ORIGINAL ARTICLE

Sublingual Immunotherapy to House Dust Mite in Pediatric Patients With Allergic Rhinitis and Asthma: A Retrospective Analysis of Clinical Course Over a 3-Year Follow-up Period

Y Nuhoglu,[1] SS Ozumut,[2] C Ozdemir,[1] M Ozdemir, C Nuhoglu,[3] M Erguven[2]

[1] Department of Pediatric Allergy, SB Istanbul Goztepe Training and Research Hospital, Istanbul, Turkey
[2] Department of Pediatrics, SB Istanbul Goztepe Training and Research Hospital, Istanbul, Turkey
[3] Department of Pediatrics, Haydarpasa Numune Training and Research Hospital Istanbul, Turkey

Abstract

Background and objective: Specific allergen immunotherapy is believed to be the only treatment able to change the natural history of allergic airway diseases. Sublingual immunotherapy (SLIT) is especially preferred because of its easy application and safety. The aim of this study was to describe the effect of SLIT in pediatric patients who have allergic airway disease.
Methods: Children with asthma and rhinitis who were allergic to house dust mite were evaluated. The effect on clinical course of 3 years of SLIT with 50 % *Dermatophagoides pteronyssinus* and 50 % *Dermatophagoides farinae* in a standardized extract was assessed retrospectively.
Results: The records of 39 patients (23 boys, 16 girls) were studied. The mean (± SD) age for starting SLIT was 8.8 ± 2.3 years. The mean number of acute asthma attacks at the onset of the disease was 8.18 ± 3.05. The mean number of attacks after 3 years of SLIT was 0.44 ± 0.79. There was a statistically significant difference in the number of acute asthma attacks before and after therapy ($P < .001$). Complete clinical remission of asthma was recorded in 37 (95%) patients. Similarly, complete clinical remission of allergic rhinitis was recorded in 32 (82%) patients.
Conclusion: This retrospective study shows that SLIT is effective in children who have allergic airway disease which cannot be controlled effectively with allergen avoidance measures only.

Key words: Sublingual immunotherapy. Asthma. Children.

Resumen

Antecedentes y objetivo: Se cree que la inmunoterapia específica es el único tratamiento que puede cambiar la historia natural de las enfermedades respiratorias de origen alérgico. La inmunoterapia sublingual (ITSL) se prefiere especialmente debido a la facilidad de administración y seguridad. El objetivo del estudio fue describir el efecto de la ITSL en pacientes pediátricos con enfermedad de las vías respiratorias de origen alérgico.
Métodos: Se evaluó a niños con asma y rinitis, alérgicos al ácaro del polvo doméstico. Se valoró retrospectivamente el efecto en la trayectoria clínica de 3 años de ITSL con un 50 % de *Dermatophagoides pteronyssinus* y un 50 % de *Dermatophagoides farinae* en un extracto estandarizado.
Resultados: Se estudiaron las historias clínicas de 39 pacientes (23 niños y 16 niñas). La media de edad (± SD) para empezar la ITSL fue de 8,8 ± 2,3 años. El promedio de ataques de asma agudos al inicio de la enfermedad era de 8,18 ± 3,05. El promedio de ataques a los tres años de tratamiento con ITSL fue de 0,44 ± 0,79. La diferencia en la cantidad de ataques de asma agudos antes y después de este tratamiento fue estadísticamente significativa ($P < 0,001$). En 37 de los pacientes (95 %) se registró la remisión clínica completa del asma. De forma similar, en 32 de los pacientes (82 %) se registró la remisión clínica completa de la rinitis alérgica.
Conclusión: Este estudio retrospectivo demuestra que la ITSL es efectiva para el tratamiento pediátrico de enfermedades respiratorias de origen alérgico que no pueden controlarse únicamente con la aplicación de medidas para evitar la exposición a los alérgenos.

Palabras clave: Inmunoterapia sublingual. Asma. Niños.

Introduction

Allergic airway disease has been effectively controlled in many pediatric patients with inhaled and nasal corticosteroids during recent decades. Disease activity usually starts again after the cessation of these drugs, however, if the underlying allergy is not controlled. The reaction to inhalant allergens can only be achieved with appropriate allergen avoidance measures and specific immunotherapy, which is believed to be the only treatment method that can change the natural history of the disease. In this respect; subcutaneous immunotherapy has been widely applied and has been shown to be effective in reducing symptoms [1]. However, uncommon but severe and nearly fatal systemic reactions have begun to worry physicians [2] and repeated injections have led to serious complaints especially among children [3]. Thus, alternative routes of immunotherapy have been proposed. Among them, sublingual immunotherapy (SLIT), by which oral tolerance is induced at mucosal surfaces, has been gaining the confidence of practitioners because of its good safety profile and its effectiveness in the context of allergic airway disease [4].

We report clinical outcomes in a group of pediatric patients with allergic rhinitis and asthma who had been treated with SLIT.

Methods

Children who attended the outpatient clinic with allergic mild-to-moderate asthma and allergic rhinitis were studied retrospectively. The asthma diagnosis was made according to American Thoracic Society criteria [5], on the basis of recurrent cough, wheeze, and chest tightness that reversed spontaneously or with bronchodilator therapy. The severity was reported according to the guidelines of the Global Initiative for Asthma [6]. Allergic rhinitis was diagnosed if the patient had at least 1 rhinitis symptom (stuffiness, rhinorrhea, sneezing) for more than 1 hour a day on most of the days of the week. The patients were monosensitized to house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*).

A skin prick test was performed on each patient with the most common aeroallergen solutions (Stallergenes SA, Antony Cedex, France). A multi-test applicator (Hollister-Stier Laboratories, Spokane, Washington, USA) was used during the procedure. A wheal diameter of more than 3 mm was accepted as positive.

In our outpatient allergy clinic the number of acute asthma attacks reported by the patient is recorded at the time of diagnostic interview, before any anti-inflammatory medication is started. An attack is defined as cough, wheeze, and dyspnea that persisted for more than 24 hours and that was resolved with bronchodilator treatment. If the severity of asthma is mild, moderate or severe and persistent the patients are treated with inhaled budesonide and nasal budesonide for their allergic rhinitis if present. The inhaled budesonide dose is 200 μg twice daily and the nasal budesonide dose is 50 μg for each nostril twice daily. At the same time allergen avoidance measures (no carpets in the home and use of allergy control barrier bedding) are described. The patients visit the outpatient clinic every 3 months and a pediatric allergist records the number of acute asthma attacks lasting more than 24 hours and resolved with bronchodilator treatment, as noted in the patients' diary cards. If the patient is having an acute attack at the time of the routine visit, as detected during the pediatric allergist's examination, that is also recorded in the file. After at least 6 months of using anti-inflammatory medication and allergen avoidance, if a patient's symptoms are not completely controlled, pulmonary function tests are performed and SLIT is prescribed for patients who have a forced expiratory volume in 1 second (FEV_1) above 70 %. The patients receive SLIT for 3 years. At the same time, anti-inflammatory medication is also prescribed and the dose is arranged according to clinical progress as noted in visits once in every 3 months with the pediatric allergist. When the patient does not have any acute asthma attacks or allergic rhinitis symptoms during the previous year, the anti-inflammatory medication is stopped. When the patient still does not have any symptoms for at least 6 months with no anti-inflammatory medication, they are accepted as being in complete remission.

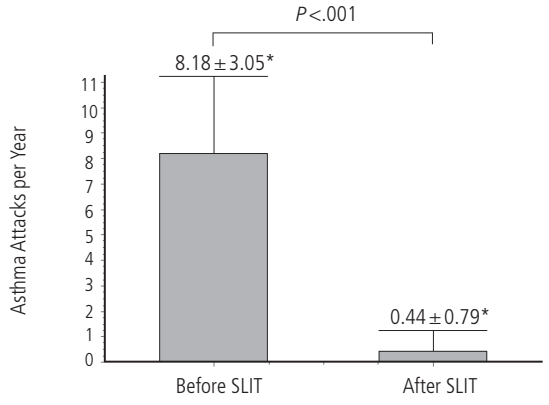
The main outcome measures for this study of patients undergoing those procedures were the number of acute asthma attacks that had been recorded before and after SLIT and the rate of complete remission.

A standardized extract of house dust mites (50% *D pteronyssinus*/50 % *D farinae*) (Stallergenes) was used. Twenty drops of the solution (100 index of reactivity [IR]) was placed under the tongue for 3 minutes on 3 alternate days a week.

The comparison of the number of acute asthma attacks before and after SLIT was made with the Wilcoxon signed-rank test.

Results

The records of 39 patients (23 boys and 16 girls) were studied. The mean (±SD) age at the onset of the first signs and



Mean (±SD) number of acute asthma attacks per year before and after sublingual immunotherapy (SLIT)

symptoms of allergic airway disease was 3.6 ± 2.5 years and the mean age at the time of diagnosis was 8.1 ± 2.1 years. The mean age upon beginning SLIT was 8.8 ± 2.3 years. The severity of asthma was assessed as mild-to-moderate persistent.

The mean number of acute asthma attacks reported for the previous year at the time of diagnosis (with no anti-inflammatory medication) was 8.18 ± 3.05. The mean number of attacks after 3 years of SLIT (with no anti-inflammatory medication) was 0.44 ± 0.79. There was a statistically significant difference in the number of acute asthma attacks before and after therapy ($P < .0001$) (figure). Complete clinical remission of asthma was recorded in 37 (95 %) patients. Similarly, complete clinical remission of allergic rhinitis was recorded in 32 (82 %) patients. No significant side effects were reported.

Discussion

In this study we observed a significant effect of SLIT on pediatric patients with allergic rhinitis and mild-to-moderate asthma with ongoing symptoms despite adequate avoidance measures and adequate anti-inflammatory therapy. These results are consistent with evidence that SLIT is an effective method of desensitization in allergic rhinitis (level of evidence 1A) [7] and asthma (level of evidence, 1B) [8]). It is especially preferred in children with immunoglobulin (Ig) E mediated diseases because of its good safety profile [9]. However, a meta-analysis published by the Cochrane Library on the clinical efficacy of SLIT in patients with rhinitis included 22 double-blind, placebo-controlled clinical trials and a total of 979 patients failed to find a clear relation between the duration of treatment and clinical efficacy due to insufficient data [10]. Similarly, the doses of allergen used in different SLIT studies was found to range from 3 to 5 times to 375 times the effective cumulative dose of subcutaneous immunotherapy when this feature was analyzed by Canonica and Passalacqua [11] and no clear relation between the dose administered and clinical efficacy was reported in that meta-analysis. We are reporting the data of patients treated with a SLIT dose of 100 IR after 3 years of follow-up.

A double-blind, placebo-controlled study conducted by Bousquet and colleagues [12] in adults with perennial asthma sensitive to house dust mites, in which SLIT with 300 IR was prescribed for 24 months, found that inhaled corticosteroid use was significantly less after therapy. That study in adults was of a shorter duration than our study, yet our clinically good results are similar to the good progress and less use of inhaled corticosteroids they reported. A retrospective analysis of a group of adult patients with allergic rhinitis and bronchial hyperreactivity who had been treated with SLIT to house dust mites was reported by Marogna et al [13]. The investigators had divided the patients into 4 groups according to the duration of the therapy (1, 2, 3, and 4 years). After analyzing the symptom scores and lung function of patients before and after therapy, they reported a significant difference in symptom scores only in the 4-year therapy group. No significant difference was reported with respect to lung function parameters. Our study is similar to that one with respect to its retrospective design and the good clinical outcomes, even though those investigators achieved significant clinical progress only after 4 years. We observed a significant difference with respect to symptoms after 3 years of therapy. Our study analyzed pediatric patients, however, and the age factor might have been the reason for the discrepancy, as response to immunotherapy is stated to be better in younger patients in whom allergen-specific memory type 2 helper T cells are not well established and are more susceptible to downregulation [14].

The long-term effect of SLIT was investigated in an open, controlled, observational study which included 60 mite-sensitive asthmatic children aged from 3 to 17 years old [8]. SLIT was given for 4 to 5 years and the children were followed for 10 years, at which time there was a significant reduction in the prevalence of asthma, use of asthma medication and a significant increase in peak expiratory flow rate in the SLIT group compared with the control group. Although our study was not placebo controlled and the duration was shorter, the results with respect to asthma remission seem to be similar.

One other study by Bahceciler and colleagues [15] enrolled 15 children with allergic rhinitis and asthma due to house dust mites in a placebo controlled manner. The investigators used low-dose SLIT (100 IR) for 6 months and found a significant reduction in the daily asthma score in the therapy group in comparison with the placebo group. In our study the same dose of allergen was used with longer treatment duration. The comparison of clinical status was made within the same group, yet both studies report symptom improvement after therapy.

Recently, Lue and colleagues [16] studied the effect of SLIT to *D pteronyssinus* and *D farinae* at a dose of 300 IR (maximum cumulative dose, 41 824 IR) for 6 months in a group of 36 pediatric patients in a double-blind, placebo controlled fashion. After treatment they observed significant differences in the nighttime asthma symptoms and specific IgG4 levels. The authors had analyzed FEV_1 both before and after therapy and observed significant improvement. Similarly, Niu and colleagues [17] analyzed the effect of high-dose SLIT in pediatric patients sensitized to house dust mites in a double-blind fashion. Symptom scores and lung function test parameters were compared. The authors reported a significant difference with respect to both measures after SLIT treatment. Lung function tests were carried out only once before treatment in our study, however. The assessment of clinical response in our study relied solely on the symptoms recorded on the patients' diary cards and during the pediatric allergist's physical examination.

In conclusion, this retrospective study with a 3-year follow-up of children with allergic airway disease treated with SLIT shows that this treatment could be an effective method for children whose asthma and rhinitis cannot be controlled adequately with avoidance measures.

References

1. Bousquet J, Lockey R, Malling HJ. WHO position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Allergy. 1998;53 (Suppl) 1-42.
2. Passalacqua G, Guerra L, Pasquali M, Lombardi C, Canonica GW. Efficacy and safety of sublingual immunotherapy. Ann

Allergy Asthma Immunol. 2004;93:3-12.
3. Bousquet J. Sublingual immunotherapy: validated. Allergy. 2006; 61(Suppl.81): 5-6.
4. Akdis CA, Barlan IB, Bahceciler N, Akdis M. Immunological mechanisms of sublingual immunotherapy. Allergy. 2006; 61(Suppl 81):11-4.
5. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis. 1987;136:225-44.
6. Global Strategy for Asthma management and Prevention, 2002. NIH Publication No: 02-3659.
7. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108: S147-S334.
8. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. Allergy. 2006;61(Suppl 82):14-7.
9. Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, Canonica GW, Passalacqua G. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy. 2003;33:206-10.
10. Wilson DR, Torres Lima M, Durham SE. Sublingual immunotherapy for allergic rhinitis: systemic review and meta-analysis. Allergy.2005;60: 4-12.
11. Canonica GW, Passalacqua G. Non-injection routes for immunotherapy. J Allergy Clin Immunol. 2003;111:437-48.
12. Bousquet J, Scheinmann P, Guinnepain MT, Perrin-Fayolle M, Sauvaget J, Tonnel AB, Pauli G, Caillaud D, Dubost R, Leynadier F, Vervloet D, Herman D, Galvain S, Andre C. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. Allergy. 1999;54(3):249-60.
13. Marogna M, Bruno M, Massolo A, Falagiani P. Long lasting effects of sublingual immunotherapy for house dust mite in allergic rhinitis with bronchial hyperreactivity: A Long term (13 years) retrospective study in real life. Int Arch Allergy Immunol. 2006;142(1):70-8.
14. Holt PG, Upham JW, Sly PD. Contemporaneous maturation of immunologic and respiratory functions during early childhood: implications for development of asthma prevention strategies. J Allergy Clin Immunol 2005;116:16-24.
15. Bahceciler NN, Is?k U, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmonol. 2001;32(1):49-55.
16. Lue KH, Lin YH; Sun HL, Lu KH, Hsieh JC, Chou MC. Clinical and immunological effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo controlled study. Pediatr Allergy Immunol. 2006;17:408-15.
17. Niu CK, Chen WY, Huang JL, Lue, KH, Wang JY. Efficacy of sublingual immunotherapy with high dose mite extracts in asthma: a multi-center, double-blind, randomized and placebo-controlled study in Taiwan. Respir Med. 2006;100(8):1374-8.

Manuscript received February 5, 2007; accepted for publication April 18, 2007

Yonca Nuhoglu

Yesilbahar Sokak, Savas Apt. No: 16/16
Goztepe 34730 Istanbul, Turkey
E-mail: yonca@nuhoglu.com