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House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis

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Clinical & Experimental Allergy

Summary

Background Immunotherapy in elderly patients is controversial, and there is still no evidence supporting this treatment's safety and efficacy in this population. This study was performed to evaluate the safety and efficacy of specific sublingual immunotherapy for house dust mite (HDM) allergens in patients over 60 years of age with allergic rhinitis and a confirmed allergy to HDM.

Objective This study sought to assess nasal symptoms during HDM season, reduce medication use and monitor for adverse reactions during immunotherapy.

Methods One hundred and eleven 60- to 75-year-old patients with allergic rhinitis and a confirmed *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* allergy were included in the study. The patients were individually randomized to active or placebo groups using a double-blind method (NCT001605760 ClinicalTrials.gov). A total of 51 subjects in the sublingual allergen-specific immunotherapy (SLIT) group (Staloral 300R, Stallergenes, France) and 57 subjects in the placebo group were monitored for 3 years.

Results Forty-seven patients completed 3 years of SLIT, and 48 subjects finished the placebo treatment in the same time period. The total nasal symptom score decreased by 44% in the active group and 6% in the placebo group after 3 years of SLIT. This difference was only significant in the active group ($P < 0.05$). At the end of therapy, the total medication score of the active group decreased significantly by a maximum of 51% ($P < 0.05$), whereas the total medication score of the placebo control group showed an insignificant decrease ($P = 0.56$). There were no systemic adverse reactions during the study.

Conclusions & Clinical Relevance Sublingual allergen-specific immunotherapy in elderly patients with a HDM allergy to *D. pteronyssinus* and *D. farinae* generated a significant clinical improvement in the active group compared with the placebo group, particularly during the heating season. This therapy was well tolerated.

Keywords allergic rhinitis, elderly, IgE, immunotherapy

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Introduction

Allergic rhinitis, bronchial asthma and allergic skin diseases are often under-diagnosed and untreated in the elderly. The guidelines discussing the diagnosis and treatment of allergic diseases rarely focus on the elderly population and often ignore this population completely. However, allergic rhinitis and asthma caused by inhaled allergens, such as house dust mites (HDM), are more common in patients over 50 years of age [1, 2]. Therefore, it is vital that the new allergy treatment methods commonly used in young people be investigated for

their efficacy in elderly people. Sublingual allergen-specific immunotherapy (SLIT) has offered a safe and effective treatment method, especially for allergic rhinitis. Several studies have confirmed this therapy's efficacy in young people [3–5]. HDM is a major allergen for patients with allergies, and several randomized controlled immunotherapy trials exhibiting a high degree of safety and efficacy have been reported [3, 4, 6–10]. However, while doubts regarding immunotherapy's efficacy in adults and children remain, no such data exist for elderly patients. Despite the lack of objective contraindications, specific immunotherapy has not found a

significant role in older patients, which may be due to the lack of safety evidence in this group. Finally, there is also a question of whether immunotherapy can produce sufficient allergen tolerance in patients with an ageing immune system.

The aim of this study was to assess the safety and efficacy of SLIT for HDM allergens in elderly patients with allergic rhinitis and a confirmed HDM allergy.

Methods

Patients

One hundred and sixty-four patients 60 and 75 years of age were recruited from the outpatient allergy clinic to assess their eligibility for the study. The subjects with allergic rhinitis, who fulfilled the Allergic Rhinitis and its Impact on Asthma (ARIA) criterion and had a positive skin prick test (SPT), were positive for specific immunoglobulin E (sIgE) and had positive nasal provocation tests (NPTs) with *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) were included in the study. Patients with any of the following characteristics were excluded: hypersensitivity to other allergens, non-allergic rhinitis (especially senile or vasomotor rhinitis) or severe non-stable diseases (especially bronchial asthma). However, stable coronary disease, diabetes, arterial hypertension and well controlled, mild or atopic bronchial asthma were permitted. All of the subjects were required to abstain from anti-allergy drugs and glucocorticoid nasal drops for at least 6 weeks prior to the start of the study.

The patients were individually randomized in equal numbers to one of two 'parallel' groups, either the active or placebo treatment group, using a double-blind method. A total of 51 subjects in the SLIT group and 57 subjects in the placebo group were monitored for 3 years. The groups were comparable at baseline (Table 1).

Diagnostic procedures

A careful examination of the eyes, ears, nose and throat was performed on all of the patients. The severity of seasonal allergic rhinitis was assessed using the ARIA guidelines [11]. The patients with other nasal problems, such as chronic nasal obstruction, reduced olfaction, bacterial colonization and chronic sinusitis, were diagnosed based on a CT scan and nasal endoscopy. As a result of these problems, a portion of the patients were excluded from further observation. The subjects with other chronic or acute clinical disorders or with a history of respiratory tract infections within 4 weeks prior to the investigation were also excluded. The SPT was performed using inhalant allergens

Table 1. Characteristics of patients prior to randomization

	Active	Placebo	P-value
Age (years)	65.78 ± 4.89	66.71 ± 3.77	0.873
Male/female ratio	23/28	27/30	0.231
Duration of rhinitis (years)	15.7 ± 4.9	14.3 ± 6.4	0.521
Number of subject with asthma	6	5	0.885
Number of patients with eczema	4	6	0.501
Number of smokers	3	3	1.0
Number of patients with stable coronary disease	5	4	0.843
Number of patients with arterial hypertension	11	13	0.631
Number of patients with diabetes	2	4	0.745
Mean weekly nasal symptom score	4.768 ± 0.654	4.270 ± 0.594	0.250
Mean weekly non-nasal symptom score	3.369 ± 0.755	3.402 ± 0.677	0.102
Mean weekly medication score	0.532 ± 0.086	0.498 ± 0.089	0.683
Total IgE	378.99 ± 25.81	402.1 ± 67.98	0.361
Specific IgE to Der p (kU/L)	44.1 ± 9.55	39.56 ± 6.03	0.141
Specific IgE to Der f (kU/L)	50.09 ± 12.09	45.98 ± 11.6	0.178
Mean symptom score after nasal provocation tests (NPT) by Der p	5.78 ± 1.1	6.01 ± 1.34	0.112
Mean% of nasal flow decrease after NPT by Der p	85.4	81.8	0.879
Mean symptom score after NPT by Der p	4.78 ± 0.94	5.03 ± 0.64	0.345
Mean% of nasal flow decrease after NPT by Der p	74.6	80.1	0.098

(Stallergenes, Antony, France) from the following panel: *D. pteronyssinus*, *D. farinae*, mixed grass, mixed tree, mugwort, *Alternaria*, *Cladosporium*, dog and cat allergoids. Positive (10 mg/mL histamine) and negative (saline) controls were included. An HDM allergy was defined as having positive skin tests for two allergens, Der p and Der f, with a minimum weal diameter at least 3 mm greater than that elicited by the negative control [12]. Those patients with negative tests for histamine sensitivity were excluded from further analysis. The serum sIgE response to the Der p and Der f allergens was measured using the immunoenzymatic test from Pharmacia (Thermo Fisher, Uppsala, Sweden). The results were considered positive when the sIgE concentration was > 0.35 IU/mL (according to the manufacturer's instructions). NPTs using active anterior rhinomanometry with commercial Der p and Der f (Allergharma, Reinbeck,

Germany) allergens were performed using the methods described by Bachert et al. and Dordal et al. [13, 14]. A reduction in the peak nasal inspiratory flow $\geq 40\%$ and an increase in symptoms ≥ 5 points were considered by Bachert et al. and Dordal et al. [13, 14] to be positive NPT criteria. Only those patients with a positive provocation to both allergens, Der p and Der f, were included in the study. The NPTs were also repeated after 3 years of treatment.

Treatment

The patients were randomly selected to receive oral Staloral 300 SR Der p and Der f 50/50% extract (Stallergenes) or placebo (Fig. 1). The recruitment period was limited to 3 months (November–January). Staloral (R) 300 is a sublingual allergen extract solution used for allergen immunotherapy. There was a 2-week run-in period. During the first 8 days, the patients took daily increasing doses in the form of 1–8 puffs of the 100 IR/mL extract. Next, on days 9–16, the patients took 1–8 puffs of the 300 IR/mL extract. Next, the patients received maintenance treatments consisting of five applications of 18 puffs (1 puff = 30 IR) of 300 IR/mL extract five times a week. The mean treatment duration was 28.2 months (range: 3–36 months). Each dose had to be taken in the morning before breakfast, and the allergen drops had to be kept under

the tongue for at least 2 min before swallowing. Using this schedule, an average cumulative dose of 421 200 IR of allergens was administered to each patient undergoing active treatment for all 3 years of the study. The Staloral and placebo were dispensed in drops from bottles identical in appearance. These treatments were pre-packaged in bottles and consecutively numbered for each participant according to the randomization schedule. Each patient was assigned an order number and received the box corresponding to the pre-packaged bottles. The volume of residual SLIT medication was assessed for every patient. When necessary, the patients were allowed to use the following drugs: antihistamine (5 mg levocetirizine tablets), intra-nasal corticosteroid (mometasone), topical ocular antihistamine drops (ebastine) and a 4 mg tablet of methylprednisolone. Other anti-allergic drugs were not permitted during the study. The nasal corticosteroid was the first-line treatment. The patients recorded the use of medications on the diary card, and a specific weekly score was assigned (1 point: used only nasal corticosteroids or eye drops at a minimum of per 1 day per week; 2 points: the previous therapy plus one tablet of levocetirizine at a minimum of per 1 day; 3 points: the previous therapies plus one 4 mg tablet of methylprednisolone at a minimum of per 1 day). The number of participants who completed the study is shown in Fig. 1.

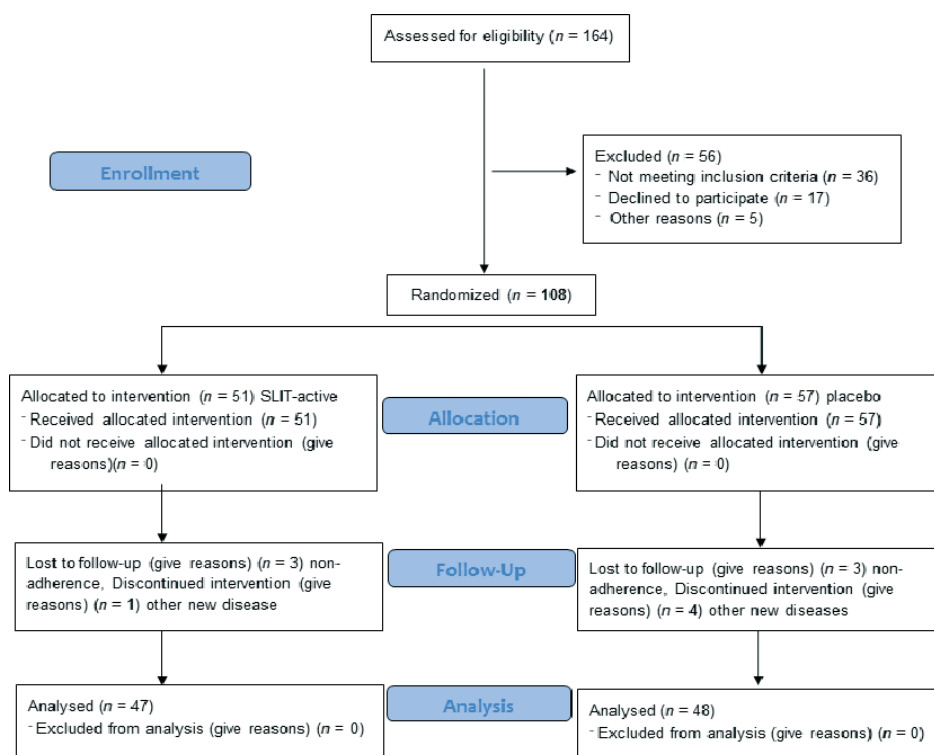


Fig. 1. Number of participants assessed for eligibility that completed the study.

Symptoms and diary

The patients' allergic rhinitis symptoms were monitored using a 7-point visual graphic scale (published by the Joint Task Force and modified by ARIA) for grading the severity of nasal (sneezing, runny nose, congestion, itchy nose and post-nasal drip) and non-nasal (eye symptoms, throat symptoms, chronic cough, ear symptoms, headache) symptoms in addition to mental function and quality of life changes [15]. This scale was based on the patients' diaries completed during the 3-year observation period (144 weeks), when SLIT was instituted. The patients' Peak Expiratory Flow (PEF) was measured each day just before administering SLIT, and the patients were monitored for possible adverse reactions for 30 min after SLIT administration.

The statistical analysis was performed using Statistica version 8.12 (SoftPol, Warsaw, Poland). Student's *t*-test for unpaired data was used to analyse differences in medication and symptom scores, NPT scores, sIgE and IgE. The Wilcoxon test was used to analyse other differences between groups. The chi-square test was used to analyse differences between NPT flow and the rate of adverse events in each study group. A correction for multiple comparisons for the heating season was performed. The differences were considered significant at $P < 0.05$. The study was approved by the local ethics committees (approval number 657898/2008). The study was registered in ClinicalTrials.gov as trial no. NCT01605760.

Results

Forty-seven patients completed 3 years of SLIT, while 48 subjects finished the placebo treatment within that time frame. Four patients in the active group and nine patients in the placebo group prematurely terminated study participation, as shown in Fig. 1. The nasal symptom scores of the active group and the placebo group were significantly different at the end of the study (Table 2); however, there was no such difference in non-nasal symptoms. The total nasal symptom score decreased by 44% (4.768 ± 0.654 vs. 2.656 ± 0.634) in the active group and 6% (4.270 ± 0.594 vs. 3.977 ± 0.501) in the placebo group. This difference was significant only in the active group ($P < 0.05$). These data are shown in Fig. 2. The mean nasal symptom score trend is presented in Fig. 3.

Medication scores

After 21 months of treatment, the total medication score started to significantly decrease in the active group (Fig. 4). However, this decrease was particularly evident in the heating season ($P < 0.05$). The total

Table 2. Clinical and laboratory parameters of all subjects after 3 years of treatment

	Active	Placebo	<i>P</i> -value
Mean weekly nasal symptom score	2.656 ± 0.634	3.975 ± 0.501	0.011
Mean weekly non-nasal symptom score	2.239 ± 0.276	3.398 ± 0.244	0.341
PEFR value before medication use (L/min)	340.1 ± 11.21	372 ± 13.3	0.201
PEFR value after medication use (L/min)	337.8 ± 8.3	353 ± 7.4	0.238
Mean weekly medication score	0.345 ± 0.076	0.467 ± 0.063	0.034
Total IgE at 36 months (kU/L)	398.5 ± 48.97	376.8 ± 59.91	0.391
Specific IgE to Der p at 36 months (kU/L)	38.89 ± 11.41	39.8 ± 16.56	0.421
Specific IgE to Der f at 36 months (kU/L)	42.57 ± 11.81	48.23 ± 13.52	0.116
Mean symptom score after nasal provocation tests (NPT) by Der p at 36 months	4.57 ± 0.83	3.66 ± 1.21	0.074
Mean% of nasal flow decrease after NPT by Der p at 36 months	67.54	78.76	0.023
Mean symptom score after NPT by Der f at 36 months	4.21 ± 0.3	3.95 ± 0.61	0.088
Mean% of nasal flow decrease after NPT by Der f at 36 months	63.03	78.91	0.013

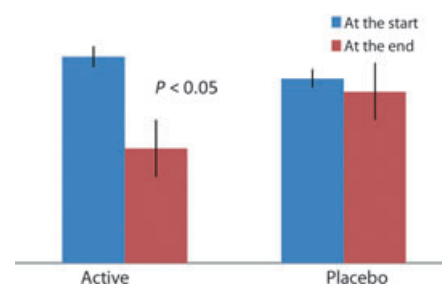


Fig. 2. Comparison of mean weekly nasal symptom score at the start vs. at the end of study in active group and placebo.

medication score decreased by a significant 35% in the active treatment group ($P < 0.05$), but did not decrease significantly in the placebo group ($P = 0.56$) (Fig. 5). Additionally, the medication scores were significantly lower in the active group as opposed to the placebo group at the end of the study (Table 2).

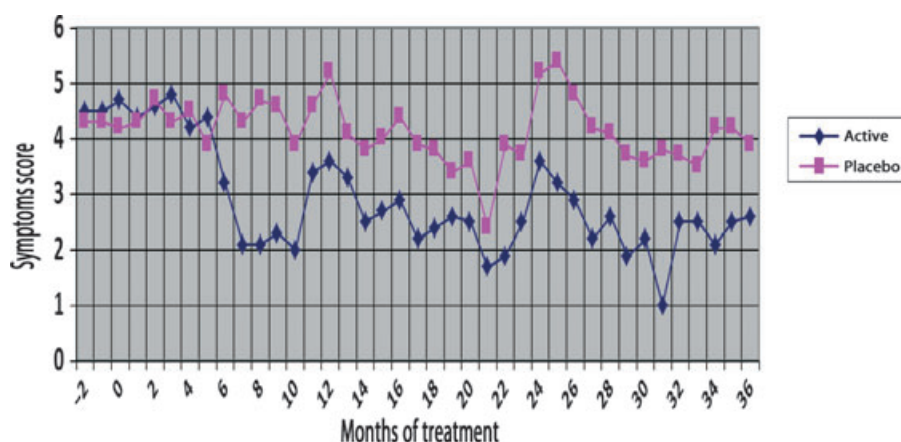


Fig. 3. Mean weekly nasal symptom scores shown in monthly intervals. 0–14, 12–16, 24–28, and 36 months during heating season.

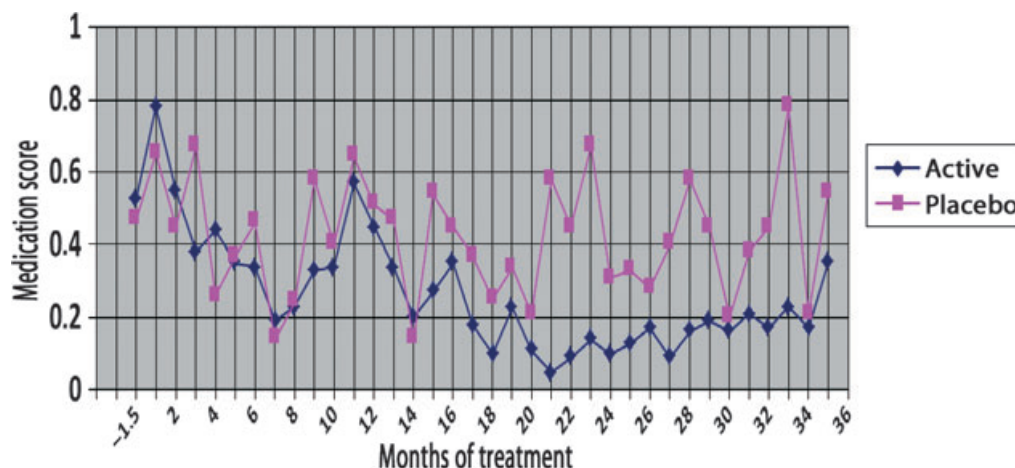


Fig. 4. Mean weekly nasal symptom scores shown in monthly intervals. 0–14, 12–16, 24–28, and 36 months during heating season. (–1.5): The initial medication score was calculated on the basis of using of drug just before their withdrawal for 6 weeks prior study.

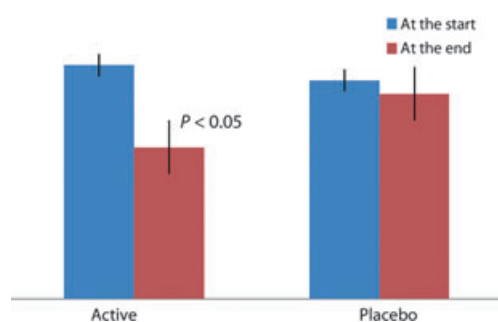


Fig. 5. Comparison of mean medication score at the start vs. at the end of study in active group and placebo.

Safety assessment

There were no systemic adverse reactions or severe local reactions in either group during the entire study. Three patients in the active group had local adverse

reactions (oral pruritus: 2; facial flushing: 1) that spontaneously resolved. In the placebo group, one patient reported an episode of rhinorrhoea after placebo use.

Nasal provocation test and immunological parameters

The active group exhibited decreased reactivity of the nasal mucosa after Der p and Der f provocation over the 3-year course of SLIT treatment compared with the placebo group ($P < 0.05$); however, the clinical symptom score reactions during the provocations were unchanged (Table 2). Additionally, the mean nasal flow decrease during the NPT was approximately 17.86% ($P = 0.032$) for Der p and approximately 11.57% ($P = 0.046$) for Der f at the end of the study compared with the start of the study.

There were no significant changes in the NPT with Der p or Der f in the placebo group at the start vs. the end of the study.

Discussion

To the best of our knowledge, this was the first double-blind, placebo-controlled SLIT trial performed in elderly patients. Immunotherapy in patients > 60 years of age remains uncommon. However, the prevalence of IgE-dependent allergic rhinitis and other atopic diseases in elderly patients is reportedly increasing. This increase is relevant because of the ageing world population and the global trend of increased allergic diseases [1, 2, 16]. An important issue in this study was the difficulty in identifying those elderly patients with only allergic rhinitis and no other ENT problems. This scarcity significantly reduced the target group of respondents.

According to the criteria defined by Malling, the efficacy of immunotherapy in double-blind, placebo-controlled trials must be supported by symptom and medication score improvements of more than 30% [17]. In this study, the active treatment group showed 44% and 35% improvement respectively. It is important that these differences relative to the placebo group were particularly evident in successive heating seasons, which corresponds to the highest period of dust mite allergen exposure in Poland. These results also indicate that the ageing immune system has no significant influence on the effectiveness of immunotherapy. However, the typical ageing of oral mucosa was probably responsible for only a small number of side-effects. The similar problem of ageing nasal mucosa in elderly patients probably caused fewer allergic rhinitis symptoms in this group than in young patients. Ageing probably resulted in relatively low nasal symptom scores. For this reason, we used the 7-point visual analogue scale, which easily picks up small differences in nasal reactions. Diaries were filled weekly to simplify this procedure for elderly patients. Naturally, this approach could slightly reduce the reliability of the observations.

The efficacy of 3 years of SLIT therapy for HDM allergies in the elderly is comparable with the data previously reported for younger patient populations with allergic rhinitis [18, 19]. In addition, reducing the need for symptom-targeted drugs, primarily antihistamines, improves the safety profile of treatment in the elderly. In older patients, the most frequent adverse reactions are to antihistamine drugs. However, several studies argue the positive role of SLIT. Guez et al. [7] showed that SLIT with HDM extracts for perennial allergic rhinitis is well tolerated but does not produce any significant clinical improvement in the active group. This observation is not isolated. However, this finding provides evidence that immunotherapy in elderly patients, despite low popularity, should be considered for the treatment of allergic rhinitis more frequently. Unfortunately, the few studies that support the safety and effectiveness of immunotherapy in the elderly are not

blinded [20, 21]. Of course, this gap in the literature requires further controlled studies in this area. Furthermore, one major problem is determining if elderly patients qualify for immunotherapy. In addition to clear indications such as allergies, other overlapping diseases must be excluded. In the case of the patients analysed in this study, those who were excluded were mainly those with senile rhinitis and vasomotor rhinitis. Despite a clear diagnosis of a dust mite allergy and positive NPTs, other diagnoses cannot be ruled out in some patients. The challenge is that ARIA emphasizes a specific mechanism associated with chronic rhinitis [15]. Another challenge is the coexistence of other serious chronic diseases, which are often unstable and preclude immunotherapy. Patients with such diseases were excluded from this study. However, mild stable cardiovascular disease and type 2 diabetes did not affect the safety of immunotherapy in the patient population studied, and vice versa. This study supports the use of immunotherapy in elderly patients through the demonstration of a good safety profile without any systemic reactions during 3 years of therapy. These observations have previously been made [20, 21]. The results of the NPT emphasize its value not only in diagnosing allergies but also in monitoring the effectiveness of immunotherapy, as mentioned earlier [22–24]. The reduced allergen-induced nasal reactivity observed after 3 years of desensitization is proof of this finding. Unfortunately, no data supporting this observation in a clinical setting are available. A lack of change in the concentration of allergen-specific IgE or total IgE in the serum supports the idea that this marker is not valuable for monitoring the efficacy of immunotherapy; however, this topic is still discussed in the literature [7, 25, 26]. Additionally, this study did not rely on exposure to natural allergens, which may have influenced the serum IgE concentration after Der p and Der f provocation in patients in the active and placebo treatment groups. This effect was observed in a previous study [7]. Therefore, other parameters evaluating the *in vitro* efficacy of immunotherapy need to be identified.

In conclusion, this study showed that SLIT with HDM allergens from *D. pteronyssinus* and *D. farinae* resulted in a significant clinical improvement in the active group compared with the placebo group, particularly in the heating season. This therapy was well tolerated. These observations may lead to the more frequent use of SLIT immunotherapy in the elderly. However, further controlled studies are required for this oral treatment, especially with other allergens, and injection-based treatment studies should also be performed.

Conflicts of interest: The authors declare no conflicts of interest.

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