The Journal of Laryngology & Otology (2017), ***131***, *997–1001*.

doi:10.1017/S0022215117002110

MAIN ARTICLE

Long-term effects of allergen-specific subcutaneous immunotherapy for house dust mite induced allergic rhinitis

E SAHIN[1], D DIZDAR[2], M E DINC[3], A A CIRIK[4]

[1]*Department of Otolaryngology, Head and Neck Surgery, Bayındır Hospital Icerenkoy, Istanbul,* [2]*Department of Otorhinolaryngology, Medical Park Bahçelievler Hospital, Faculty of Medicine, Istanbul Kemerburgaz University, Istanbul,* [3]*Department of Otorhinolaryngology, Gaziosmanpasa Taksim Education and Research Hospital, Turkish Ministry of Health, Istanbul, and* [4]*Department of Otolaryngology, Head and Neck Surgery, Umraniye Research and Training Hospital, Istanbul, Turkey*

Abstract

Background: Allergic rhinitis is strongly associated with the presence of house dust mites. This study investigated the long-term effects of allergen-specific immunotherapy. Allergen-specific immunotherapy was applied over three years. The study was based on a 10-year follow up of patients with allergic rhinitis.

Methods: The study was conducted between 2001 and 2015. Skin prick test results and symptom scores were evaluated before (26 patients) and after 3 years (20 patients) of allergen-specific immunotherapy (using data from a previously published study), and 10 years after allergen-specific immunotherapy had ended (20 of 26 patients).

Results: The symptom scores before allergen-specific immunotherapy were significantly higher than those obtained after 3 years of allergen-specific immunotherapy and 10 years after allergen-specific immunotherapy ($p < 0.0175$). There were no significant differences between the scores obtained at 3 years and 10 years after allergen-specific immunotherapy ($p > 0.0175$).

Conclusion: Subcutaneous immunotherapy is an effective treatment for house dust mite induced allergic rhinitis.

Key words: Allergy; Immunotherapy; Subcutaneous Immunotherapy

Introduction

The house dust mite has a known role in the aetiology of persistent allergic rhinitis and allergic asthma.[1,2] The prevalence of allergic rhinitis and allergic asthma is increasing steadily, and is strongly associated with the presence of the house dust mite, a common allergen.[3] These atopic diseases increase healthcare costs, especially for patients with uncontrolled or poorly controlled allergies.[4–6]

The development of allergic rhinitis and allergic asthma can be partially prevented by avoiding allergens and by using certain pharmacotherapeutic agents, but it is difficult to change the course of allergic diseases associated with the house dust mite. Allergen immunotherapy or specific immunotherapy are effective treatments for allergic rhinitis associated with the house dust mite.[3]

Allergen-specific subcutaneous immunotherapy has been used effectively as a treatment for allergic rhinitis and/or allergic asthma. However, because of the discomfort of injections and serious side effects, non-injectable alternative options have been studied.[7] House dust mite extracts delivered via subcutaneous immunotherapy is an effective method for treating allergies.[8]

The present study investigated the long-term effects of allergen-specific immunotherapy delivered via subcutaneous immunotherapy. Skin prick tests demonstrated positive results for house dust mite species *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Subcutaneous immunotherapy was applied over the course of 3 years, and our study was based on a 10-year follow up of the allergic rhinitis patients. Skin prick test results and symptom scores were evaluated before and after 3 years of allergen-specific immunotherapy, and 10 years after allergen-specific immunotherapy had ended.

Materials and methods

This study was conducted between 2001 and 2015. We used data collected for a previously published study

Accepted for publication 15 June 2017 First published online 17 October 2017

comparing the effects of three years' allergen-specific immunotherapy (20 of 26 patients) with pre-immunotherapy findings (26 patients).[9] This comparative study was also the focus of the thesis by the first author,[10] which used data from 20 of the patients in the studies by Platts-Mills *et al*.[1] and Sporik *et al*.[2] to attain values pre-immunotherapy and after 3-years of immunotherapy. Ten-year follow-up data were also obtained for these 20 patients, and this dataset is the focus of the present study. This approach enabled comparisons of the results before and after allergen-specific immunotherapy and those obtained after 3 and 10 years' allergen-specific immunotherapy.

The study protocol was approved by the ethics committee (approval number 2016/01) and was conducted in accordance with the Declaration of Helsinki.

Subjects

Twenty patients (3 males, 17 females) with allergic rhinitis, admitted to the otolaryngology department of the Dr Sadi Konuk Training and Research Hospital, Istanbul, Turkey, in 2001 and 2002, were included in this study. The initial evaluation of these patients had been performed in both the otolaryngology and pulmonary diseases departments.

In 2001, the patients were aged 23–42 years. At the end of the study (2015), their mean age (± standard deviation) was 35.7 ± 1.0 years (range, 27.0–56.0 years). These 20 patients had positive skin prick test results for *D pteronyssinus* and *D farinae* house dust mites. They were treated with allergen-specific immunotherapy for three years via subcutaneous immunotherapy, receiving subcutaneous injections once per week over the three years.

Inclusion criteria

The study included adult patients with a diagnosis of allergic rhinitis, with continuous moderate or severe symptoms, who consented to undergo a skin prick test, and subsequently demonstrated house dust mite allergy (*D pteronyssinus* and *D farinae*). All patients had suffered symptoms for at least one season, and symptoms could not be sufficiently reduced with antihistamines or topical nasal corticosteroids.[9–11]

Exclusion criteria

Patients with malignancy, immune system disorders, adrenaline-related contraindications, coronary heart disease, hypertension, acute tuberculosis or any psychiatric condition that would prevent co-operation with long-term treatment, pregnant individuals, or those using beta-blockers or angiotensin-converting-enzyme inhibitors, were excluded.[9–11]

Instrumentation

Skin prick test. The skin prick test had been performed before allergen-specific immunotherapy and after 3 years of allergen-specific immunotherapy.[9,10] For this study, the skin prick test was performed again 10 years after allergen-specific immunotherapy.

The skin prick test (Prick Test Kit; Stallergenes, Antony, France) contained the following eight allergens: (1) positive control, (2) negative control, (3) *D pteronyssinus*, (4) *D farinae*, (5) grass pollens, (6) cereals, (7) tree pollen mixture and (8) moulds. Patients did not use antihistamines during the 10 days prior to testing. A prick lancet (Mizollen; H Herenz, Hamburg, Germany) was used for standardised skin pricking. Témoin was used as the negative control, and 10 mg/ml histamine hydrochloride was administered as the positive control.

Reactions were examined by the researcher 20 minutes after the test. The induration diameter was assessed; values of 3 mm or more were considered positive.[11,12] All patients had positive skin prick test results for *D pteronyssinus* and *D farinae* house dust mites.

Symptom scores. Nasal congestion, nasal discharge, nasal itching, sneezing, eye discomfort and headaches were considered symptoms. These were rated on a 0–3 points scale (0 = no symptoms and 3 = severe symptoms).[9,10]

Comparison

The skin prick test results for *D pteronyssinus* and *D farinae* were compared according to time of measurement (before and after 3 years of allergen-specific immunotherapy, and 10 years after allergen-specific immunotherapy).

Statistical analysis

SPSS statistical software, version 16.0 (SPSS, Chicago, Illinois, USA) was used. The Friedman test was employed to analyse differences among measurements taken before and after 3 years of allergen-specific immunotherapy and 10 years after allergen-specific immunotherapy. A p-value of less than 0.05 was deemed to indicate statistical significance.

When statistically significant differences were obtained, pairwise comparisons were performed using the Wilcoxon signed-rank test with the Bonferroni adjustment, to identify the value causing the difference. An adjusted p-value of less than 0.0175 was considered to be statistically significant.

Results

The skin prick test results and symptom scores obtained before and after 3 years of allergen-specific immunotherapy, and 10 years after allergen-specific immunotherapy, are displayed in Table I. Differences among these values were analysed using the Friedman test, and all differences were significant ($p < 0.05$) (Table I).

In order to identify the value causing the difference, pairwise comparisons were performed using the Wilcoxon signed-rank test with the Bonferroni

https://doi.org/10.1017/S0022215117002110 Published online by Cambridge University Press

TABLE I
SKIN PRICK TEST RESULTS AND SYMPTOM SCORES

Parameter	Pre-immunotherapy			After 3 years' immunotherapy			10 years after immunotherapy			p^*
	Median	Min	Max	Median	Min	Max	Median	Min	Max	
Skin prick test results[†]										
– *D pteronyssinus*	3.0	3.0	4.0	2.0	2.0	3.0	3.0	1.0	4.0	0.000
– *D farinae*	3.0	2.0	4.0	2.0	1.0	4.0	3.0	1.0	4.0	0.000
Symptom scores[‡]										
– Nasal congestion	2.0	1.0	3.0	1.0	0.0	2.0	1.0	0.0	3.0	0.000
– Nasal discharge	3.0	0.0	3.0	1.0	0.0	2.0	1.0	0.0	3.0	0.000
– Nasal itching	3.0	0.0	3.0	1.0	0.0	3.0	1.0	0.0	3.0	0.000
– Sneezing	3.0	1.0	3.0	1.0	0.0	2.0	1.0	0.0	3.0	0.000
– Eye complaints	2.0	0.0	3.0	1.0	0.0	3.0	1.0	0.0	3.0	0.000
– Headache	1.0	0.0	3.0	0.0	0.0	2.0	1.0	0.0	2.0	0.000

*Analysed using the Friedman test. [†]Induration diameter (mm). [‡]Rated on a 0–3 points scale, whereby 0 = no symptoms and 3 = severe symptoms.

adjustment. An adjusted p-value of less than 0.0175 was considered to indicate statistical significance (Table II).

Regarding the positivity of *D pteronyssinus* and *D farinae*, the mean ranks of the pre-immunotherapy values were significantly higher than those of the values after 3 years of allergen-specific immunotherapy; furthermore, the latter were significantly higher than the values 10 years after allergen-specific immunotherapy ($p < 0.0175$) (Table II). In terms of *D pteronyssinus,* the mean rank for 3 years of allergen-specific immunotherapy was 10.53, and that for 10 years after allergen-specific immunotherapy was 10.00. For *D farinae*, the mean rank for 3 years of allergen-specific immunotherapy was 10.12, and that for 10 years after allergen-specific immunotherapy was 4.50.

The symptom scores obtained pre-immunotherapy were significantly higher than those obtained after 3 years of allergen-specific immunotherapy and 10 years after allergen-specific immunotherapy ($p < 0.0175$). There were no significant differences between the scores obtained after 3 years of allergen-specific immunotherapy versus those 10 years after allergen-specific immunotherapy ($p > 0.0175$) (Table II).

Discussion

An allergy-induced late response is decreased by allergen immunotherapy, and levels of interleukin (IL)-4, IL-13 and IL-5 are reduced via inhibitory type 2 helper T cell responses. Overall, type 2 helper T cell response reduction is complemented by a switch in the immunological response towards 'protective' type 1 helper T cell pathways. Allergen immunotherapy causes a reduction in IL-10 and transforming growth factor-β, leading to the suppression of type 2 helper T cell responses. Additionally, IL-10 is involved in the change of immunoglobulin (Ig) isotypes to IgG4, and transforming growth factor-β is involved in changes to IgA.[13–15]

Reductions in the allergic response of a patient treated with allergen immunotherapy can be attributed to increased IgG1, IgG4 and IgA, and to decreased IgE. This change is associated with reductions in the number of infiltrating T cells, basophils, eosinophils

TABLE II
PAIRWISE COMPARISON BY WILCOXON SIGNED-RANK TEST WITH BONFERRONI ADJUSTMENT

Parameter	Pre- *vs* after 3 years' immunotherapy		Pre- *vs* 10 years post-immunotherapy		After 3 years' immunotherapy *vs* 10 years after immunotherapy	
	r	Adjusted p^*	r	Adjusted p^*	r	Adjusted p^*
Skin prick test results						
– *D pteronyssinus*	−4.264	0.000	−0.378	0.705	−3.962	0.000
– *D farinae*	−3.827	0.000	−0.832	0.405	−3.435	0.001
Symptom scores						
– Nasal congestion	−3.789	0.000	−3.331	0.001	−1.889	0.059
– Nasal discharge	−3.640	0.000	−3.359	0.001	−1.267	0.207
– Nasal itching	−3.612	0.000	−3.494	0.001	−0.728	0.467
– Sneezing	−3.982	0.000	−3.782	0.000	−0.642	0.527
– Eye complaints	−3.716	0.000	−3.154	0.002	−0.711	0.477
– Headache	−3.111	0.002	−2.547	0.011	−2.333	0.020

*An adjusted p-value of less than 0.0175 was considered statistically significant.

https://doi.org/10.1017/S0022215117002110 Published online by Cambridge University Press

and neutrophils. In the long-term, allergen-specific IgE levels are reduced as a result of allergen immunotherapy. A significant reduction in early-phase response has also been reported.[13,16–20]

The administration of increasing amounts of a specific allergen is the staple method of immunotherapy for allergic diseases. This approach modulates the immune response to the allergen and alleviates allergic symptoms. Immunotherapy is a unique type of therapy that alters symptoms caused by abnormal immune responses.

A period of pharmacotherapy and particular life changes are recommended before commencing subcutaneous immunotherapy. Drugs are relatively easy for most patients to use and, when effective, provide faster relief than immunotherapy.[21]

Allergens known to be effective for use in subcutaneous immunotherapy include various trees, grasses, and pollens, cat or dog hair, dust mites, cockroaches, and moulds.[21]

The present study investigated the long-term effects of allergen-specific immunotherapy, specifically subcutaneous immunotherapy. It evaluated the skin prick test results for the house dust mite (*D pteronyssinus* and *D farinae*) and the symptom scores before and after 3 years of allergen-specific immunotherapy and 10 years after allergen-specific immunotherapy. After three years of allergen-specific immunotherapy, skin prick test positivity for the house dust mite decreased compared with the pre-immunotherapy values. Moreover, 10 years after allergen-specific immunotherapy, skin prick test positivity for house dust mites was reduced further compared with the results after 3 years of allergen-specific immunotherapy. Hence, the decrease in skin prick test positivity continued after the cessation of the three-year allergen-specific immunotherapy.

The symptom scores after 3 years of allergen-specific immunotherapy and those 10 years after allergen-specific immunotherapy were significantly lower than those before allergen-specific immunotherapy. It can be concluded that allergen-specific immunotherapy for the house dust mite was effective, and that skin prick test positivity and symptom positivity decreased over time, even though the treatment was stopped after three years. In other words, although treatment was interrupted, the positive effects of allergen-specific immunotherapy continued.

In line with our results, Pevec *et al*. reported that the improvement observed may continue for months, or even years, after completion of house dust mite subcutaneous immunotherapy.[8] In their study, 56 allergic patients were treated using subcutaneous immunotherapy with house dust mite extracts. However, it was highlighted that sensitisation to tropomyosin is not clinically reduced by using house dust mite subcutaneous immunotherapy. In cases of combined allergies, such as seafood and mites, this treatment can lead to diminished food allergy symptoms. Levels of specific IgE to Der p 10 and pen 1 allergens may be useful monitoring indicators.

The potency of house dust mite subcutaneous immunotherapy has been demonstrated during the treatment period via: reductions in the severity of symptoms and skin reactivity; increased production of specific IgG4 and total IgE; and specific IgE dynamics. Alterations in the production of some T regulatory genes and FcεRI pathway genes was also observed.[22]

- **Allergen-specific immunotherapy is an effective way to treat allergic rhinitis**
- **Subcutaneous immunotherapy is effective for house dust mite induced allergy, even 10 years after treatment**

The long-term effects of subcutaneous immunotherapy were assessed in a follow-up analysis of 147 patients aged 16–25 years, who had participated as children (10 years previously) in a randomised 3-year subcutaneous immunotherapy study, with grass and/or birch pollen as allergens.[23] Allergic rhinoconjunctivitis was noted in all patients at the beginning of the study. Statistically significant improvements in rhinoconjunctivitis symptoms were observed in patients treated with subcutaneous immunotherapy compared with those treated with standard therapies, even after seven years. In the subcutaneous immunotherapy patient group, 16 of 64 patients developed asthma, compared with 24 of 53 in the control group (25 per cent *vs* 45 per cent; odds ratio = 0.4, 95 per cent confidence interval = 0.2–0.9).[23] It has also been shown that patients with sensitivity to perennial allergens, such as dust mites or indoor animals, can benefit from subcutaneous immunotherapy.[24–26]

Conclusion

This study showed that subcutaneous immunotherapy is an effective treatment for house dust mite induced allergic rhinitis; both the symptoms and skin prick test positivity values decreased during the treatment period. These positive effects continued for 10 years, even though subcutaneous immunotherapy was stopped after 3 years of treatment. Therefore, given appropriate indications, we would recommend subcutaneous immunotherapy as a treatment for house dust mite induced allergic rhinitis.

References

1 Platts-Mills TA, Erwin EA, Heymann PW, Woodfolk JA. Pro: the evidence for a causal role of dust mites in asthma. *Am J Respir Crit Care Med* 2009;**180**:109–13
2 Sporik R, Chapman MD, Platts-Mills TA. House dust mite exposure as a cause of asthma. *Clin Exp Allergy* 1992;**22**: 897–906
3 Eifan AO, Calderon MA, Durham SR. Allergen immunotherapy for house dust mite: clinical efficacy and immunological mechanisms in allergic rhinitis and asthma. *Expert Opin Biol Ther* 2013;**13**:1543–56
4 Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;**59**:469–78

https://doi.org/10.1017/S0022215117002110 Published online by Cambridge University Press

5 Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM *et al*. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015;**46**:622–39
6 Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007;**62**:17–25
7 Bahceciler NN, Cobanoglu N. Subcutaneous versus sublingual immunotherapy for allergic rhinitis and/or asthma. *Immunotherapy* 2011;**3**:747–56
8 Pevec B, Pevec MR, Markovic AS, Batista I. House dust mite subcutaneous immunotherapy does not induce new sensitization to tropomyosin: does it do the opposite? *J Investig Allergol Clin Immunol* 2014;**24**:29–34
9 Sahin E, Taş E, Dağtekin Ergür EN, Cuhali BD, Gürsel AO. The results of specific immunotherapy for house dust mites in patients with allergic rhinitis [in Turkish]. *Kulak Burun Bogaz Ihtis Derg* 2008;**18**:79–84
10 Şahin E. *Comparison of 3-year Clınıcal and Laboratory Results for Dermatophagoides Pteronyssinus and Dermatophagoides Farinae Allergen Specific Immunotherapy*, Specialization Thesis [in Turkish]. Istanbul: Turkish Ministry of Health, Bakırkoy Education and Research Hospital, 2005
11 Cingi C, Bayar Muluk N, Ulusoy S, Acar M, Şirin S, Çobanoğlu B *et al*. Efficacy of sublingual immunotherapy for house dust mite allergic rhinitis. *Eur Arch Otorhinolaryngol* 2015;**272**:3341–6
12 Lachapelle JM, Maibach HI. *Patch Testing and Prick Testing: A Practical Guide*, 2nd edn. Berlin/Heidelberg: Springer Verlag, 2009
13 Aricigil M, Muluk NB, Sakarya EU, Sakalar EG, Senturk M, Reisacher W *et al*. New routes of allergen immunotherapy. *Am J Rhinol Allergy* 2016;**30**:193–7
14 Kavut AB, Kalpaklıoğlu F. Diagnostic tools for allergic rhinitis and asthma. *J Med Updates* 2012;**2**:22–30
15 Yaz A, Cingi C, Gürbüz MK, Bal C. The long-term results of the impact of rhinophototherapy on quality of life in cases with allergic rhinitis. *J Med Updates* 2012;**2**:63–9
16 Ying S, Barata LT, Meng Q, Grant JA, Barkans J, Durham SR *et al*. High-affinity immunoglobulin E receptor (Fc epsilon RI)-bearing eosinophils, mast cells, macrophages and Langerhans' cells in allergen-induced late-phase cutaneous reactions in atopic subjects. *Immunology* 1998;**93**:281–8
17 Gaga M, Frew AJ, Varney VA, Kay AB. Eosinophil activation and T lymphocyte infiltration in allergen-induced late phase skin reactions and classical delayed-type hypersensitivity. *J Immunol* 1991;**147**:816–22
18 Garcia BE, Sanz ML, Gato JJ, Fernandez J, Oehling A. IgG4 blocking effect on the release of antigen-specific histamine. *J Investig Allergol Clin Immunol* 1993;**3**:26–33
19 Iliopoulos O, Baroody FM, Naclerio RM, Bochner BS, Kagey-Sobotka A, Lichtenstein LM. Histamine-containing cells obtained from the nose hours after antigen challenge have functional and phenotypic characteristics of basophils. *J Immunol* 1992;**148**:2223–8
20 Sampson AP. The role of eosinophils and neutrophils in inflammation. *Clin Exp Allergy* 2000;**1**:22–7
21 Creticos PS, Esch RE, Couroux P, Gentile D, D'Angelo P, Whitlow B *et al*. Randomized, double-blind, placebo controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2014;**133**:751–8
22 Pevec B, Radulovic Pevec M, Stipic Markovic A, Batista I, Rijavec M, Silar M *et al*. House dust mite specific immunotherapy alters the basal expression of T regulatory and FcεRI pathway genes. *Int Arch Allergy Immunol* 2012;**159**:287–96
23 Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A *et al*. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007;**62**:943–8
24 Bousquet J, Lockey R, Malling HJ, Alvarez-Cuesta E, Canonica GW, Chapman MD *et al*. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American Academy of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998;**81**:401–5
25 Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol* 2007;**120**(3 suppl):S25–85
26 Li JT, Bernstein DI, Calderon MA, Casale TB, Cox L, Passalacqua G *et al*. Sublingual grass and ragweed immunotherapy: clinical considerations--a PRACTALL consensus report. *J Allergy Clin Immunol* 2016;**137**:369–76

Address for correspondence:
Dr Denizhan Dizdar,
Department of Otorhinolaryngology,
Medical Park Bahçelievler Hospital,
Faculty of Medicine,
Istanbul Kemerburgaz University,
Istanbul, Turkey

E-mail: denizhandizdar@hotmail.com

Dr D Dizdar takes responsibility for the integrity of the content of the paper
Competing interests: None declared

https://doi.org/10.1017/S0022215117002110 Published online by Cambridge University Press