

Prolonged effect of allergen sublingual immunotherapy for house dust mites in elderly patients



Andrzej Bozek, MD, PhD^{*}; Liwia Starczewska-Dymek, MD[†]; Jerzy Jarzab, MD, PhD^{*}

^{*} Clinical Department of Internal Disease, Dermatology and Allergology in Zabrze, Medical University of Silesia in Katowice, Katowice, Poland

[†] Medical Center LA Dymek, Strzelce Opolskie, Poland

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ABSTRACT

Background: The prolonged effect of allergen immunotherapy is unknown, especially in older patients.

Objective: To analyze the 3-year effect of sublingual allergen-specific immunotherapy (SLIT) to house dust mites in elderly patients with allergic rhinitis.

Methods: Forty-seven elderly patients (65.78 ± 4.89 years old) underwent SLIT to house dust mites and were monitored for 3 years and compared with a placebo group. SLIT was performed with the use of oral Staloral 300 SR Der p and Der f 50/50% extract (Stallergens Greer, London, United Kingdom) or placebo. Symptoms and medication score, represented by the average adjusted symptom score (AADSS), serum level of immunoglobulin (Ig) G4 to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, Der p 1, and Der p 2, and quality of life, were assessed immediately after SLIT and 3 years later.

Results: The AADSS was significantly decreased after SLIT, and the level remained low during the 3 years after SLIT compared with placebo. Serum-specific IgG4 against *D pteronyssinus*, *D farinae*, Der p 1, and Der p 2 increased during the SLIT trial in the study group. For the 3 years of observation after SLIT, there were no significant changes of specific IgG4 levels against the analyzed allergens compared with results just after SLIT. Quality of life based on the Rhinoconjunctivitis Quality of Life Questionnaire score was significantly decreased in patients who received SLIT, from 1.48 (95% confidence interval 1.33–1.79) to 0.98 (95% confidence interval 0.67–1.07; $P < .05$) compared with 0.94 (95% confidence interval 0.55–1.04) 3 years after SLIT.

Conclusion: The prolonged positive effect after SLIT to house dust mites was observed in elderly patients with allergic rhinitis. Further trials are needed to confirm this effect.

Trial Registration: ClinicalTrials.gov Identifier: NCT01605760

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Introduction

Allergen-specific immunotherapy (SIT) is the only etiology-based treatment that has the potential for disease modification, as reflected by long-term remission after its discontinuation, and possibly the prevention of disease progression or the onset of new allergic sensitization.^{1–4} SIT has been shown to be efficacious and safe in several randomized controlled immunotherapy trials.^{5,6} Although there are no doubts on the efficacy of immunotherapy in adults and children, insufficient data are available for elderly patients. Despite the lack of objective contraindications, specific immunotherapy has not been used to treat elderly patients because of a lack of evidence of safety. There is some proof that this therapy is useful in patients older than 60 years; however, there has been no prolonged observation of such patients after SIT.^{7,8} The prolonged effect was dependent on many factors, such as cumulative doses of

SIT and the clinical type of allergy. However, it is frequently an individual problem. There is some evidence that SIT could remain effective for 4 to 6 years after its discontinuation.⁹

The aim of this study was to evaluate the clinical effect of sublingual SIT (SLIT) to house dust mites (HDM) in elderly patients with allergic rhinitis 3 years after therapy had been discontinued.

Methods

Patients

Forty-seven elderly patients (study group) who underwent SLIT to HDM 3 years previously and 48 patients who received placebo were included in the study for observation. The characteristics of the groups are presented in Table 1. All patients were individually randomized in equal numbers to the active group or the placebo group using a double-blinded method (Fig 1).

The study group was treated with SLIT for 3 consecutive years. SLIT was performed using oral Staloral 300 SR Der p and Der f 50/50% extract (Stallergens Greer, London, United Kingdom) or placebo. The protocol of the study is available in a study by Bozek

Reprints: Andrzej Bozek, MD, PhD, Clinical Department of Internal Disease, Dermatology and Allergology, MC Skłodowskiej 10, 41-800 Zabrze, Poland; E-mail: andrzejbozek@o2.pl.

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Table 1
Characteristics of Patients Before Randomization

	Active	Placebo	P value
Age (y), mean $\pm$ SD	65.78 $\pm$ 4.89	66.71 $\pm$ 3.77	.873
Men/women, n	23/28	27/30	.231
Duration of rhinitis (y)	15.7 $\pm$ 4.9	14.3 $\pm$ 6.4	.521
Patients with asthma, n	6	5	.885
Allergic	4	3	
Non-allergic	2	2	
Patients with eczema, n	4	6	.501
Smokers, n	3	3	1.0
Patients with stable coronary disease, n	5	4	.843
Patients with arterial hypertension, n	11	13	.631
Patients with diabetes, n	2	4	.745
Weekly nasal symptom score, mean $\pm$ SD	4.768 $\pm$ 0.654	4.270 $\pm$ 0.594	.250
Weekly non-nasal symptom score, mean $\pm$ SD	3.369 $\pm$ 0.755	3.402 $\pm$ 0.677	.102
Weekly medication score, mean $\pm$ SD	0.532 $\pm$ 0.086	0.498 $\pm$ 0.089	.683
AAdSS, mean $\pm$ SD	5.81 $\pm$ 2.61	5.93 $\pm$ 3.01	.612
Total IgE, mean $\pm$ SD	378.99 $\pm$ 25.81	402.1 $\pm$ 67.98	.361
Specific IgE to Der p (kU/L), mean $\pm$ SD	44.1 $\pm$ 9.55	39.56 $\pm$ 6.03	.141
Specific IgE to Der f (kU/L), mean $\pm$ SD	50.09 $\pm$ 12.09	45.98 $\pm$ 11.6	.178
Positive skin prick test reaction to <i>D pter</i>	48	52	.432
Positive skin prick test reaction to <i>D far</i>	43	48	.561

Abbreviations: AAdSS, average adjusted symptom score; *D far*, *Dermatophagoides farinae*; *D pter*, *Dermatophagoides pteronyssinus*; IgE, immunoglobulin E.

et al.¹⁰ There was a 2-week run-in period. During the initial 8 days, the patients were administered daily increasing doses in the form of 1 to 8 puffs of the 100-IR/mL extract. On days 9 to 16, the patients took 1 to 8 puffs of the 300-IR/mL extract. The patients received maintenance treatments consisting of 5 applications of 18 puffs (1 puff = 30 IR) of 300-IR/mL extract 5 times a week. The mean treatment duration was 28.2 months (range 3–36 months). The first dose of SLIT was administered in the office. Using this schedule, an average cumulative dose of 421 to 200 IR of allergens was administered to each patient undergoing active treatment for all 3 years of the study. This study is registered at ClinicalTrials.gov as trial NCT01605760. The results were recalculated and used in a retrospective analysis.

Study Design

The project was designed as a retrospective and prospective observation of all patients (active and placebo) for a total of 6 years. For the prospective observation, the patients were included in the study after completing SLIT or a symptomatic treatment in July 2013. The patients were asked to keep a diary during the entire 3-year observation period from 2013 to 2016. Every year, skin prick tests (SPTs) were performed, and specific immunoglobulin (Ig) E and IgG4 levels for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were monitored. All results were compared with the baseline diagnostic results before the start of SLIT (baseline). The number of participants who completed the study is presented in Figure 1. The study was approved by the local ethics committees, and all patients signed informed consent forms.

Symptoms and Medication Scores

The patients were monitored for their allergic clinical symptoms and medication use from July 2013 to July 2016. All symptoms and medication scores obtained during the SLIT trial (July 2011–July 2013) were recalculated post hoc according to the method described below.

The patients recorded their nasal and ocular symptoms from their daily medication use during the observation period (3 years of the trial and 3 years after observation). Four nasal symptoms (sneezing, rhinorrhea, pruritus, and congestion) and 2 ocular

symptoms (pruritus and tearing) were monitored. Each day, the patient rated the severity of each individual symptom during the past 24 hours using a 4-point scale: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms.¹¹

The rescue medication score was based on World Allergy Organization recommendations: 1 point for antihistamines, 2 points for nasal corticosteroids, and 3 points for oral corticosteroids.¹¹

Symptoms and medication scores were presented as the average adjusted symptom score (AAdSS). The AAdSS has been accepted for use as a primary end point in rhinoconjunctivitis allergen immunotherapy trials.¹² This score included the nasal and ocular total symptoms score associated with the HDM allergy as the rhinoconjunctivitis total symptoms score, which can be adjusted for the use of symptomatic treatment.¹² The following nasal symptoms were analyzed: sneezing; runny nose; non-nasal congestion symptoms of the ear, throat, and eye; cough; mental function; and quality of life. The score was based on the patients' weekly diaries during their 3-year observation. The 7-point visual graphic scale was used (published by the joint task force and modified by the Allergic Rhinitis and its Impact on Asthma), which was similarly used during the monitoring of earlier SLIT.¹⁰

In addition, a post hoc analysis, which was performed using the total combined rhinitis score (TCRS), focused on nasal domain symptoms and the medication used for treating allergic rhinitis.¹²

Symptomatic Treatment

The treatment was the same as previously described. The patients were allowed to use the following agents: antihistamine (5-mg tablets of levocetirizine), intranasal corticosteroid (mometasone), topical ocular antihistamine drops (ebastine), and a 4-mg tablet of methylprednisolone. Other antiallergic agents were not permitted during the observation period.

Quality of Life

The patients' quality of life was evaluated using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score for adults who responded to questionnaires every year during the observation period.¹³

Allergen-Specific IgE and IgG4

At baseline, at the end of the SLIT trial, and every year after observation, serum-specific IgE, IgG, and IgG4 levels to HDM (*D pteronyssinus*, *D farinae*), Der p 1, and Der p 2 were determined using ImmunoCAP (ThermoFisher Scientific, Uppsala, Sweden) according to the manufacturer's instructions.

The results were considered to be positive when the specific IgE concentration was higher than 0.35 IU/mL (according to the manufacturer's instructions).

In addition, allergen-specific IgE and serum allergen-specific IgG4 responses to Der p 1 and Der p 2 were measured using the same immuno-enzymatic test. These measurements were performed at the start and at the end of the study and were repeated every year after observation.

Skin Prick Tests

The SPTs were performed using the allergens *D pteronyssinus* and *D farinae* (Stallergens Greer, London, United Kingdom). Positive (10 mg/mL of histamine) and negative (saline) controls were included. A positive SPT result was defined as a wheal diameter at least 3 mm larger than the negative control.¹⁴ The SPT was performed before enrollment in the study and after observation.

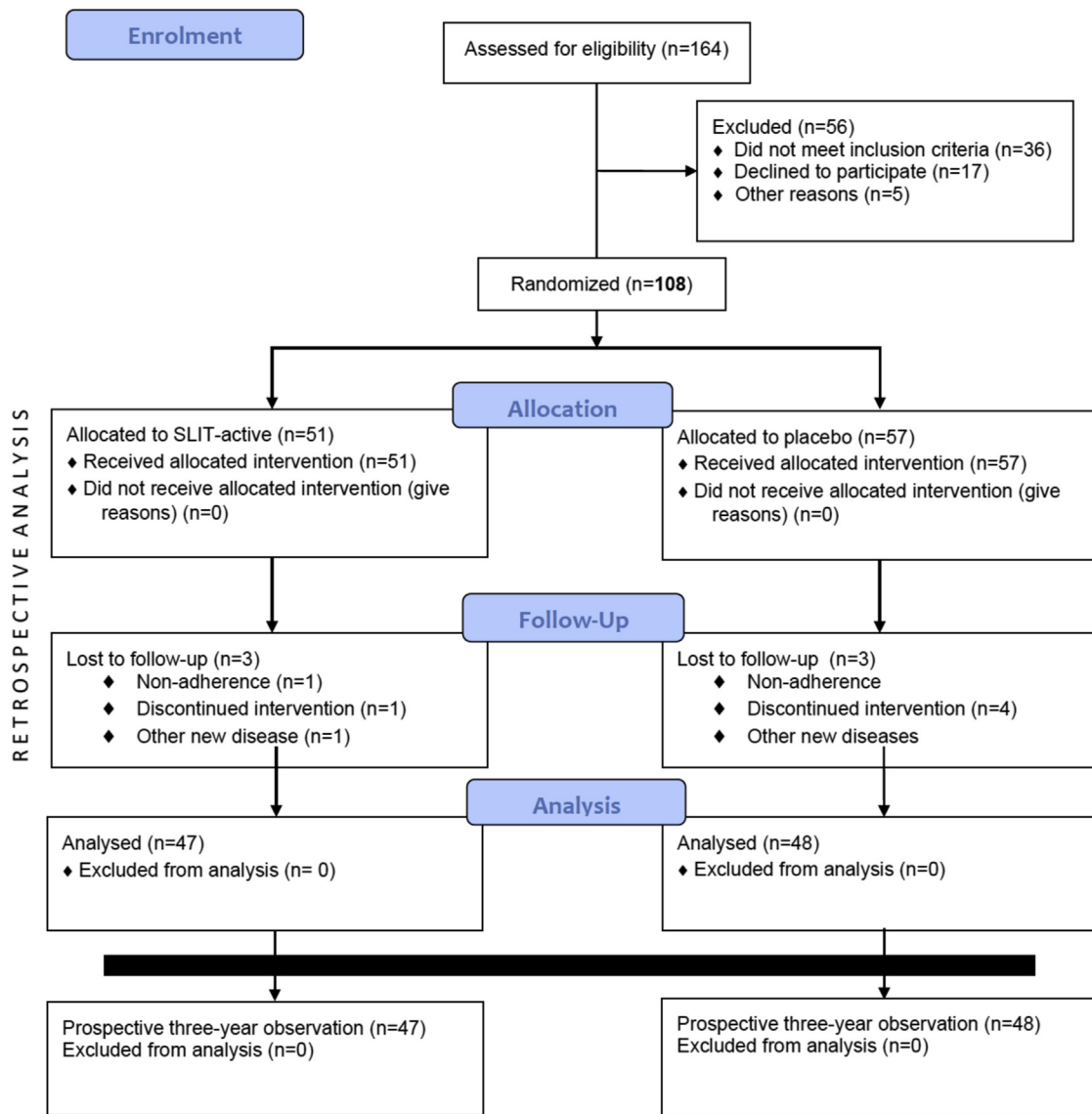


Figure 1. Number of participants assessed for eligibility who completed the study.

Statistics

The primary end point was the change from baseline in mean AAdSS and the TCRS difference in the least square means in the label compared with placebo. Analysis of covariance was used.

The second end point was the immunologic response of IgG4 and IgE to *D pteronyssinus*, *D farinae*, Der p 1, and Der p 2 after SIT. The least significant mean changes from baseline were analyzed. The changes in SPT reactions also were monitored using the mean changes in wheal size compared with baseline. The Wilcoxon test was used to analyze between-group differences. The χ^2 test was used to analyze changes in quality of life.

Statistical analysis was performed using Statistica 8.12 (SoftPol, Cracow, Poland). A *P* value less than .05 was considered statistically significant.

Results

Clinical Efficacy

After 36 months of SLIT for HDM allergy, a significant clinical effect was observed based on the AAdSS compared with baseline

and the placebo group. During the subsequent 3 years of observation, the AAdSS remained at a low level and significantly lower than that in the placebo group. The results are presented in Table 2.

The post hoc analysis of the TCRS showed that it was significantly decreased after 3 years of SLIT and that it remained constant at a low value for another 3 years of observation in the active group. The results are shown in Figure 2.

In 11 patients with concomitant asthma, SLIT did not change symptoms after immunotherapy and during 3 years after observation.

The 3 patients who smoked had the same positive prolonged effect (symptoms and medication score) after SLIT; however, the result was not statistically significant because of the small sample. The same problem was encountered when patients with asthma were assessed.

Immunologic Markers

Serum-specific IgE levels against *D pteronyssinus*, *D farinae*, D pter 1, and D pter 2 decreased during the SLIT trial and remained

Table 2
Efficacy of SLIT During Therapy and 3-Year Observation Compared With Placebo

Patients	AAdSS, mean $\pm$ SD				
	Baseline ^a	After 3 y of SLIT	Differences in adjusted means ^b	3 y of further observation	Differences in adjusted means ^c
SLIT active (n = 47)	5.81 $\pm$ 2.61	1.77 $\pm$ 0.49	–4.01	1.85 $\pm$ 0.93	–3.17
SLIT placebo (n = 47)	5.93 $\pm$ 3.01	5.78 $\pm$ 3.29	–0.15	6.03 $\pm$ 4.02	0.08
P	NS	.004	.0001	.004	.0001

Abbreviations: AAdSS, average adjusted symptoms score; NS, not significant; SLIT, sublingual allergen-specific immunotherapy.

^aOne-year observation before SLIT was started.

^bDifferences in AAdSS after 3 years of SLIT vs baseline.

^cDifferences in AAdSS after entire observation period (6 years) vs baseline.

at the same levels 3 years after immunotherapy was discontinued compared with the placebo group (Fig 3).

Serum-specific IgG4 against *D pteronyssinus*, *D farinae*, Der p 1, and Der p 2 increased during the SLIT trial in the study group. During the 3 years of observation after SLIT, there were no significant changes in specific IgG4 levels against the analyzed allergens compared with the results after SLIT (Fig 4). There was no analysis of IgG4 in the placebo group because of the constant and low levels of IgG4 against the analyzed allergens.

Skin Prick Tests

There were no significant mean changes in wheal size for *D pteronyssinus* and *D farinae* in the 2 groups of patients compared with baseline.

Quality of Life

The quality of life based on the RQLQ score was significantly decreased from 1.48 (95% confidence interval [CI] 1.33–1.79) to 0.98 (95% CI 0.67–1.07; $P < .05$) in patients who received SLIT, and it remained at a constant level of 0.94 (95% CI 0.55–1.04) after 3 years when SLIT was discontinued.

In the placebo group, quality of life was significantly lower, with a constant level of 1.46 ± 0.11 (95% CI 0.98–1.82) during the entire 6-year observation.

Discussion

The long-term effect of SIT in elderly patients has never been evaluated. There is an insufficient quantity of data on SIT in elderly people. However, there is an explicit need for this type of treatment because the prevalence of allergic rhinitis in patients older than 60 years has increased.^{15–17}

How does aging influence the permanent effect of SIT in elderly patients? Based on the obtained results, the efficacy appears to be

similar to that in younger groups. The AAdSS, as the primary end point of this analysis, decreased significantly during SLIT in the study group; however, it remained at low levels 3 years after SLIT was discontinued. These results are comparable to those of other studies including similar parameters, such as different configurations of symptoms and medication scores in younger patients after SIT to HDM.^{18,19} However, few of these observations are available.

There also was significant improvement of TCRS based on the analysis of only the rhinitis domain as the primary end point of this study. This finding is particularly important for elderly patients because nasal problems significantly decrease their quality of life.²⁰ In fact, this latter parameter was significantly improved during the observation period. It is worth emphasizing that sometimes the diseases that are considered less important, such as allergic rhinitis, can significantly decrease the quality of life in elderly patients. Therefore, allergy prevention and appropriate treatment should be emphasized in older patients.^{20,21}

Immunosenescence is an important event during aging. It also influences local nasal immune reactions. The aging immune system incurs many changes, including a decrease in nonspecific immune responses with a decrease in the activity of phagocytes and cytotoxic cells. Significant changes in the profiles of T lymphocytes during aging have been observed. The T-helper cell type 2 profile becomes predominant. The immune system of elderly people can be poorly responsive to new antigens, which is caused by a predominance of memory lymphocytes and a significant decrease of native cells. However, these changes do not seem to be crucial in the incidence of allergies.^{22–24} The increase of IgG4 for *D pteronyssinus*, *D farinae*, Der p 1, and Der p 2 during and after SLIT was conclusive. At the same time, the concentration of allergen-specific IgE for respective allergens was generally decreased, but not in all patients. Other investigators have observed the influence of SLIT on concentrations of IgG4 and specific IgE in younger patients with allergy.²⁵ There is no clear evidence that all elderly patients with allergy have significantly decreased reactivity to allergens and decreased IgE with age. We observed decreased allergen-specific IgE to HDM after SLIT in most patients. In some, but not all, patients, IgE remained decreased during the prolonged observation, and these patients had milder symptoms than the rest. However, the group was too small to confirm this outcome. In the placebo group, such a correlation between IgE and symptoms was not observed. The changes in IgE could likely be related to aging. Additional research is warranted.

Interestingly, a group of patients in the course of SLIT did not have side effects. Occasional small oral signs were observed. This condition can result from aging of the mucosa and decrease of the threshold of sensation. Further observation is required.

The main limitation of the study is the small sample of analyzed patients. We also used a more reliable parameter, the AAdSS, for evaluation according to previous recommendations. Therefore, all results obtained during SLIT were recalculated, which might have affected the final results. However, these more modern assessment tools might have influenced the more reliable and critical results, as

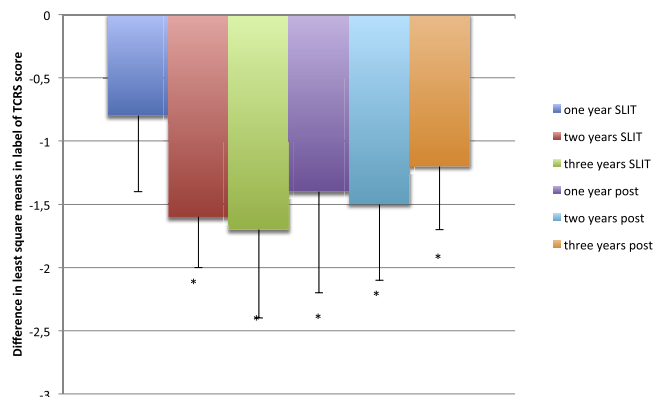


Figure 2. Decrease in TCRS in the active group during observation. *Least square mean change in TCRS was significant compared with baseline ($P < .05$). SLIT, sublingual allergen specific immunotherapy; TCRS, total combined rhinitis score.

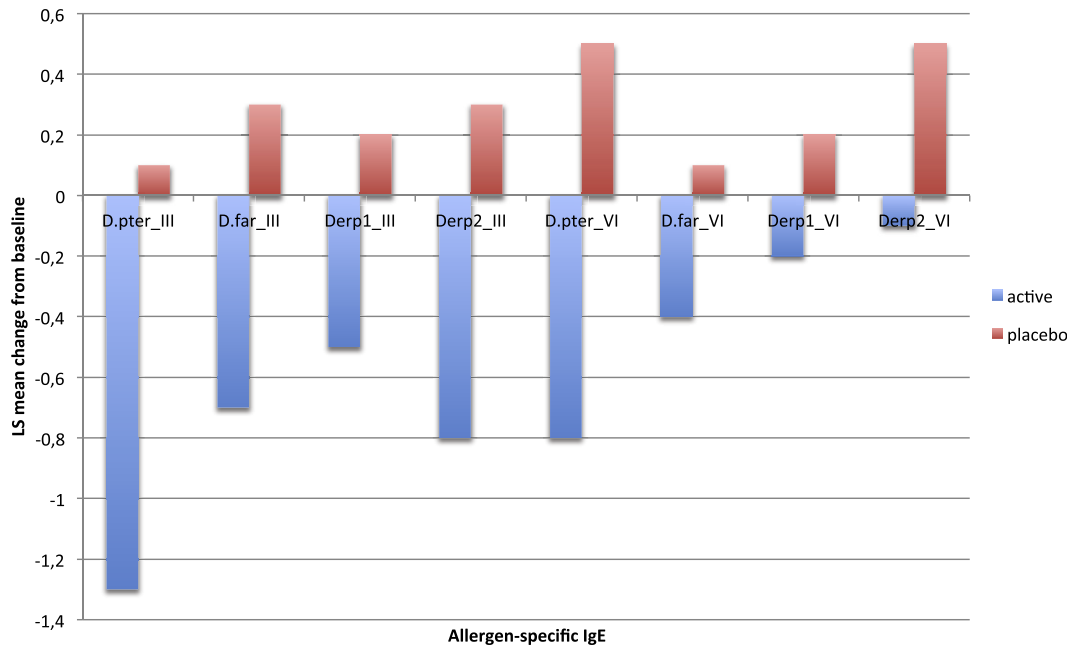


Figure 3. Decrease in house dust mite–specific IgE levels (mean $\pm$ SE) compared with placebo 3 and 6 years after the start of treatment. There were significant changes between the active and placebo groups in all analyzed parameters. D.far_III, mean change of IgE against *Dermatophagoides farinae* from baseline to 3 years after starting sublingual allergen-specific immunotherapy or placebo; D.far_IV, mean change of IgE against *Dermatophagoides farinae* from baseline to 3 years after starting sublingual allergen-specific immunotherapy or placebo and 3 years of further observation against the same allergens; D.pter_III, mean change of IgE against *Dermatophagoides pteronyssinus* from baseline to 3 years after starting sublingual allergen-specific immunotherapy or placebo; D.pter_IV, mean change of IgE against *Dermatophagoides pteronyssinus* from baseline to 3 years after starting sublingual allergen-specific immunotherapy or placebo and 3 years of further observation against the same allergens; Derp1_III, mean change of IgE against antigen D pter 1 from baseline to 3 years after starting sublingual allergen-specific immunotherapy or placebo; Derp1_IV, mean change of IgE against antigen D pter 1 from baseline to 3 years after starting sublingual allergen-specific immunotherapy or placebo and 3 years of further observation against the same allergens; Derp2_III, mean change of IgE against antigen D pter 2 from baseline to 3 years after starting sublingual allergen-specific immunotherapy or placebo; Derp2_IV, mean change of IgE against antigen D pter 2 from baseline to 3 years after starting sublingual allergen-specific immunotherapy or placebo and 3 years of further observation against the same allergens; IgE, immunoglobulin E; LS, least significant.

suggested by other researchers.¹² We did not analyze specific IgE and IgG4 for other mite antigens, preventing the assessment of diverse mite allergies in the patients studied and the different responses to SLIT. In addition, we did not monitor house dust avoidance by the study patients in their homes (in addition to the general recommendation of eliminating dust in the environment at the commencement of the study), which could have affected the final effects.

A positive effect was obtained during the course of SLIT to HDM and was sustained after it provided a substantial advantage to

elderly patients. Thus, this method of therapy could be beneficial in older people.

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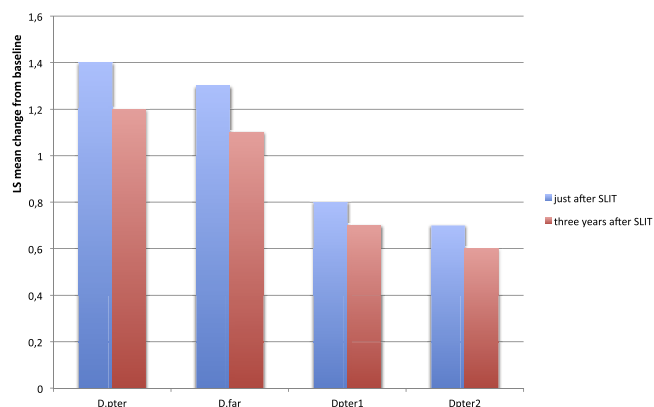


Figure 4. Increase in house dust mite–specific immunoglobulin G4 levels (mean $\pm$ SE) 3 and 6 years after the start of treatment. D.far, mean change of immunoglobulin E against *Dermatophagoides farinae* from baseline; D.pter, mean change of immunoglobulin E against *Dermatophagoides pteronyssinus* from baseline; Derp1, mean change of immunoglobulin E against antigen D pter 1 from baseline; Derp2, mean change of immunoglobulin E against antigen D pter 2 from baseline; LS, least significant; SLIT, sublingual allergen-specific immunotherapy.

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