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RHINOLOGY

Efficacy of sublingual immunotherapy for house dust mite allergic rhinitis

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Abstract In the present study, we investigated the outcomes of sublingual immunotherapy (SLIT) in house dust mite-induced allergic rhinitis (HDM-AR) patients. In this prospective, multicentric study, 186 patients with AR who had positive skin prick test results for HDMs were included. The patients were administered SLIT using Staloral 300 for 1 year. Evaluation of the patients regarding symptom scores, clinical findings and Rhinitis Quality of Life Questionnaire (RQLQ) scores was performed at baseline, and then at 6 and 12 months of therapy. Our results showed that, for all of the evaluated items (symptom scores, clinical findings and RQLQ scores), 12-month values were significantly lower than those at 6 months and baseline. Similarly, 6-month values were significantly lower than those at baseline. There were no complications in any of our patients. SLIT for HDM-AR is a treatment modality that can be used safely. We obtained better results than expected, and the treatment showed a positive psychological effect; the patients believed that SLIT was the final step of treatment and, which made them feel better.

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Introduction

Sublingual administration of allergen extracts has been shown to be a well-tolerated and efficacious approach to the treatment of allergic rhinitis (AR). Sublingual immunotherapy (SLIT) reduces the symptoms and medication requirements [1]. The immunologic mechanisms of SLIT are less well established. An increase in IgG4 and induction of allergen-specific IgA without a change in IgE values have been reported with use of SLIT [2].

House dust mites (HDMs) cause persistent allergic respiratory diseases, such as AR and allergic asthma (AA) [3, 4]. Subcutaneous allergen immunotherapy (SCIT) and SLIT are beneficial in patients with AR and allergic asthma (AA) induced by HDMs [5]. Calderon et al. [5] reported that there is no consensus regarding basic treatment parameters (e.g., dose and duration) in HDM SCIT and SLIT. In the present study, we investigated the efficacy of SLIT in HDM-induced allergic rhinitis (HDM-AR). This was conducted in a multicenter study. In this multicenter study, the patients were followed for a year.

Patients and methods

This study was conducted as a prospective, multicenter study. Ethics committee approval was obtained from the GOP Taksim Education and Research Hospital. The study was conducted according to the rules outlined in the Declaration of Helsinki [6].

Subjects

Two-hundred cases with AR who had positive skin prick test results for HDMs were assessed for participation in this multicenter study. However, 186 cases finally underwent treatment for a year. Fourteen patients moved to other cities or did not attend the control examination. Patients were included in the study after providing informed consent.

There were 135 (72.6 %) females and 51 (27.4 %) males, aged 19–51 years (mean age 27.04 years).

Inclusion criteria

- Adult patients with a diagnosis of AR
- Moderate or severe symptoms that was continuous
- Skin prick test to be performed, and HDM allergy to be demonstrated
- Symptoms to go on as a perennial manner
- Symptoms cannot be reduced sufficiently by antihistamines and topical nasal corticosteroids. These medications were taken 3 months ago. Since that time, they did not use any medications

Exclusion criteria

- Malignancy
- Immune system disorders
- Adrenaline contraindications

  Coronary heart disease
  Hypertension
  Users of beta-blockers and angiotensin-converting-enzyme inhibitors

- Psychiatric condition that prevents cooperation with long-term treatment
- Acute tuberculosis
- Pregnancy
- Chronic rhinosinusitis

Study protocol

1. Baseline examination: Patients with AR symptoms such as nasal discharge, nasal itching, nasal congestion and sneezing, and those with positive skin prick test results for HDMs, were included in the study. Patients were evaluated using symptom scores, clinical examination, and Rhinitis Quality of Life Questionnaire (RQLQ) [7, 8].
2. The patients were administered sublingual immunotherapy (SLIT) with Staloral 300 (Stallergenes, Istanbul, Turkey) for a year (*Dermatophagoides pteronyssinus* 50 %; *Dermatophagoides farinae* 50 %).
3. Six-month evaluation: symptom scores, clinical parameters, and RQLQ were re-evaluated; and SLIT via Staloral 300 was continued.
4. Twelve-month evaluation: symptom scores, clinical examination, and RQLQ were re-evaluated. No complication occurred, and no treatment discontinuation was required for reasons of allergy or discomfort.

Instrumentations

Skin prick test

The Prick test [Prick test kit; Stallergenes S.A., France (SAY Pharmaceuticals, Turkey)] contained the following eight allergens: (1) positive control, (2) negative control, (3) *D. pteronyssinus*, (4) *D. farinea*, (5) grass pollens, (6)

cereals, (7) tree pollen mixture, and (8) molds. Patients did not use antihistamines during the 10 days prior to undergoing the test. To provide standard drilling, a prick lancet (Mizollen; H. Herenz GmbH, Hamburg, Germany) was used. Témoin was used as the negative control, and 10 mg/ml histamine hydrochloride was used as the positive control. Reactions were read 20 min after the test by the researcher. Skin tests were evaluated according to the induration diameter; values ≥3 mm were considered positive [9]. All of the patients had positive skin prick test results for HDMs.

Symptom scores

Symptoms were assessed using a questionnaire (0 = no, 1 = mild, 2 = moderate, 3 = severe). The rhinitis symptom score included nasal discharge, nasal congestion, sneezing, and nasal itching.

Clinical findings

Clinical findings were evaluated by physical examination. Lower turbinate color (0 = natural, 1 = pale, 2 = bluish and 3 = severely pale or bluish) [10], and turbinate edema were assessed during ear, nose and throat examination using a 0–3 scale (0 = no, 1 = mild, 2 = moderate, 3 = severe).

RQLQ [7, 8]

The RQLQ was completed at baseline and 6 and 12 months later. In the RQLQ, seven parameters (limited activities, sleep disorders, nose symptoms, eye symptoms, symptoms other than those of the nose or eye, general problems, and emotional functions) were evaluated by 28 questions. Rhinoconjunctivitis was evaluated by means of a 7-step scale over 1 week (0 = no suffering to 6 = suffered too much). This scale included the following: three questions about activities at home and work; social activities and open-air activities; three questions about sleep quality; seven questions concerning fatigue, dehydration, decreased productivity, tiredness, lack of concentration, headache, and deprivation; three questions about general issues; four questions about nose symptoms; four questions about eye symptoms; and four questions about emotional parameters.

Statistical analysis

SPSS 16.0 (2007; SPSS Inc., Chicago, IL, USA) was used. A dependent-samples *t* test was used for analysis. A *p* value less than 0.05 was deemed to indicate statistical significance.

Results

Symptom scores are shown in Table 1 and Fig. 1. Among the symptom scores (nasal discharge, sneezing, congestion and itching), 12-month values were significantly lower than those at 6 months and baseline. Similarly, 6-month values were significantly lower than those at baseline ($p < 0.05$).

Results of physical examination (clinical findings) are shown in Table 2 and Fig. 2. Among turbinate color and edema scores, 12-month values were significantly lower than those at 6 months and baseline. Similarly, 6-month values were significantly lower than those at baseline.

RQLQ results are shown in Table 3 and Fig. 3. All RQLQ domains and overall RQLQ scores at 12-month values were significantly lower than those at 6 months and baseline. Similarly, 6-month values were significantly lower than those at baseline.

Discussion

HDMs are one of the most common sources of indoor allergens, and trigger perennial AR and asthma. The two main species are *D. pteronyssinus* and *D. farinae* [11]. In patients with AR and/or asthma tested for allergic causality, a prevalence of HDM sensitization of ~48 % has been

Table 1 Symptom results

Symptoms	Baseline (mean ± SD) $n = 186$	p_{B-6m}*	6th Month (mean ± SD) $n = 186$	p_{6-12m}*	12th Month (mean ± SD) $n = 186$	p_{B-12m}*
Nasal discharge	2.03 ± 0.87	<0.001	1.59 ± 0.94	<0.001	1.40 ± 0.90	<0.001
Sneezing	1.77 ± 0.97	<0.001	1.20 ± 0.85	<0.001	1.07 ± 0.79	<0.001
Congestion	2.14 ± 0.89	<0.001	1.58 ± 0.87	<0.001	1.41 ± 0.85	<0.001
Itching	1.61 ± 0.86	<0.001	1.15 ± 0.75	<0.001	0.98 ± 0.70	<0.001

*p_{B-6m} statistical significance between baseline and 6 months by dependent-samples *t* test

*p_{6-12m} statistical significance between 6 and 12 months by dependent-samples *t* test

*p_{B-12m} statistical significance between baseline and 12 months by dependent-samples *t* test

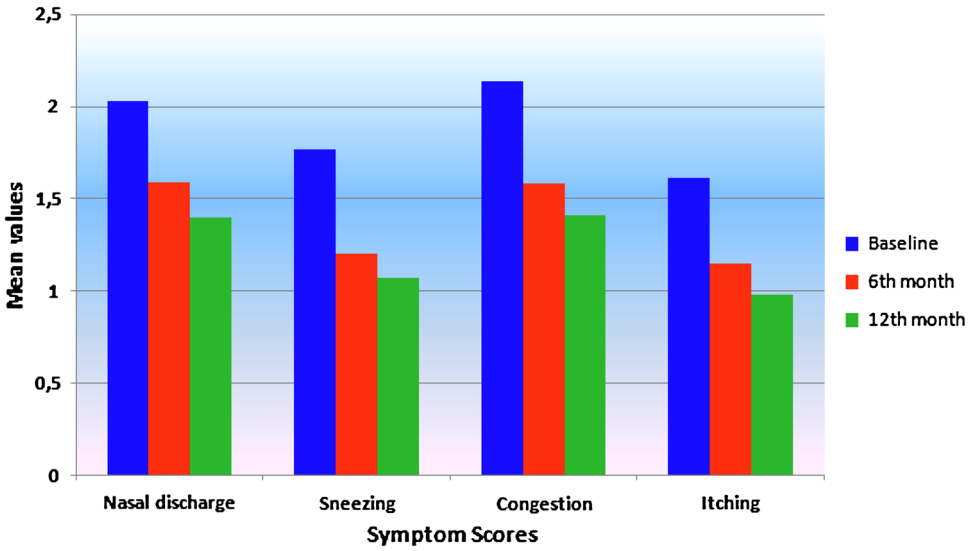

Fig. 1 Symptom scores at baseline, 6 and 12 months of sublingual immunotherapy

reported [12]. The vast majority of patients with AA and HDM sensitization also have AR, and approximately half of those with AR and HDM sensitization also have asthma [13].

The use of allergen immunotherapy with sublingual solutions of HDM extracts has shown benefit in adults and children with HDM-related rhinitis [14]. Bergmann et al. [15] reported that, in adults with HDM-associated AR, 12 months of treatment with 500-IR and 300-IR sublingual tablets of HDM allergen extracts were efficacious and well tolerated. HDM SLIT also appears to be effective in children and adolescents with rhinitis and/or asthma due to HDM allergens, with no tolerability issues and with benefits similar to those in adults [16].

In the present study, we investigated the outcomes of SLIT in HDM-AR patients. The treatment was continued for a year. Evaluation of the patients regarding symptom scores, clinical findings and RQLQ scores were performed at baseline, and at 6 and 12 months of therapy. Our results showed that, for all of the evaluation items, the 12-month values were significantly lower than the 6-month and baseline values. Similarly, 6-month values were significantly lower than those at baseline.

Wise, et al. [17] reported that SLIT is an alternative administration route for allergen-specific immunotherapy. Compared to SCIT, SLIT has a shorter escalation phase, equal or greater efficacy for rhinitis, and an improved safety profile. In their study, patients choosing SLIT completed the mini-Rhinoconjunctivitis Quality of Life Questionnaire (m-RQLQ), a 14-item Likert-type questionnaire, at baseline and during maintenance therapy. Patients typically reached maintenance dosing in less than 5 weeks. Initial m-RQLQ results indicated statistically significant ($p < 0.05$) improvement on 12 of 14 domains, including impact on regular and recreational activities, sleep, nose rubbing and nose blowing, stuffy nose and runny nose, itchy eyes, sore eyes, watery eyes, thirst, and tiredness. In addition, total m-RQLQ score showed statistically significant improvement ($p = 0.001$). No serious adverse events occurred with the initiation of SLIT.

SLIT was reported to be safe and significantly reduces symptoms and medication requirements in AR [18]. In the present study, we used Staloral 300 for SLIT in HDM-AR patients, and no complication occurred. Additionally, no discontinuation of Staloral 300 treatment occurred for reasons of allergy or discomfort. We did not observe any side effects of SLIT; and we can say that SLIT is a safe treatment, as Wang, et al's study [19].

Wang et al. [19] reported that SLIT with a mixture of *D. pteronyssinus* and *D. farina* extract is effective and safe for patients with HDM-AR. An effect can be observed as early

Table 2 Physical examination results

Physical examination	Baseline (mean ± SD)	p_{B-6m}*	6th Month (mean ± SD)	p_{6-12m}*	12th Month (mean ± SD)	p_{B-12m}*
Turbinate color	1.62 ± 0.75	<0.001	1.08 ± 0.62	<0.001	0.93 ± 0.61	<0.001
Odema	1.60 ± 0.74	<0.001	1.15 ± 0.67	<0.001	0.95 ± 0.69	<0.001

*p_{B-6m} statistical significance between baseline and 6 months by dependent-samples *t* test

*p_{6-12m} statistical significance between 6 and 12 months by dependent-samples *t* test

*p_{B-12m} statistical significance between baseline and 12 months by dependent-samples *t* test

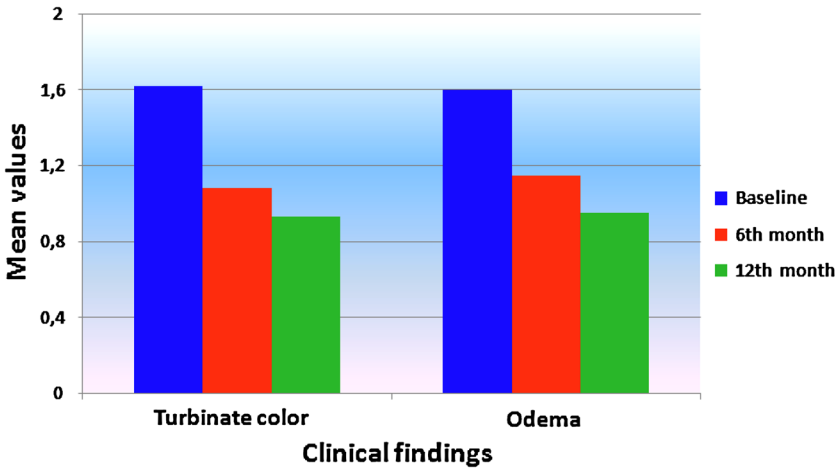

Fig. 2 Clinical findings at baseline, 6 and 12 months of sublingual immunotherapy

Table 3 RQLQ results

RQLQ domains	Baseline (mean ± SD)	p_{B-6m}*	6th Month (mean ± SD)	p_{6-12m}*	12th Month (mean ± SD)	p_{B-12m}*
Eye problems	1.05 ± 0.84	<0.001	0.63 ± 0.49	<0.05	0.58 ± 0.46	<0.001
Nasal problems	4.13 ± 0.79	<0.001	2.88 ± 0.72	<0.001	2.71 ± 0.72	<0.001
None-nose/eye	1.79 ± 0.55	<0.001	1.32 ± 0.57	<0.001	1.14 ± 0.49	<0.001
Sleep	3.29 ± 1.03	<0.001	2.44 ± 0.95	<0.05	1.95 ± 0.9	<0.001
Activity	3.60 ± 1.3	<0.001	2.44 ± 0.94	<0.001	1.79 ± 0.86	<0.001
Emotions	1.97 ± 1.27	<0.001	1.14 ± 0.71	<0.001	1.34 ± 0.71	<0.001
Practical problems	3.45 ± 0.99	<0.001	2.01 ± 0.73	<0.001	1.67 ± 0.88	<0.001
Overall	2.75 ± 0.53	<0.001	1.87 ± 0.4	<0.001	1.57 ± 0.39	<0.001

*p_{B-6m} statistical significance between baseline and 6 months by dependent-samples *t* test

*p_{6-12m} statistical significance between 6 and 12 months by dependent-samples *t* test

*p_{B-12m} statistical significance between baseline and 12 months by dependent-samples *t* test

as 14 weeks after treatment. In the present multicenter study, SLIT was used to treat HDM-AR. A total of 120 AR patients, aged 4–60 years, were treated for 6 months. Eighty-five patients (70.8 %) completed the study. The total symptom and visual analog scores (VAS) in the SLIT group decreased significantly compared with those of the placebo controls ($p < 0.05$) after week 14, and showed significant ($p < 0.05$) improvement in all individual AR symptoms in the SLIT group (e.g., sneezing, nasal discharge, itching, and nasal obstruction) after week 22. There was a significant ($p < 0.05$) increase in the level of IgG4 to both *D. pteronyssinus* and *D. farina* in the SLIT group—but not in the placebo group—after treatment.

Bozek et al. [20] reported that SLIT in elderly patients with 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 also well tolerated.

SLIT using *D. pteronyssinus* allergen alone increased levels of serum IgG4 against Dpt, Der *p* 1, and Der *p* 2, and those of serum IgG1 and salivary IgA against Dpt and Der *p* 1. These results may explain the SLIT-induced clinical improvement and long-term reduction in symptom/medication scores with modulation of mucosal/systemic antibody responses [21].

In the present study, we show that SLIT is effective for the treatment of HDM-AR. The effect of SLIT becomes more pronounced over time. The effectiveness of treatment at 12 months was better than that at 6 months and baseline, interms of the symptom scores, clinical findings and RQLQ scores. No complication was noted in any of our patients. Thus, SLIT can be used safely in HDM-AR patients.

SLIT for HDM-AR is a safe treatment modality. We obtained better results than expected. SLIT also showed a positive psychological effect. The patients believed that SLIT was the final step of treatment, which made them feel better.

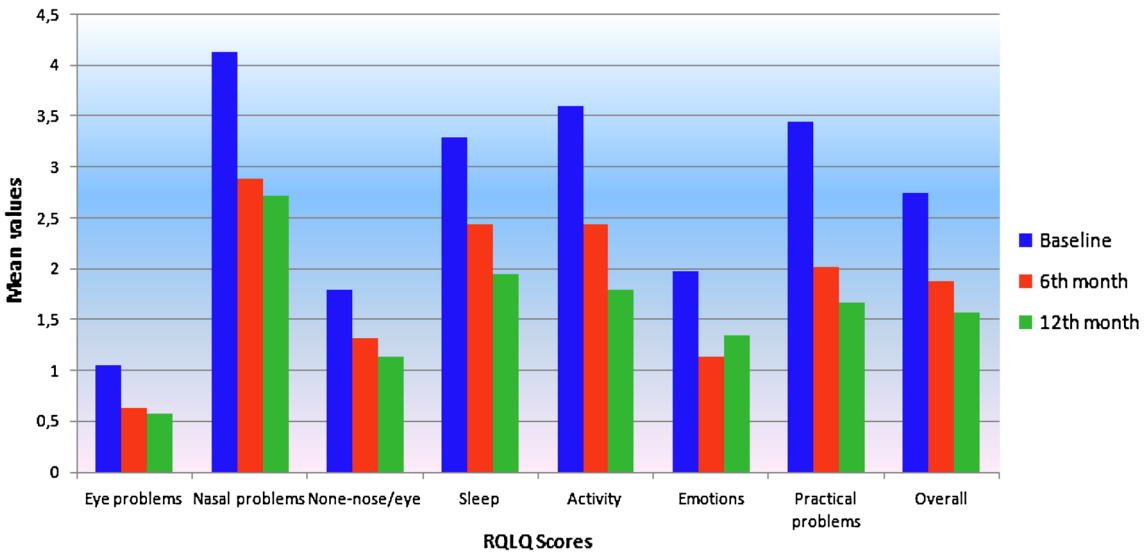

Fig. 3 RQLQ results at baseline, 6 and 12 months of sublingual immunotherapy

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Conflict of interest The authors declare that there is no conflict of interest.

References

1. Wilson DR, Lima MT, Durham SR (2005) Sublingual immunotherapy for allergic rhinitis. Systematic review and meta-analysis. Allergy 60:4–12
2. Bahceciler NN, Arikan C, Taylor A et al (2005) Impact of sublingual immunotherapy on specific antibody levels in asthmatic children allergic to house dust mites. Int Arch Allergy Immunol 136(3):287–294
3. Platts-Mills TAE, Erwin EA, Heymann PW, Woodfolk JA (2009) Pro: the evidence for a causal role of dust mites in asthma. Am J Respir Crit Care Med 180:109–121
4. Sporik R, Chapman MD, Platts-Mills TA (1992) House dust mite exposure as a cause of asthma. Clin Exp Allergy 22:897–906
5. Calderon MA, Casale TB, Nelson HS, Demoly P (2013) An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. J Allergy Clin Immunol 132(6):1322–1336
6. WMA, Declaration Of Helsinki (2008) Ethical principles for medical research ınvolving human subjects. In: 59th WMA general assembly, W.M. Association, Editor, Seoul
7. Juniper EF, Guyatt GH (1991) Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exper Allergy 21:77–83
8. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ (1996) Interpretation of rhinoconjunctivitis quality of life questionnaire data. J Allergy Clin Immunol 98:843–845
9. Lachapelle JM, Maibach HI (2009) Patch Testing and Prick Testing: A Practical Guide, vol 2. Springer, Berlin
10. Cingi C, Gunhan K, Gage-White L, Unlu H (2010) Efficacy of Leukotriene Antagonists as Concomitant Therapy in Allergic Rhinitis. Laryngoscope 120:1718–1723
11. Radulovic S, Calderon MA, Wilson D, Durham S (2010) Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev 12:CD002893
12. Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F (2002) Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. BMJ 325:411–414
13. Linneberg A, Henrik Nielsen N, Frolund L, Madsen F, Dirksen A, Jorgensen T (2002) The link between allergic rhinitis and allergic asthma: a prospective populationbased study. The Copenhagen Allergy Study. Allergy 57:1048–1052
14. Mosbech H (1985) House dust mite allergy. Allergy 40:81–91
15. Bergmann KC, Demoly P, Worm M et al (2014) Efficacy and safety of sublingual tablets of house dust mite allergen extractsin adults with allergic rhinitis. J Allergy Clin Immunol 133(6):1608.e6–1614.e6
16. Trebuchon F, Lhéritier-Barrand M, David M, Demoly P (2014) Characteristics and management of sublingual allergen immunotherapy in children with allergic rhinitis and asthma induced by house dust mite allergens. Clin Transl Allergy 29(4):15
17. Wise SK, Woody J, Koepp S, Schlosser RJ (2009) Quality of life outcomes with sublingual immunotherapy. Am J Otolaryngol 30(5):305–311. doi:10.1016/j.amjoto.2008.06.003
18. Wilson DR, Torres LI, Durham SR (2003) Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2:CD002893
19. Wang DH, Chen L, Cheng L et al (2013) Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. Laryngoscope 123(6):1334–1340. doi:10.1002/lary.23935
20. Bozek A, Ignasiak B, Filipowska B, Jarzab J (2013) House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. Clin Exp Allergy 43(2):242–248
21. Queirós MG, Silva DA, Siman IL et al (2013) Modulation of mucosal/systemic antibody response after sublingual immunotherapy in mite-allergic children. Pediatr Allergy Immunol 24(8):752–761. doi:10.1111/pai.12163