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Evaluation of Children with Allergic Rhinitis and Asthma Who Have Completed Allergen Immunotherapy: 19 Years of Real-Life Data, Single-Center Study

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ABSTRACT

Objective: Allergic rhinitis and allergic asthma are the most common chronic diseases in children. Allergen immunotherapy has also been shown to improve symptoms and medication scores in patients with allergic rhinitis and/or asthma. In our study, it was aimed to evaluate the patients who have completed allergen immunotherapy in terms of clinical improvement and new allergic sensitizations in the skin prick test.

Materials and Methods: Patients who received allergen immunotherapy between 1999 and 2018 were included in the study. Age, sex, diagnosis, medications, sensitizations in the first skin test, immunoglobulin E level, eosinophil count, allergen immunotherapy content and duration, and time after the end of immunotherapy were recorded from patient files. It was asked from the patients to compare their clinical findings before and after allergen immunotherapy as the same, better, or worse. Skin prick tests were performed with inhalant allergens in all patients.

Results: A total of 154 patients were included in the study, 68 of whom were subcutaneous and 86 were sublingual immunotherapy. Age, sex, disease severity, immunoglobulin E levels, and eosinophil counts of patients were similar in the subcutaneous and sublingual immunotherapy groups. In the subcutaneous immunotherapy group, self-reported clinical improvement for allergic rhinitis and asthma were 53.3% and 60.4%, respectively. In the sublingual immunotherapy group, self-reported clinical improvement for allergic rhinitis and asthma were 61.9% and 61.6%, respectively. New sensitization in the subcutaneous immunotherapy group was 12.1% and it was 3.5% in the sublingual immunotherapy group.

Conclusion: More than half of our patients who received immunotherapy reported clinical improvement according to self-report. In the subcutaneous immunotherapy group, new sensitizations were higher than the sublingual immunotherapy group, but it was thought that longer follow-up time in the subcutaneous immunotherapy group may have also contributed to this result.

Keywords: Subcutaneous immunotherapy, sublingual immunotherapy, asthma, allergic rhinitis, children

INTRODUCTION

Allergic rhinitis (AR) and allergic asthma are the most common chronic diseases in children (1). In the treatment of patients with AR and allergic asthma, it is aimed to control of the disease with appropriate treatment. (1,2). Allergen immunotherapy (AIT) is an effective treatment for severe allergic rhinitis, mild to moderate asthma, and venom allergy (3). Studies have shown that AIT may change the natural course of IgE-mediated allergic diseases, and prevent progression to asthma and sensitization to new allergens in patients with AR (4-7). It is known that there was a significant improvement in the medication and symptom scores of the patients who underwent AIT during the treatment, and this effect continued after the treatment was completed (8). Allergen and patient selection are very important factors for effective AIT. The guidelines have been prepared to determine which patients and allergens are suitable for maximum effect of AIT (8,9).

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Allergen immunotherapy can be applied as subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT).

In our study, it was aimed to evaluate the patients who have completed allergen immunotherapy in terms of clinical improvement and new allergic sensitizations in the skin prick test.

MATERIALS and METHODS

Study Design

The study was performed at our pediatric allergy department. The study protocol was in accordance with the Helsinki Declaration and approved by the local institutional review board (03.06.2015/105).

Study Population

Patients who underwent AIT for at least three years with the diagnosis of AR and/or asthma at our tertiary pediatric allergy clinic between 1999-2018 were included in the study. Patients with chronic diseases other than asthma and allergic rhinitis were excluded from the study.

Study Procedures

Of the 452 patients who were followed up at our allergy outpatient clinic and completed AIT, 335 patients could be reached. A total of 154 patients, 68 SCIT and 86 SLIT, agreed to participate in the study.

All the patients who were contacted were informed about the study, and those who agreed to participate in the study were given an appointment for a visit and a new skin prick test (SPT). At the visit, it was questioned whether there was a change in the clinical findings after AIT, and the subject was asked to evaluate them as the same, better, or worse. Age, gender, diagnosis, medications, sensitized allergens at the first SPT, total immunoglobulin E (IgE) level, and eosinophil count, and the beginning time, coverage, and duration of AIT were recorded from the patient files. Allergen immunotherapy data were extracted from the medical records. Novo-Helisen Depot® (*Allergopharma, Germany*), Phostal® (*Stallergenes, France*), Alutard SQ® (*ALK-Abello, Denmark*) were used for SCIT and Stalloral 300® drops (*Stallergenes®, France*) for SLIT. Patients who underwent AIT for all of the sensitizing allergens were grouped as fully covered immunotherapy, and patients who underwent AIT for some of the sensitizing allergens were grouped as partially covered immunotherapy.

Skin Prick Test

All patients underwent new SPT with inhalant allergens (grass pollens, tree pollens, weed pollens, house dust mites, molds, and animal danders) by using an allergen test solution (*Stallergenes®, France*). The number of positive allergens in SPT before and after AIT were compared, and new sensitizations were recorded.

Statistical Analysis

The data was recorded in the SPSS 20.0 for Windows v.21 (*SPSS, Inc., Chicago, Illinois, USA*) program. Descriptive data were expressed as mean, standard deviation or median, minimum, and maximum values for quantitative variables, while categorical variables were shown as numbers and percentages. The normal distribution of parametric variables was assessed with the Shapiro-Wilk test. A comparison of groups was carried out with a test of significance between two means or the Mann-Whitney U test. The Chi-square test was employed to analyze whether there was a significant relationship between categorical variables. A p value < 0.05 was recognized as statistically significant.

RESULTS

In our study, 68 of 154 patients received SCIT, and 86 received SLIT. The mean age at the first visit was 7.2 ± 2.9 years in the SCIT group and 7.0 ± 3.0 years in the SLIT group. The female/male ratio was 25/43 in SCIT and 29/77 in SLIT. The most common sensitized allergens were grass pollen and mites (SCIT: 72.1%, 72.1%; SLIT: 76.7%, 64.0%, respectively). We found that 73.5% of the patients in the SCIT group and 75.6% of the patients in the SLIT group were polysensitized. Familial atopy was more common in the SCIT group (p=0.043). The clinical findings and laboratory results of the patients in the SCIT and SLIT groups at the first visit were shown in Table I.

The mean age at onset of immunotherapy was 8.9 ± 2.7 years in the SCIT group and 9.4 ± 2.6 years in the SLIT group. We found that 57.4% of patients in the SCIT group and 62.8% of patients in the SLIT group had received immunotherapy for all sensitized allergens. At the current assessment, the mean age of the patients was 19.7 ± 4.6 years in the SCIT group and 16.5 ± 3.5 years in the SLIT group. The mean follow-up period after the end of immunotherapy was 5.0 [1 - 15] years in the SCIT group and 2.0 [1 - 10] years in the SLIT group.

Table I: Characteristics of patients at first evaluation, data expressed as n (%).

	SCIT (n=68)	SLIT (n=86)	p-value
Age, (years)*†	7.2 ± 2.9 7.0 (4) [3-14]	7.0 ± 3.0 6.5 (4) [3-14]	0.632
Gender (M)	43 (63.2)	57 (66.3)	0.694
Diagnosis			
Allergic rhinitis	15 (22.1)	13 (15.1)	
Asthma	24 (35.8)	23 (26.8)	0.158
Allergic rhinitis + asthma	29 (42.6)	50 (58.1)	
Severity of allergic rhinitis			
Mild	24 (53.3)	44 (79.8)	0.080
Moderate / Severe	21 (46.7)	19 (30.2)	
Severity of asthma			
Mild	31 (58.5)	46 (63.0)	0.607
Moderate persistent	22 (41.5)	27 (37.0)	
Sensitizations in SPT			
House dust mites	49 (72.1)	55 (64.0)	0.286
Molds	11 (16.2)	14 (16.3)	0.986
Animal danders	24 (35.3)	36 (41.9)	0.407
Grass pollens	49 (72.1)	66 (76.7)	0.507
Weeds	20 (29.4)	27 (31.4)	0.791
Tree pollens	36 (52.9)	40 (46.5)	0.428
SPT results			
Monosensitized	18 (26.5)	21 (24.4)	0.771
Polysensitized	50 (73.5)	65 (75.6)	
Family history of atopy	55 (80.9)	57 (66.3)	***0.043***
IgE (kU/L) †	302 (357) [46 – 1220]	313 (527) [1 - 5750]	0.882
Eosinophil (%)*†	5.8±3.3 5.0 (4.0) [0 – 16.0]	4.9±2.7 5.0 (3.0) [0.9 – 11.0]	0.216

SCIT: Subcutaneous immunotherapy, **SLIT:** Sublingual immunotherapy, **SPT:** Skin prick test.
***:** mean ± standard deviation, **†:** data expressed as median (interquartile range) [minimum-maximum.

At the last visit, a new sensitivity was found in 12.1% of the SCIT group and 3.5% of the SLIT group in SPT. Patients in the SCIT group were older than the SLIT group ($p< 0.001$). In the SCIT group, the follow-up time after the end of AIT was longer than in the SLIT group ($p<0.001$). In the SCIT group, house dust mite allergy and the number of positive allergens in the skin test was higher than in the SLIT group ($p=0.010$, $p=0.036$). Self-reported clinical improvement was 53.3% of patients with AR and 60.4% of patients with asthma in the SCIT group and 61.9% of patients with AR and 61.6% of patients with asthma in the SLIT group. An overview of the characteristics of children in the SCIT and SLIT groups are shown in Table II. Clinical findings and laboratory results in patients who self-reported clinical improvement after AIT are shown in Table III and Table IV. It was determined that the severity of the disease, mono/polysensitization, SCIT or SLIT duration, and the follow-up period after SCIT or SLIT did not affect clinical improvement (Tables III, IV).

DISCUSSION

In our study, we evaluated new sensitizations and self-reported clinical improvement in patients who completed AIT with AR and/or asthma. In this study, approximately

Table II: The features of the patients and administration of SCIT and SLIT, data expressed as n (%).

	SCIT (n=68)	SLIT (n=86)	p
Age at first SPT, years*†	7.2 ± 2.9 7.0 (4) [3-14]	7.0 ± 3.0 6.5 (4) [3-14]	0.632
Age at last SPT, years*†	19.7 ± 4.6 19 (5) [10 - 35]	16.5 ± 3.5 17 (4) [5 - 32]	***<0.001***
Age at onset of AIT, years*†	8.9 ± 2.7 9.0 (4) [5-15]	9.4 ± 2.6 9.0 (4) [5-16]	0.289
Follow-up period after the end of AIT*†	5.8 ± 3.3 5.0 (4.0) [1-15]	2.9 ± 2.2 2 (2.0) [1 – 10]	***<0.001***
AIT allergen			
House dust mites	45 (66.2)	39 (45.3)	***0.010***
Grass pollen	44 (64.7)	53 (61.6)	0.694
Tree pollen	22 (32.4)	28 (32.6)	0.978
Number of allergen for AIT			
1 allergen	32 (47.1)	54 (62.8)	0.085
≥2 allergens	36 (53.0)	32 (35.2)	
Fully / Partially covered AIT			
Fully	39 (57.4)	54 (62.8)	0.493
Partially	29 (42.6)	32 (37.2)	
Duration of AIT			
3 years	7 (10.3)	15 (17.4)	
4 years	13 (19.1)	19 (22.1)	0.347
5 years	48 (70.6)	52 (60.5)	
Self-reported clinical improvement	56 (65.1)	39 (57.4)	0.404
New sensitization according to SPT	8 (12.1)	3 (3.5)	0.058

SPT: Skin prick test, **AIT:** Allergen immunotherapy, **SCIT:** Subcutaneous immunotherapy, **SLIT:** Sublingual immunotherapy.
*: Mean ± standard deviation, †: Data expressed as median (interquartile range) [minimum-maximum].

two-thirds of patients reported clinical improvement. The rates were similar in the SCIT and SLIT groups. The rate of new sensitization in the SCIT group was higher than in the SLIT group, but it was not statistically significant.

AIT has been recommended in many guidelines as an effective treatment method in moderate-severe AR and mild-moderate asthma (8-11). Although immunotherapy efficacy has been shown in patients with mild to moderate asthma, the level of evidence is lower than in AR. In patients with severe asthma, AIT is not recommended (9). In our study, it was determined that self-reported clinical improvement was similar in asthma and AR. Also, it was determined that self-reported clinical improvement in patients with mild asthma was higher than in patients with moderate asthma, but the difference was not statistically significant.

In epidemiological studies, it has been determined that most of atopic patients were polysensitized (12). In some studies, immunotherapy efficacy was shown to be lower in polysensitized patients than in monosensitized patients (13). Some studies have found that the use of a single allergen in AIT or the use of a mixture of well-known homologous allergens increases the treatment effect, while a mixture of non-similar allergens or more than two groups of allergens reduces the treatment effect (13-15). Therefore, AIT in some polysensitized patients is not recommended due to concerns about efficacy. In our study, 73.5% of our patients were polysensitized and 42.6% received partially covered AIT. There was no difference in self-reported clinical improvement of patients who underwent polysensitized/monosensitized or fully/partially covered immunotherapy in our patients.

Table III: The evaluation of the factors associated with self-reported clinical improvement in the SCIT group, data expressed as n (%).

	Self-reported clinical improvement	p
Allergic rhinitis		
Mild, n=24	12 (50.0)	0.632
Moderate-severe, n=21	12 (57.1)	
Asthma		
Mild, n=31	22 (71.0)	0.061
Moderate, n=22	10 (45.5)	
SPT result		
Monosensitized, n=18	10 (55.6)	0.857
Polysensitized, n=50	29 (58.0)	
SCIT coverage		
Partially covered SCIT, n=39	23 (59.0)	0.754
Fully covered SCIT, n=29	16 (55.2)	
Duration of SCIT		
3 years, n=7	4 (57.1)	
4 years, n=13	7 (53.8)	0.959
5 years, n=48	28 (58.3)	
Follow-up period after the end of AIT		
0-5 years, n=24	16 (66.7)	
6-10 years, n=34	19 (55.9)	0.348
≥ 11 years, n=10	4 (40.0)	

SPT: Skin prick test, **AIT:** Allergen immunotherapy, **SCIT:** Subcutaneous immunotherapy.

Table IV: The evaluation of the factors associated with clinical improvement in the patients receiving SLIT, data expressed as n (%).

	Self-reported clinical improvement	p
Allergic rhinitis		
Mild, n=44	30 (68.2)	0.118
Moderate-severe, n=19	9 (47.4)	
Asthma		
Mild, n=46	30 (65.2)	0.412
Moderate, n=27	15 (55.6)	
SPT result		
Monosensitized, n=21	14 (66.7)	0.864
Polysensitized, n=65	42 (64.6)	
SCIT coverage		
Partially covered SLIT, n=54	35 (64.8)	0.939
Fully covered SLIT, n=32	21 (65.6)	
Duration of SLIT		
3 years, n=15	9 (60.0)	
4 years, n=19	10 (52.6)	0.315
5 years, n=52	37 (71.2)	
Follow-up period after the end of AIT		
0-2 years, n=16	12 (75.0)	
3-5 years, n=59	35 (59.3)	0.233
≥ 6 years, n=11	9 (81.8)	

SPT: Skin prick test, **AIT:** Allergen immunotherapy, **SLIT:** Sublingual immunotherapy.

In a study, it was determined that at least 3 years of treatment was required for AIT to be effective and that 4 or 5 years of treatment did not provide any additional benefit (15). We also found that self-reported clinical improvement was similar with three, four, or five years of AIT.

In the natural course of AR, progression to asthma may occur in 10-15% of the patients (2). Although it has been suggested that allergen immunotherapy may prevent the progression to asthma in AR patients, this is still unclear.

In some studies, it was determined that asthma development was lower than in the control group as a short-term effect after AIT (16-18). While it was determined that AIT could prevent the development of asthma in two-year follow-up in patients with AR (17,19,20), no similar effect was found in long-term follow-up (8). In our study, the follow-up period of patients with AR ranged from 1 to 15 years, and no asthma developed in any of our patients during this period.

Although it is reported that the development of new sensitization after AIT is lower than in the patients without AIT, the relationship between AIT and new sensitizations is controversial (19-25). In the EAACI guidelines on allergen immunotherapy, the data that indicated that AIT can prevent sensitization against new allergens has not reached a sufficient level of evidence; therefore further trials are needed to prove this association (4). In our study, new sensitization in SPT was 12.1% in the SCIT group and 3.5% in the SLIT group. The new sensitization was higher in the SCIT group than in the SLIT group, which may be related to the longer follow-up time in the SCIT group.

It has been reported that allergic rhinitis patients who received SLIT for pollens had better symptom and

medication scores than the placebo group (26-27). Wahn et al. (28) reported lower symptoms and medication scores in AR patients with pollen AIT even six years after AIT ended. In our study, the follow-up period after the end of AIT ranged from 1 to 15 years. More than half of our patients reported clinical improvement compared to the pre-AIT period. Since we could not compare clinical improvement in patients with the control group, it is not clear whether this result is due to the natural course of the disease or the effect of AIT.

Retrospective evaluation of the patients' data at the time of diagnosis is the most important limitation of our study. The study population is heterogeneous because of different duration and method of AIT, allergens used in AIT, and follow-up time after AIT. The evaluation of clinical improvement based on the self-report and the lack of a control group are other limitations of our study. Also, the different follow-up periods in the SLIT and SCIT groups are limitations. The results of our study are important for the presentation of real-life data. In addition, the long follow-up periods of the patients and the evaluation of the patients with a new skin test are also the strengths of our study.

As a result, we found that more than half of the patients self-reported clinical improvement and new sensitizations were low in patient who received AIT. In this study, the data of our patients in our allergy center were presented retrospectively for 19 years but randomized controlled trials with more patients are needed to determine the long-term efficacy of AIT.

Authorship Contributions

Concept: **Emine Ece Özdoğru, Özlem Sancaklı, Tuba Tuncel,** Design: **Emine Ece Özdoğru, Özlem Sancaklı, Tuba Tuncel,** Data collection or processing: **Emine Ece Özdoğru, Özlem Sancaklı,** Analysis or Interpretation: **Özlem Sancaklı, Tuba Tuncel,** Literature search: **Özlem Sancaklı, Tuba Tuncel,** Writing: **Özlem Sancaklı,** Approval: **Emine Ece Özdoğru, Özlem Sancaklı, Tuba Tuncel.**

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