

House Dust Mite Sublingual Immunotherapy in Children Versus Adults With Allergic Rhinitis

American Journal of Rhinology & Allergy

0(0) 1–8

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DOI: 10.1177/1945892420931713

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Abstract

Background: There are only a few studies in which the clinical efficacy of SLIT has been compared between children and adults. In addition, there is a lack of research on other factors, associated with the treatment, including immunological parameters and quality of life (QOL).

Objective: To compare the effects of sublingual immunotherapy (SLIT) in adults and children on various factors: clinical efficacy, quality of life (QOL), satisfaction, immunological parameters, and adverse events.

Methods: Subjects who were sensitized to house dust mites and treated with SLIT for at least 2 years were enrolled. Seventy patients who completed questionnaires measuring nasal symptoms and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores and underwent serologic tests for immunological parameters at initial, 1-year, and 2-year follow-up were selected and divided into two groups based on age: a child group (age 4–12 years, $n = 44$) and an adult group (age 19–59 years, $n = 26$).

Results: The Total Nasal Symptom Score (TNSS) was significantly decreased after 2 years of SLIT in both the child and adult groups ($p < 0.001$, both); however, changes in TNSS from baseline did not significantly differ between the two groups ($p = 0.365$). More patients in adult group were satisfied with SLIT than those in child group ($p = 0.050$), and changes in RQLQ score from baseline tended to be larger in adult group ($p = 0.089$). The levels of immunological parameters at baseline were significantly higher in the child group than in the adult group; however, changes in the levels of these parameters were not significantly different.

Conclusion: Although more adult patients were satisfied with SLIT, the clinical effects of SLIT on nasal symptoms were comparable between child and adult groups. Despite different immunological values at baseline between the two groups, changing patterns of immunological parameters did not differ.

Keywords

adult, child, clinical efficacy, house dust mite, immunological, nasal, quality of life, rhinitis, allergic, sublingual immunotherapy

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Introduction

Allergic rhinitis (AR) is a common immunoglobulin E (IgE)-mediated disease, and its prevalence has been increasing for several decades. Allergen-specific immunotherapy (AIT) is the only treatment option that can modify the natural course of allergic disease.¹ Subcutaneous immunotherapy has been used as the traditional form of immunotherapy. Recently, sublingual immunotherapy (SLIT) has been administered as an alternative to subcutaneous immunotherapy, and meta-analyses have demonstrated its efficacy.²⁻⁴ Although the clinical efficacy of SLIT in pediatric patients has been shown in several studies,^{2,5-7} there are only a few studies in which the clinical efficacy of SLIT has been compared between children and adults. Furthermore, there is a lack of research on other factors, associated with the treatment, including immunological parameters and quality of life (QOL). In a previous study, we reported comparable clinical efficacy of 1-year SLIT in children compared to that in adults⁸; however, effects of SLIT on various factors such as immunological parameters and QOL were not demonstrated. The primary objective of the present study was to compare the clinical and immunological effects of SLIT with standardized house dust mite (HDM) extracts between AR children and adults. The secondary objective was to compare the effects of SLIT on QOL and adverse events.

Materials and Methods

Study Design and Subjects

The present study was based on the data of patients who were prospectively enrolled in the SLIT cohort study, which has been performed since 2009 at a tertiary referral center. Between July 2009 and April 2014, a total of 448 AR patients who were sensitized to HDM at the initial visit and treated with SLIT were initially enrolled; however, only 170 patients continued SLIT for more than 2 years. After screening, 84 eligible patients who completed questionnaires measuring nasal symptoms and serologic tests at initial, 1-year, and 2-year follow-up were selected and divided into two groups depending on age: a child group (age 4–12 years, $n=44$) and an adult group (age 19–59 years, $n=26$). Adolescents (age 13–18 years, $n=14$) were excluded for obvious discrimination of clinical and immunological characteristics between child and adult groups. SLITone[®] (50% *Dermatophagoides pteronyssinus* [Dp]/50% *Dermatophagoides farinae* [Df], ALK-Abello, Madrid, Spain) was used for immunotherapy. A prepared single-dose (0.2 mL, 1000 STU/mL solution) was administered daily without escalation to child and adult patients. This study was approved by the Institutional

Review Board of Seoul National University Hospital (IRB No.1810-116-982).

Clinical Effects

Efficacy: Total nasal symptom score and rescue medication. All subjects were asked to complete questionnaires about their symptoms before and after 2 years of SLIT. The questionnaire evaluated 4 nasal symptoms (rhinorrhea, sneezing, nasal obstruction, and nasal itching). The symptoms were graded using a scale ranging from 0 to 3 points: 0 points for no symptoms; 1 point for mild symptoms; 2 points for moderate symptoms; and 3 points for severe symptoms. The Total Nasal Symptom Score (TNSS) was calculated as the sum of each of the symptom scores. Rescue medication use such as oral levocetirizine and mometasone nasal spray was allowed to control their allergic symptoms, if necessary, in this study. Participants' usage of rescue medication was classified into one of the following three categories after completion of 2 years of SLIT: "increased", "unchanged", and "decreased".

Quality of life. QOL was measured by the Korean version of the modified Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),^{9,10} which consists of 3 practical problems, 3 sleep problems, 4 nasal symptoms, 6 generalized symptoms, 4 activity problems, 3 emotional problems, and 3 ocular symptoms. Responses were graded on a scale ranging from 1 to 5 points: 1 point for not affected; 2 points for rarely affected; 3 points for mildly affected; 4 points for moderately affected; and 5 points for severely affected. The RQLQ was completed with the technical assistance by one senior research nurse. RQLQ score was calculated as the sum of each score, and higher scores representing poorer rhinitis-related quality of life. Among 70 patients, 66 subjects completed the RQLQ before and after 2 years of SLIT.

Satisfaction. Participants' subjective satisfaction was classified into one of three categories of satisfaction after completion of 2 years of SLIT: "satisfied", "fair", and "dissatisfied".

Immunological Parameters

Skin prick tests (SPTs) were initially performed in all subjects, and a wheal diameter of at least 3 mm was considered positive. Patients with positive SPT to Dp and/or Df at baseline were regarded as sensitized to HDM. Specific IgE (sIgE) for Dp and Df, specific IgG4 (sIgG4) for Dp and Df, and total IgE (tIgE) were measured using ImmunoCAP[®] (Thermo Fisher Scientific, Uppsala, Sweden). Peripheral blood eosinophils were counted using XE-2100 (Sysmex, Kobe, Japan).

Adverse Events

Adverse events possibly related to SLIT were recorded on weekly cards and reported at 1-year and 2-year follow-up.

Statistical Analysis

Continuous variables of demographics, total symptom scores, QOL scores, and immunological parameters are shown as mean $\pm$ standard deviation (SD) and analyzed with the two-sample t-test. The Chi-squared test and Fisher's exact test were performed to evaluate categorical variables. To assess the changes in continuous values, changes from baseline were calculated (post-baseline). All statistical analysis was carried out using R for Windows, version 3.4.2 (R Foundation for Statistical Computing). A p value of <0.05 was considered to be significant.

Results

General Characteristics and Distribution of Age

The demographic data of child and adult groups are shown in Table 1. Because the subjects were divided into two groups depending on age, there were significant differences in age and duration of symptoms between the child and adult groups. However, the child group did not differ significantly from the adult group in sex ratio, baseline TNSS, ratio of monosensitized and polysensitized subjects, and rate of history of asthma.

Clinical efficacy. TNSS was significantly decreased after 2 years of SLIT in both the child and adult groups (Figure 1; $p < 0.001$, both). However, changes in TNSS from baseline were not significantly different between the child and adult groups ($p = 0.365$). Each nasal symptom is shown in Table 2. More patients in the adult group than in the child group suffered from

sneezing at baseline. Otherwise, there were no differences in the 4 nasal symptoms between the two groups. Usage of rescue medication decreased in 35 out of 44 children (79.5%) and in 20 out of 26 adults (76.9%) after 2 years of SLIT; however, there was no significant difference in this factor between the two groups ($p = 1.000$).

Satisfaction. Participants' subjective satisfaction was determined with questionnaires after 2 years of SLIT. In the child group, the level of satisfaction of 59.1% of respondents was classified as satisfied, and that of 40.9% was classified as fair, while the corresponding levels were 84.6% and 15.4%, respectively, in the adult group. Patients in the adult group were more satisfied with SLIT than those in the child group ($p = 0.050$).

Quality of life. There was a significant decrease in the RQLQ score after 2 years of SLIT in both the child and adult groups (Figure 2; $p < 0.001$, both). Despite a lack of significance, the RQLQ score at baseline and the changes in RQLQ score were higher in patients in the adult group than those in the child group ($p = 0.091$ and $p = 0.089$, respectively). In addition, the reduction rate of RQLQ score in adult group tends to be higher than that in child group (29.8 and 38.0 in child and adult groups, respectively, $p = 0.109$).

Specific items of the RQLQ are described in Table 3. Subjects in the adult group suffered more from generalized symptoms and activity problems, and the changes in the score for generalized symptoms were larger in this group than those in the child group after 2 years of SLIT ($p = 0.013$, $p = 0.050$ and $p = 0.018$, respectively).

Immunological Effects

Immunological parameters at baseline and post-treatment, as well as changes from baseline (post-baseline), were compared between the child and adult groups

Table 1. Demographics and Clinical Characteristics of the Study Population.

	Child Group (n = 44)	Adult Group (n = 26)	P Value
Age, y	8.5 $\pm$ 2.3	31.3 $\pm$ 11.7	<0.001*
Gender (male : female)	35 : 9	15 : 11	0.093 [†]
Duration of symptoms, y	3.4 $\pm$ 2.0	12.1 $\pm$ 7.5	<0.001*
Baseline total nasal symptom score	8.4 $\pm$ 2.1	9.0 $\pm$ 2.3	0.321*
Monosensitized: Polysensitized	11: 33	4: 22	0.386
Asthma history	6/44 (13.6%)	2/26 (7.6%)	0.701 [‡]

The values are demonstrated as mean $\pm$ SD, except for gender and asthma history.

Bold text indicates statistical significance ($P < 0.05$).

*Two sample t-test.

[†]Chi-squared test.

[‡]Fisher's exact test.

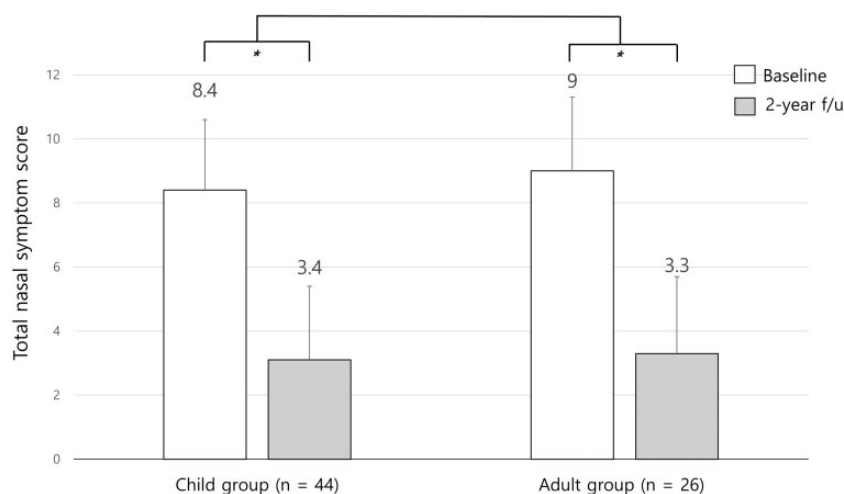


Figure 1. Comparison of total nasal symptom score between child and adult groups *: $p < 0.001$.

Table 2. Comparison of Nasal Symptoms Between Child and Adult Groups.

	Child Group (n = 44)	Adult Group (n = 26)	P Value
Nasal obstruction			
Baseline	2.5 ± 0.6	2.2 ± 0.9	0.082
Post	1.1 ± 1.0	0.8 ± 0.8	0.233
Post-baseline	-1.4 ± 1.0	-1.4 ± 1.1	0.854
Sneezing			
Baseline	1.8 ± 0.9	2.3 ± 0.8	0.017
Post	0.7 ± 0.7	0.8 ± 0.7	0.411
Post-baseline	-1.1 ± 0.9	-1.5 ± 1.1	0.151
Watery rhinorrhea			
Baseline	2.2 ± 0.8	2.5 ± 0.8	0.085
Post	0.9 ± 0.8	1.1 ± 0.7	0.399
Post-baseline	-1.3 ± 1.0	-1.4 ± 0.9	0.482
Nasal itching			
Baseline	1.9 ± 0.9	1.9 ± 1.0	0.877
Post	0.7 ± 0.8	0.5 ± 0.6	0.357
Post-baseline	-1.2 ± 1.0	-1.4 ± 1.0	0.418
Total nasal symptom score			
Baseline	8.4 ± 2.1	9.0 ± 2.3	0.321
Post	3.4 ± 2.5	3.3 ± 2.4	0.815
Post-baseline	-5.0 ± 2.9	-5.7 ± 3.1	0.365

The values are demonstrated as mean ± SD.

Bold text indicates statistical significance ($P < 0.05$).

(Table 4). Although Dp and Df sIgE levels, Dp and Df sIgG4, tIgE levels, and eosinophil counts were significantly higher in the child group than in the adult group at baseline and at 2-year follow-up ($p < 0.05$), changes at 2 years did not show any statistical significance. Figure 3 shows the changes in immunological parameters in the child and adult groups.

Adverse Events

Nine patients (20.5) in the child group and 5 patients (19.2%) in the adult group reported adverse events at 1-year follow-up ($p = 1.000$). Subsequently, at 2-year follow-up, 7 patients (15.9%) in the child group and 6 patients (23.1%) in the adult group described adverse events ($p = 0.645$). The details of adverse events are shown in Table 5, and no severe systemic adverse events were reported.

Discussion

Despite the clinical efficacy of SLIT in pediatric patients reported in previous studies,^{2,5-7} there is a lack of research on the clinical and immunological effects of SLIT in children compared with that in adults. In a previous study utilizing Pangramin® SLIT (ALK-Abello, Madrid, Spain), we compared the clinical efficacy of 1-year SLIT between children and adults,⁸ and found that TNSS was improved in both groups; however, the changes were comparable. In this study, we compared various effects of 2-year SLIT, including clinical and immunological effects, QOL, and subjective satisfaction between children and adults. In addition, adverse events were assessed in both groups.

In the present study, the 70 subjects were divided into two groups depending on age: 44 children and 26 adults. After 2 years of SLIT, there were significant decreases in TNSS in both groups; however, the changes in TNSS from baseline were not significantly different between the groups. In addition, there was no significant difference in the rate of patients who decreased their usage of rescue medication between the two groups. These results suggest comparable clinical effects of SLIT in the child and adult groups. In the comparison of specific nasal symptoms, more patients in the adult group than in

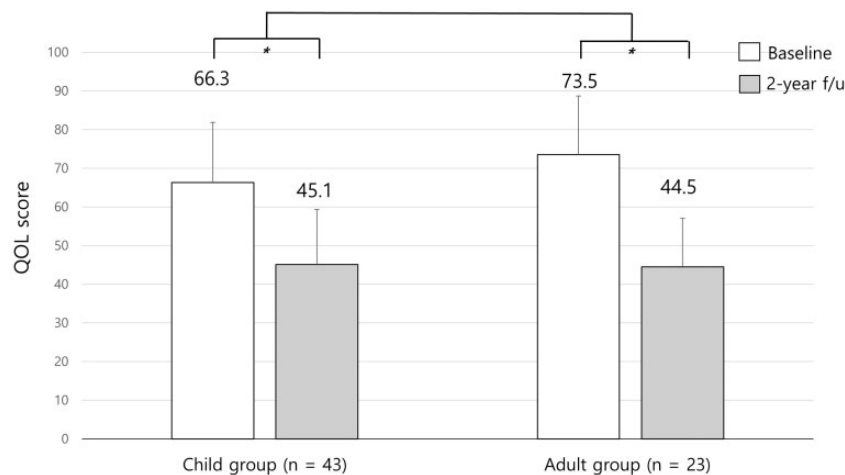


Figure 2. Comparison of quality of life (QOL) score between child and adult groups *: $p < 0.001$.

Table 3. Comparison of Quality of Life Between Child and Adult Groups.

	Child Group (n = 43)	Adult Group (n = 23)	P Value
Practical problems			
Baseline	9.9 ± 2.3	10.7 ± 2.5	0.239
Post	6.3 ± 2.6	6.0 ± 2.4	0.720
Post-baseline	-3.7 ± 2.8	-4.6 ± 3.1	0.210
Sleep problems			
Baseline	7.2 ± 2.9	6.6 ± 2.5	0.418
Post	4.9 ± 2.2	4.5 ± 1.7	0.468
Post-baseline	-2.3 ± 2.8	-2.1 ± 2.4	0.777
Nasal symptoms			
Baseline	13.2 ± 2.4	13.7 ± 2.8	0.459
Post	9.0 ± 2.7	8.5 ± 1.8	0.454
Post-baseline	-4.3 ± 3.2	-5.2 ± 3.0	0.233
Generalized symptoms			
Baseline	13.7 ± 4.4	16.8 ± 5.4	0.013
Post	10.2 ± 3.8	10.3 ± 3.3	0.937
Post-baseline	-3.5 ± 4.6	-6.6 ± 5.3	0.018
Activity problems			
Baseline	8.6 ± 3.7	10.5 ± 3.9	0.050
Post	5.5 ± 2.2	6.3 ± 2.6	0.225
Post-baseline	-3.0 ± 3.7	-4.3 ± 3.0	0.181
Emotional problems			
Baseline	7.0 ± 3.1	8.3 ± 2.7	0.098
Post	4.6 ± 2.1	4.8 ± 2.3	0.751
Post-baseline	-2.4 ± 3.2	-3.6 ± 2.8	0.162
Ocular symptoms			
Baseline	6.7 ± 2.8	6.8 ± 2.7	0.833
Post	4.7 ± 1.5	4.2 ± 1.3	0.228
Post-baseline	-2.0 ± 2.7	-2.6 ± 2.4	0.363
RQLQ score			
Baseline	66.3 ± 16.7	73.5 ± 15.2	0.091
Post	45.1 ± 14.1	44.5 ± 12.5	0.876
Post-baseline	-21.2 ± 17.8	-29.0 ± 16.2	0.089

Abbreviation: RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
The values are demonstrated as mean ± SD.
Bold text indicates statistical significance ($P < 0.05$).

Table 4. Comparison of Immunological Parameters Between Child and Adult Groups.

	Child group (n = 44)	Adults group (n = 26)	P value
Dp, wheal diameter, mm			
Baseline	11.3 ± 4.5	10.8 ± 7.7	0.805
Post	9.4 ± 3.7	10.8 ± 4.9	0.226
Post-baseline	-1.7 ± 4.9	-1.1 ± 4.8	0.673
Df, wheal diameter, mm			
Baseline	10.4 ± 4.2	11.0 ± 4.0	0.649
Post	8.8 ± 3.4	9.3 ± 3.8	0.678
Post-baseline	-1.0 ± 3.4	-1.9 ± 4.1	0.476
Dp-specific IgE, KU/L			
Baseline	51.2 ± 55.9	13.5 ± 15.1	0.018
Post	94.8 ± 98.1	37.2 ± 42.9	0.042
Post-baseline	43.6 ± 87.8	23.6 ± 33.6	0.417
Df-specific IgE, KU/L			
Baseline	106.9 ± 136.7	27.0 ± 24.7	0.038
Post	147.4 ± 136.1	59.1 ± 55.8	0.027
Post-baseline	40.5 ± 174.9	32.1 ± 41.8	0.847
Dp-specific IgG4, mg/L			
Baseline	0.36 ± 0.26	0.17 ± 0.08	0.009
Post	0.55 ± 0.39	0.27 ± 0.15	0.009
Post-baseline	0.19 ± 0.34	0.10 ± 0.12	0.338
Df-specific IgG4, mg/L			
Baseline	0.46 ± 0.34	0.19 ± 0.11	0.005
Post	0.66 ± 0.54	0.32 ± 0.24	0.025
Post-baseline	0.20 ± 0.46	0.13 ± 0.18	0.545
Total IgE, KU/L			
Baseline	477.8 ± 433.7	271.1 ± 297.8	0.035
Post	560.9 ± 464.3	315.2 ± 349.1	0.023
Post-baseline	83.1 ± 417.4	44.1 ± 206.6	0.658
Eosinophil count, /μL			
Baseline	504 ± 358	297 ± 176	0.012
Post	381 ± 219	229 ± 130	0.003
Post-baseline	-122 ± 251	-68 ± 121	0.334

Abbreviations: Dp, Dermatophagoides pteronyssinus, Df, Dermatophagoides farinae.
The values are demonstrated as mean ± SD.
Bold text indicates statistical significance ($P < 0.05$).

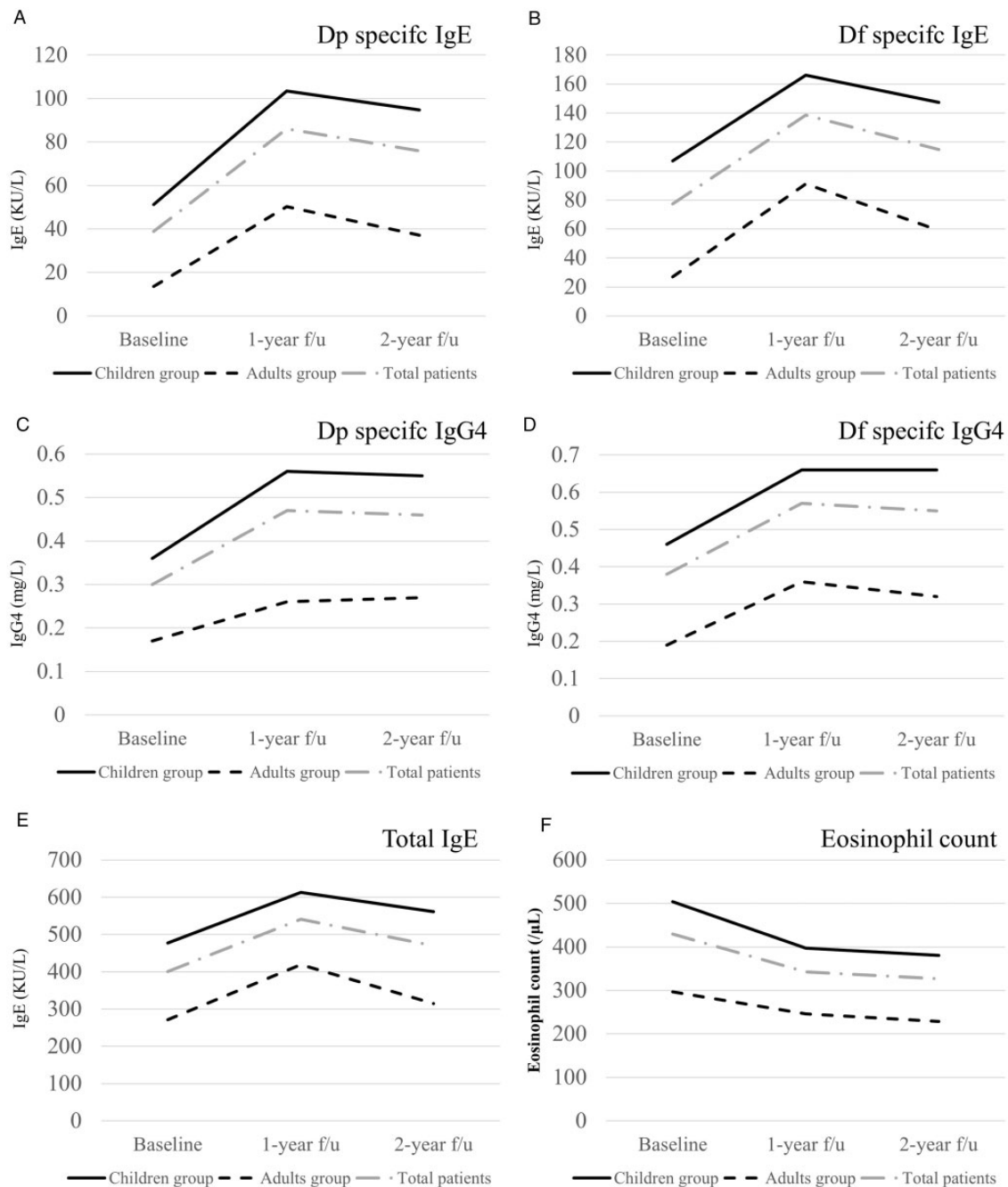


Figure 3. Levels of immunological parameters at baseline, 1-year f/u, and 2-year f/u (A) Dp specific IgE, (B) Df specific IgE, (C) Dp specific IgG4, (D) Df specific IgG4, (E) Total IgE, (F) Eosinophil counts.

the child group suffered from sneezing at baseline, and child group tended to have more nasal obstruction at baseline than in the adult group. In the Pediatric Allergies in America survey,¹¹ 75% of respondents reported nasal congestion as an extremely or moderately bothersome symptom, whereas 50% reported repeated sneezing as an extremely or moderately bothersome symptom, fewer than those reporting runny nose

(65%) and nasal itching (57%). These results demonstrate that children may not feel as much discomfort in sneezing as in nasal congestion, runny nose, or nasal itching, which is a possible explanation for the difference in the symptom score of sneezing between children and adults. Considering the RQLQ, patients in the adult group had a larger improvement in generalized symptoms than those in the child group. Questions for

Table 5. Adverse Events of Sublingual Immunotherapy in Child and Adult Groups at 1-Year and 2-Year Follow-Up.

	Child Group (n = 44)	Adult Group (n = 26)
1-Year Follow-Up		
Oral itching	3	2
Gastrointestinal complaints	0	1
Ocular itching	5	2
Urticaria	3	1
Dyspnea	0	0
Wheezing	1	0
2-year follow-up		
Oral itching	1	2
Gastrointestinal complaints	0	0
Ocular itching	4	4
Urticaria	2	1
Dyspnea	0	1
Wheezing	2	0

The numbers are not mutually exclusive.

generalized symptoms and activity problems include fatigue, concentration, and headache, which may be more pertinent to adults, who commonly experience work-related pressure, than to children. In the present study, 84.6% of adults and 59.1% of children were satisfied with 2-year SLIT. Although statistical significance was not reached, the adult group tended to exhibit more satisfaction ($p = 0.050$). The differences in satisfaction may be attributed to different changes in RQLQ scores between the two groups.

There were no significant differences in the wheal diameters of Dp and Df. However, children had higher levels of immunological parameters at baseline than adults in serologic tests. Dp and Df sIgE levels were significantly higher at baseline and 2-year follow-up in the child group than in the adult group, a finding consistent with the results of previous studies.^{12,13} However, changes in Dp and Df sIgE levels were not significantly different between the two groups. In addition, Dp and Df sIgG4 levels were also significantly higher at baseline and 2-year follow-up in the child group than in the adult group, consistent with the findings of previous research.¹³ In contrast to the study by Lai,¹³ however, in which a greater increase in Dp sIgG4 levels was observed in children than in adults, changes in Dp and Df sIgG4 levels did not significantly differ between the child and adult groups in the present study. This discordance could be due to the treatment period. The increase in Dp sIgG4 level was greater in children than adults at week 52, whereas there was no significant difference in Dp sIgG4 levels between the two groups at 104 and 156 weeks in the study by Lai.¹³ Because the present study investigated the changes after 2 years of SLIT, the results should be compared with those at

104 weeks, in which the increase in Dp and Df sIgG4 levels may not be significantly different between the two groups. Moreover, similar changes were observed in tIgE levels and eosinophil counts, with higher tIgE levels and eosinophil counts found in children, without difference in changes; these results are consistent with those of previous studies.^{12,14,15} These trends in immunological parameters suggest comparable immunological effects of SLIT despite the different immunological values at baseline between children and adults.

In previous studies, adverse events were reported in 53%–87% of children and 7.5%–88.2% of adults treated with SLIT.^{16–21} However, most of these were mild and local side effects, and severe systemic adverse events were not reported in these previous studies. In the present study, there was no significant difference in the rate of adverse events between the child and adult groups, and no severe systemic adverse events were reported.

There are some limitations in the present study. First the number of patients in child group was larger than that in adult group. In Korea, parents have a great interest in AR treatment for their children, and they are willing to cover expensive fee for SLIT. However, adults commonly want to control their disease with allergic medication and hesitate to spend time and money for SLIT. This specific custom may affect the distribution of age among the patients treated with SLIT. Second the QOL of the children was assessed with the RQLQ, which is a questionnaire for the general population. Because children have different lifestyles and expectations, questionnaires for children with rhinitis, such as the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) and Pediatric Allergic Disease Quality of Life Questionnaire (PADQLQ), may be more precise to evaluate their QOL.^{22–25} However, concordance between questionnaires was necessary to compare QOL of children with that of adults. Last, patient selection could be biased, because only patients who maintained 2 years of SLIT were enrolled. There were no subjects who reported dissatisfaction with SLIT in the questionnaires regarding satisfaction, which might result from the selection bias. Despite these limitations, the strength of the present study is that it compared the effects of SLIT between children and adults on various factors such as clinical efficacy, QOL, satisfaction, immunological parameters, and adverse events.

In conclusion, clinical effects of SLIT on nasal symptoms were comparable between the two groups, although more adult AR patients were satisfied with SLIT. Despite different immunological values at baseline between the two groups, the changes in immunological parameters did not differ, which suggests comparable immunological effects of SLIT in children and adults.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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