

ORIGINAL ARTICLE

Clinical efficacy of sublingual immunotherapy in pediatric patients with allergic rhinitis sensitized to house dust mites: Comparison to adult patients

DOO HEE HAN¹, YOON-SEOK CHOI¹, JI-EUN LEE¹, DONG-YOUNG KIM^{1,3},
JEONG-WHUN KIM^{1,3}, CHUL HEE LEE^{1,3} & CHAE-SEO RHEE^{1,2,3,4}

¹Department of Otorhinolaryngology, ²Graduate School of Immunology, Seoul National University College of Medicine, ³Sensory Organ Research Institute and ⁴Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, Korea

Abstract

Conclusion: Sublingual immunotherapy (SLIT) with house dust mite (HDM) extracts in school-age children and adolescents seems to be as effective as in adults. SLIT could be recommended as a therapeutic modality in pediatric allergic rhinitis (AR) patients sensitized to HDMs. **Objectives:** To investigate the efficacy of HDM SLIT in pediatric patients with AR. **Materials and Methods:** Seventy-six patients treated with HDM SLIT for at least 1 year between November 2007 and February 2010 were enrolled in this study. A young age group ($n = 54$) between 6 and 18 years old was compared with an adult group ($n = 22$). Standardized extract of HDM (Pangramin[®] SLIT) was used. Total symptom scores (TSS) and anti-allergic medication scores (AMS) were evaluated before and 1 year after SLIT. **Results:** TSS improved in both groups, and the change was comparable in the 2 groups (Δ TSS, 5.1 vs 5.3; $p = 0.538$). Also among the young age group, Δ TSS did not significantly differ between school-age children and adolescents (5.2 vs 4.9, $p = 0.429$). Thirty-five out of 54 youngsters (64.8%) and 11 out of 22 adults (50.0%) showed improvement in TSS over 30%. AMS were significantly decreased in both groups. Δ AMS tended to be higher in the young age group, but the difference did not reach statistical significance (57.2 vs 35.7, $p = 0.060$).

Keywords: Immunotherapy, sublingual administration, rhinitis, house dust mites, child, adolescent

Introduction

Recently, the sublingual administration of allergen extract has become popular in many countries and its efficacy in allergic rhinitis (AR) has been demonstrated [1]. Sublingual immunotherapy (SLIT) has been shown to reduce symptoms and the need for medication [2].

SLIT is considered safer and more convenient than subcutaneous therapy and therefore has been proposed as especially suitable for children. There have been several recent studies of SLIT in pediatric patient groups. Prospective studies using grass pollen, ragweed, parietaria, and mite allergens confirm the safety of SLIT in children and in adults, presenting

with either AR or mild-to-moderate asthma [3]. SLIT could be an optimal candidate for use in pediatric age groups, due to its excellent safety [4]. However, a previously reported meta-analysis showed that there was no significant reduction in symptoms and medication scores in those studies involving only children [1]. A patient-friendly grass pollen tablet was developed and it was easier to administer for pediatric patients. Recently, the efficacy of SLIT with a grass pollen tablet in children and adolescents has been demonstrated in double-blind placebo-controlled (DBPC) studies [5,6].

However, there were few previous studies on SLIT with extracts of house dust mite (HDM) in pediatric AR patients. Recently, a report on the effectiveness

of SLIT with HDM in children with AR was published [7]. Another study about the efficacy of SLIT with HDM extracts in pediatrics was reported in Japan [8]. The efficacy of SLIT with extracts of HDM in adult patients with AR was previously reported in Korea [9]. The purpose of this study was to investigate the efficacy of SLIT with HDM extracts in pediatric AR patients compared to adult patients.

Materials and methods

Study design

This was a retrospective study at a tertiary referral center. Youngsters aged 6–18 years suffering from AR symptoms were compared with adult patients with AR after 1-year SLIT for HDMs. Total symptom scores (TSS) including rhinorrhea, sneezing, nasal obstruction, itchy nose, and eye discomfort, and anti-allergic medication scores (AMS) were evaluated before and 1 year after SLIT. The Institutional Review Board of the Biomedical Research Institute at Seoul National University Hospital approved the study protocol.

Patient selection

Patients who were sensitized to HDMs and treated with SLIT for at least 1 year between November 2007 and February 2010 were included in this study. The patients were diagnosed as having AR according to the results of skin prick test (SPT) and/or multiple allergen simultaneous test (MAST), and clinical symptoms including sneezing, itching, rhinorrhea, and nasal congestion with or without eye symptoms. The patients were regarded as sensitized to *Dermatophagoides pteronyssinus* (Dp) and/or *Dermatophagoides farinae* (Df) if they had positive SPT results (allergen/histamine ratio ≥ 1) and/or MAST class ≥ 2 . Patients who had undergone previous immunotherapy in the preceding 3 years or who had systemic immunological disorders were excluded.

Seventy-six patients were enrolled in this study. Fifty-four patients (71.1%) were youngsters and 22 (28.9%) were adults. The mean age of the youngsters was 11.2 years (range 6–18 years) and that of the adults was 30.4 years (range 19–53 years). The average duration of AR symptoms was 5.8 years (range 1–17 years) in youngsters and 11.4 years (range 0.5–30 years) in adults, respectively (Table I). Youngsters were divided into two subgroups: school-age children aged 6–12 years and adolescents aged 13–18 years.

Table I. Demographics of study population.

Parameter	Youngsters (<i>n</i> = 54)	Adults (<i>n</i> = 22)
Mean age (years)	11.2 (6–18)	30.4 (19–53)
Symptom duration (years)	5.8 (1–17)	11.4 (0.5–30)
Total symptom scores	12.2 $\pm$ 5.2	12.6 $\pm$ 5.9

Immunotherapy

Patients underwent immunotherapy with standardized extracts of HDM (50% Dp/50% Df, Pangramin® SLIT, ALK-Abelló, Madrid, Spain) as described previously [9,10]. When AR symptoms were persistent or aggravated during SLIT, patients were allowed to use oral antihistamine and/or intranasal corticosteroid spray.

Outcome measurement

All the patients were asked to complete questionnaires before SLIT and 1 year after receiving SLIT. The questionnaires included questions on rhinorrhea, sneezing, nasal obstruction, itchy nose and eye discomfort. Each symptom was graded from 0 to 5 (0 = no symptom, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe). TSS were defined as the sum of the scores of five allergic symptoms including rhinorrhea, sneezing, nasal obstruction, itchy nose, and eye discomfort. Rescue medication scores referring to concurrent use of anti-allergic medication were recorded on diary cards. AMS were the sum of daily medication points. Oral antihistamine was scored as 1 point and intranasal corticosteroid was scored as 2 points. AMS were calculated every 2 months during 1 year of SLIT.

Serum total IgE, eosinophil counts, and eosinophil cationic protein (ECP) levels were checked at the beginning and 1 year after SLIT.

Statistical analysis

Symptoms before and after SLIT were analyzed statistically by paired *t* test. Student's *t* test, paired *t* test, and the Wilcoxon signed rank test were used to compare the symptomatic changes. All the data were analyzed using SPSS v.17.0 (SPCC Inc., Chicago, IL, USA). A *p* value < 0.05 was considered statistically significant.

Results

All the allergic symptoms including rhinorrhea, sneezing, nasal obstruction, nose itching, and eye

discomfort were improved significantly after 1-year SLIT in youngsters (Figure 1). In the adult group, the allergic symptoms except eye discomfort were improved significantly (Figure 2).

TSS significantly improved in both youngsters and adults, and the change in TSS was comparable in the 2 groups (Δ TSS, 5.1 vs 5.3; $p = 0.538$) (Figure 3). Thirty-five out of 54 youngsters (64.8%) and 11 out of 22 adults (50.0%) showed improvement in TSS over 30% (n.s.). Twenty-two out of 36 school-age children (61.1%) and 12 out of 18 adolescents (66.7%) showed improvement in TSS over 30% (n.s.).

Among the youngsters, the changes of TSS were almost similar between school-age children and adolescents (Δ TSS, 5.2 vs 4.9; $p = 0.429$), and compared to the adult group, neither of the subgroups of youngsters showed a significant difference in the change of TSS (Figure 3).

AMS were significantly decreased in both youngsters and adults. Forty-two out of 49 youngsters (85.7%) and 19 out of 20 adults (95.0%) showed improvement in AMS. The change of AMS tended to be higher in the youngster group (57.2 vs 35.7, $p = 0.060$) although not statistically significant (Figure 4). Compared to the adult group, neither of the subgroups of youngsters showed any significant difference in the change of AMS (Figure 4).

No significant changes in serum total IgE were detected in either group (391 vs 293 IU/ml, $p = 0.189$ in the youngster group and 161 vs 211 IU/ml, $p = 0.542$ in the adult group). Although eosinophil counts were decreased in both groups, significant decrease was observed only in adults (440 vs 370/ μ l, $p = 0.085$ in the youngster group and 306 vs 200/ μ l, $p = 0.016$ in the adult group).

The ECP levels were also decreased in both groups; however, only statistically significant in the youngster group (22.9 vs 17.3 μ g/L, $p = 0.041$ in the youngster group and 24.4 vs 19.0 μ g/L, $p = 0.442$ in the adult group).

Four youngsters and three adult patients showed adverse events, which included skin or oral itching sensation and mild chest discomfort. Anaphylactic shock and severe systemic adverse events related to the treatment were not observed during SLIT.

Discussion

The efficacy and safety of SLIT in adult patients has been demonstrated in several DBPC studies [1]. However, other reports show that SLIT did not show consistent clinical or immunological benefits in pediatric patients [11,12]. In the present study, we demonstrated that all the nasal symptoms were improved after 1-year SLIT in children and adolescents. SLIT with HDM extract in pediatric populations showed improvement in TSS and AMS comparable to that in adults.

Mean eye symptom score was not significantly decreased in the adult group where only seven patients (31.8%) were improved. In a previous report of SLIT with a grass pollen tablet, individual eye and nasal symptoms were significantly reduced [13]. Further study with a larger sample size is required to determine the change in eye symptoms in adult patients after SLIT with HDM extract.

There are several reports about the efficacy of SLIT with grass pollen for the pediatric patient group. The 1-year grass pollen SLIT in children showed no significant difference in symptom-medication scores between active and placebo treatment group [14].

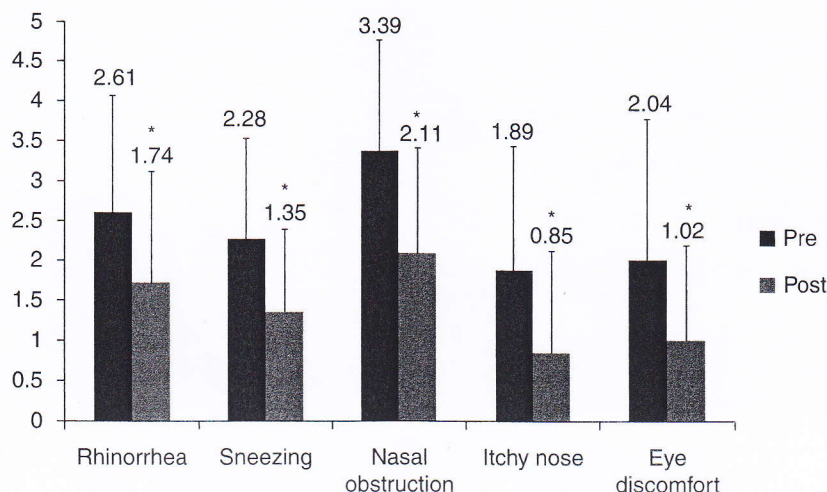


Figure 1. Allergic symptoms in youngsters. All allergic symptoms were improved in youngsters after 1-year SLIT (* $p < 0.05$).

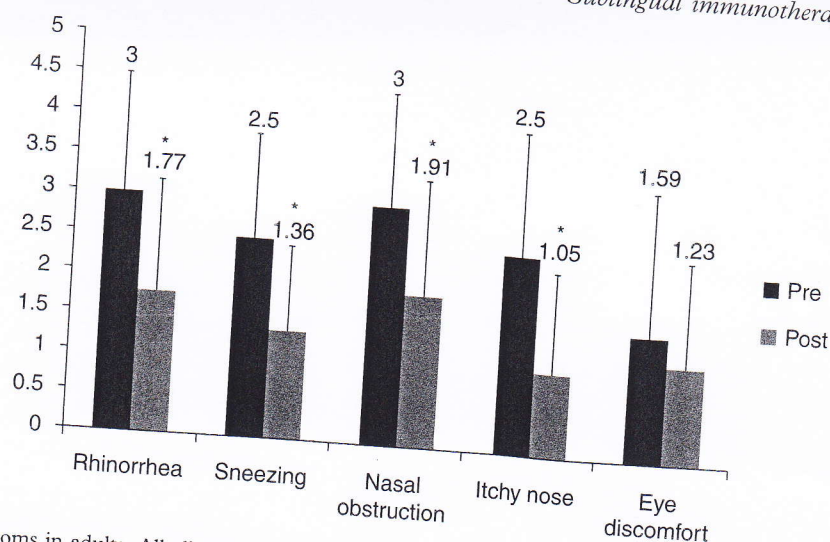


Figure 2. Allergic symptoms in adults. All allergic symptoms were improved in adults after 1-year SLIT (* $p < 0.05$).

However, another report demonstrated effectiveness on medication scores, without definite improvement in nasal symptoms [15]. Recent DBPC studies demonstrated improvement in both symptom scores and medication scores after SLIT with a grass pollen tablet in children and adolescents [5,6].

There are some reports about the effectiveness of SLIT with HDM [16,17]. In a DBPC study, SLIT with HDM appeared to be safe. However, there was a lack of consistent clinical benefit. In our previous report, SLIT improved the symptoms and medication scores in Korean AR patients sensitized to HDM [10]. Only 6-month SLIT showed improvement of all the nasal symptoms [9]. In the present study, 1-year SLIT could improve nasal symptoms and reduce rescue medication. In addition, SLIT for pediatric patients tended to be more effective than for adult patients (64.8% vs 50.0%), although it did not reach statistical significance. However, since

35.2% are still less effective after 1-year SLIT, it is important to find out the predicting factors for effective responsiveness.

There was no significant difference in the changes of serum total IgE levels between the 2 groups in this study. Allergen-specific IgE antibodies (sIgE) are the hallmark of the immune response to allergens. Recently, it was shown that a serum sIgE/total IgE ratio may be a useful tool in predicting the clinical response to allergen-specific immunotherapy [18]. In the present study, eosinophil counts and ECP levels had a tendency to decrease after 1-year SLIT in both groups. Furthermore, our previous study suggested ECP as a possible predicting factor for effective response to SLIT [10]. A future study regarding the correlation between symptom-medication scores

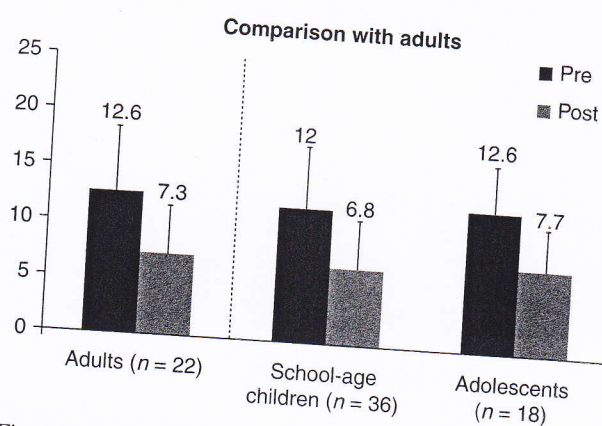


Figure 3. Total symptom scores (TSS) in youngsters and adults. Δ TSS were comparable in the 2 groups (5.1 vs 5.3, $p = 0.538$). School-age children and adolescents did not show significant differences in Δ TSS compared to adults ($p > 0.05$, Student's t test).

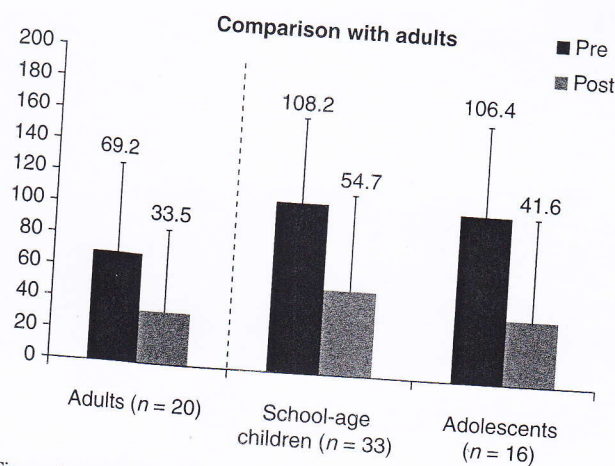


Figure 4. Anti-allergic medication scores (AMS) in youngsters and adults. Δ AMS tended to be higher in the youngster group (57.2 vs 35.7, $p = 0.060$). School-age children and adolescents did not show significant differences in Δ AMS compared to adults ($p > 0.05$, Student's t test).

and possible predicting factor for successful response to SLIT is needed.

One of the advantages of SLIT is a good safety profile and acceptance by patients. In this study, only minor adverse events were reported in both patient groups. No severe systemic allergic reaction such as anaphylaxis was reported in our series. Especially in a pediatric population, some patients are reluctant to use long-term medication with antihistamine and intranasal corticosteroid. These patients are good candidates for immunotherapy according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [19].

In the present study, we observed that subjective symptoms were improved and anti-allergic medication was also decreased with 1-year SLIT with the extract of HDMs. Because it has been reported that patients who did not show improvement in symptoms or medication scores in the first year of treatment showed such improvements in subsequent years of treatment [20], further follow-up study is required to evaluate whether allergic symptoms are reduced in more patients after long-term treatment. Additionally, a retrospective study showed that long-lasting effect of SLIT is strictly related to the treatment duration [21] which is why a long-term follow-up study might be needed to evaluate the carry-over effect of SLIT with HDM in the pediatric group.

In conclusion, SLIT with HDMs in pediatric AR patients is effective and safe. The improvement of medication scores in the pediatric group tended to be greater than in the adult group. Thus, SLIT could be an effective and useful treatment in children with HDM allergy. However, since some patients still are not sufficiently improved by SLIT, we should endeavour to find predictive factors for SLIT responsiveness and time to quit treatment for unresponsive patients.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- [1] Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;60:4–12.
- [2] Smith H, White P, Annala I, Poole J, Andre C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004;114:831–7.
- [3] Andre C, Vatrinet C, Galvain S, Carat F, Sicard H. Safety of sublingual-swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000;121:229–34.
- [4] Baena-Cagnani CE, Passalacqua G, Baena-Cagnani RC, Croce VH, Canonica WG. Sublingual immunotherapy in pediatric patients: beyond clinical efficacy. *Curr Opin Allergy Clin Immunol* 2005;5:173–7.
- [5] Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160–6.
- [6] Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123:167–73.
- [7] Ferres J, Justicia JL, Garcia MP, Munoz-Tuduri M, Alva V. Efficacy of high-dose sublingual immunotherapy in children allergic to house dust mites in real-life clinical practice. *Allergol Immunopathol (Madr)* 2011;39:122–7.
- [8] Yonekura S, Okamoto Y, Sakurai D, Horiguchi S, Hanazawa T, Nakano A, et al. Sublingual immunotherapy with house dust extract for house dust-mite allergic rhinitis in children. *Allergol Int* 2010;59:381–8.
- [9] Chang H, Han DH, Mo JH, Kim JW, Kim DY, Lee CH, et al. Early compliance and efficacy of sublingual immunotherapy in patients with allergic rhinitis for house dust mites. *Clin Exp Otorhinolaryngol* 2009;2:136–40.
- [10] Kim ST, Han DH, Moon IJ, Lee CH, Min YG, Rhee CS. Clinical and immunologic effects of sublingual immunotherapy on patients with allergic rhinitis to house-dust mites: 1-year follow-up results. *Am J Rhinol Allergy* 2010;24:271–5.
- [11] Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Pediatr Allergy Immunol* 1997;8:21–7.
- [12] Bahceciler NN, Isik U, Barlan IB, Basaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. *Pediatr Pulmonol* 2001;32:49–55.
- [13] Durham SR, Riis B. Grass allergen tablet immunotherapy relieves individual seasonal eye and nasal symptoms, including nasal blockage. *Allergy* 2007;62:954–7.
- [14] Bufe A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004;59:498–504.
- [15] Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV, et al. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004;59:1285–93.
- [16] Guez S, Vatrinet C, Fadel R, Andre C. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000;55:369–75.
- [17] Nuhoglu Y, Ozumut SS, Ozdemir C, Ozdemir M, Nuhoglu C, Erguven M. 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. *J Investig Allergol Clin Immunol* 2007;17:375–8.
- [18] Di Lorenzo G, Mansueto P, Pacor ML, Rizzo M, Castello F, Martinelli N, et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific

- immunotherapy. *J Allergy Clin Immunol* 2009;123:1103-10; 10 e1-4.
- [19] Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147-334.
- [20] Cox LS, Larenas Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006;117:1021-35.
- [21] Marogna M, Bruno M, Massolo A, Falagiani P. Long-lasting effects of sublingual immunotherapy for house dust mites in allergic rhinitis with bronchial hyperreactivity: a long-term (13-year) retrospective study in real life. *Int Arch Allergy Immunol* 2007;142:70-8.