapy is a double blind, double dummy design, for the ethical reasons, we switched to an open protocol after one year of the DBPC, double dummy phase. In our first paper, we concluded that SCIT was superior to SLIT; However, at the end of second year of immunotherapy carried out in an open protocol, SLIT was found to be as effective as SCIT. This finding indicates the importance of both the design and duration of studies comparing these two routes of immunotherapy.

In conclusion, our study shows that although both clinical and immunologic improvement with SCIT begins from the first year of immunotherapy, it requires longer treatment with SLIT in HDM-sensitized children with rhinitis and asthma. Additionally, two years immunotherapy in mite sensitive children leads to more pronounced immunologic effects in patients received SCIT than those of the received SLIT. More studies in children to address the long-term efficacy of these two most-used modes of immunotherapy are needed in a larger population.

Acknowledgment
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References


20. EAACI Subcommittee on provocation tests with allergens. EAACI provocation tests with allergens. Allergy 1997;52 (Suppl. 35):5-36.


