

Allergy Immunotherapy as an Early Intervention in Patients with Child-Onset Atopic Asthma

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Key Words

Allergy immunotherapy · Asthma · Forced expiratory volume in 1 s

Abstract

Background: In patients with bronchial asthma an effective treatment is required at early stages of the disease to prevent irreversible structural changes of the airways. The objective of this study was to evaluate the beneficial effects of our routine immunotherapy as an early intervention on FEV₁ in patients with child-onset atopic asthma. **Methods:** Beneficial effects of successful immunotherapy on FEV₁ were analyzed retrospectively in 43 unselected patients who received our routine standard subcutaneous immunotherapy with periodic FEV₁ measurements and became asymptomatic. **Results:** Although there was no significant correlation between the duration of asthma symptoms prior to immunotherapy and the changes in FEV₁ before and after immunotherapy in 43 unselected patients, there was a significant inverse correlation between these two parameters in 23 patients whose asthma duration was less than 20 years. As the FEV₁ increased after immunotherapy in all 14 patients whose asthma duration was less than 5 years, the 43 patients were divided into a group 1 including these 14 patients and a group 2 including 29 patients whose asthma duration was more than 5 years. The FEV₁ de-

creased in 7 of the 29 asymptomatic patients in group 2. There was no difference in the initial FEV₁ between the two groups, but the final FEV₁ and the mean of the average increase in FEV₁ per year by immunotherapy were significantly higher in group 1 than in group 2. **Conclusions:** Immunotherapy should be started as early as possible at the youngest age in order to increase a beneficial effect of successful immunotherapy on FEV₁ improvement.

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Introduction

Allergy immunotherapy (AI) and allergen avoidance are the only treatments that can change the natural course of allergic rhinitis and atopic asthma [1]. In the last 90 years many studies, including double-blind controlled studies, have proved the efficacy of AI and suggest that it prevents the development of bronchial asthma in patients with allergic rhinitis [1–4].

Although asthma attacks may be transient and clinically self-limited, it has been well established that recurrent allergic inflammation in the bronchial tissues can cause irreversible structural changes with the potential to progress into chronic obstructive pulmonary insufficiency [5]. AI is indicated when avoidance of specific allergens and symptomatic medications fail to relieve the allergy

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symptoms [1]. However, it may be necessary to initiate an allergen-specific prophylactic treatment against unavoidable allergens in the earliest possible stage of the disease in order to prevent any structural damage in the airways [4, 6].

Forced expiratory volume in 1 s (FEV₁) is less variable and, therefore, more useful than peak expiratory flow in predicting the prognosis of bronchial asthma [7, 8]. Inhaled corticosteroids (ICS) are very effective in achieving high FEV₁ if introduced soon after the onset of bronchial asthma as a first-line prophylactic treatment [9, 10]. However, in young children ICS may not reach the peripheral airways due to small airway diameters [11] and they have potential side effects on growth and development [12]. Furthermore, asthma exacerbated with declining FEV₁ within 1 year when ICS had been discontinued [13].

Our primary purpose in this study was to examine whether AI that we use routinely in our clinic is truly beneficial for every patient who improves as assessed by the criteria of the 1997 NIH guidelines' classification of clinical symptoms [5]. This study was prompted by our daily observation that FEV₁ in relatively old patients who had had child-onset atopic asthma for longer periods of time did not improve as well as in younger patients even though clinically they were just as asymptomatic as younger patients. Beneficial effects of successful immunotherapy on FEV₁ improvements were analyzed retrospectively and evaluated whether or not the beneficial effects are influenced by the duration of asthma symptoms prior to immunotherapy.

Material and Methods

Patients

A total of 43 patients with child-onset atopic asthma who had been followed prospectively with regular immunotherapy injections and periodic FEV₁ measurements at the Allergy Clinic of Kugayama Hospital for 1–11 years and became asymptomatic were the subjects of this study. Patients who did not become asymptomatic over the course of immunotherapy were not included in the study. Immunotherapy in this population may not have been optimal because of a suboptimal selection of allergens for immunotherapy and/or insufficient allergen doses. In order to avoid a bias as to who should or should not be on immunotherapy, we tried to place every patient with child-onset atopic asthma on immunotherapy as early as possible. At the beginning of immunotherapy in the study population, the ages of the patients ranged from 4 to 65 years and there were 23 males and 20 females. This study was exempt from a review of the ethical standards of the hospital since we planned to treat the study patients like any other patients attending the clinic without requiring extra procedures or medications.

Onset and Duration of Asthma Symptoms

Each patient developed atopic asthma before the age of 15 and had the asthma severity classification of 'mild persistent' or greater just prior to starting immunotherapy. Patients who had been diagnosed to have bronchial asthma prior to age 15 but were in remission for varying periods of time were considered to have developed asthma at the time of the initial diagnosis. Patients who coughed with wheezing and dyspnea when they had exacerbations of allergic rhinitis or respiratory tract infection without being diagnosed to have asthma were considered to have developed asthma at the time of onset of first asthma-like symptoms if they were diagnosed to have asthma later.

Allergy Test

Patients were prick-tested against 60 inhalant allergens and blood samples were tested with radioallergosorbent test (RAST) against at least 10 inhalant allergens including *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, cat, dog and cockroach. Patients were considered to have atopic asthma if they showed 3 or 4+ prick test reactions or positive RAST against at least one of the following allergens including *D. farinae*, *D. pteronyssinus*, cat, dog, cockroach, *Alternaria*, *Cladosporium*, *Cephalosporium*, *Fusarium* or two or more common ragweeds or grasses with the methods described previously [14]. In addition, many patients including some children at the age of 4 or 5 were reactive against multiple other pollens and fungi and their total serum IgE levels and peripheral blood eosinophil counts (%) were also elevated.

Lung Function

Pulmonary function tests were performed using a 10 L Chestac-33 rolling-seal-type spirometer (Chest MI, Tokyo, Japan). FEV₁ values were expressed as percentages of predicted vital capacity (VC_p), FEV₁/VC_p × 100 (%). FEV₁ was measured prior to immunotherapy and periodically as needed thereafter usually once or twice a year in stable respiratory conditions. Changes in FEV₁ values were evaluated by averaging the differences between the initial and final values per year of immunotherapy.

Allergy Immunotherapy

Immunotherapy was performed with conventional standard subcutaneous methods [15]. Selection of allergens for immunotherapy was based on prick test and RAST reactions of individual patients and their clinical relevance as causes of respiratory symptoms. Allergen solutions were purchased from Hollister-Stier Laboratories (Spokane, Wash., USA) including standardized mite, cat, grass, short ragweed and other nonstandardized allergen extracts. Although the major allergens for immunotherapy were mite or cat or both, common nonstandardized allergens, such as dog, cockroach, birch, cypress, alder, sagebrush, plantain pollens or *Alternaria* were also included in the immunotherapy under our routine clinical settings. Standardized Japanese cedar (*Cryptomeria japonica*) pollen solutions were purchased from Torii, Tokyo, Japan. The highest dose per injection for standardized allergens were approximately 600 allergy units of *D. farinae* and *D. pteronyssinus* mixture (1.5 µg of Der f 1 and 3.0 µg of Der p 1), 2,000 bioequivalent allergy units (BAU) of timothy grass (7 µg of Phl p 5), 1,000 BAU of cat (6 µg of Fel d 1), 4 µg of short ragweed (Amb a 1) and 1.25 µg of Japanese cedar (Cry j 1), respectively. The frequency of immunotherapy injections varied from 2–3 times a week to once every 2–4 weeks depending on the stage of immunotherapy.

Medications

At their initial visits patients were prescribed inhalation of β_2 -agonists and corticosteroids and oral theophylline. Every patient was maintained on ICS even after they became asymptomatic unless their FEV_1/VC_p exceeded 100%. Administration of β_2 -agonists and theophylline was determined by their symptomatology. Patients who were on oral corticosteroids prior to immunotherapy or who needed short courses of oral steroids during immunotherapy were eventually able to discontinue oral steroids completely on immunotherapy. In order to minimize the effect of oral steroids on FEV_1 , the final FEV_1 values were obtained at least 1 year after the last dose of oral steroids.

Asthma Severity

The severity of asthma was graded according to the classification of the NIH guidelines of 1997 [5]. Since one of the purposes of this study was to evaluate whether or not an early intervention with successful immunotherapy was effective in improving FEV_1 , it was necessary for every patient included in this study to have improved more than the criteria for 'mild intermittent' classification in clinical symptoms. Therefore, all 43 patients were practically asymptomatic having had only transient mild wheezing less than once in 3 months with no night symptoms. In an attempt to assess whether the severity of asthma prior to immunotherapy had any effect on improvement of FEV_1 , we assigned a severity of 1 through 4 to mild intermittent, mild persistent, moderate persistent and severe persistent classes, respectively.

Statistical Analysis

The correlation between the duration of asthma prior to immunotherapy and the changes in FEV_1 after immunotherapy was evaluated by the Spearman correlation coefficient. Total serum IgE levels and peripheral blood eosinophil counts (%) were analyzed with unpaired t tests (two tailed). Lung function data (initial and final FEV_1/VC_p %) were analyzed using a repeated measures analysis of variance (ANOVA) with variables of group (group 1 vs. group 2) and time (initial vs. final). Planned comparisons ($p < 0.05$) in the form of unpaired t tests were used for pairwise comparisons of the means after a significant omnibus F ratio in the ANOVA. The asthma severity scores were analyzed with a nonparametric Mann-Whitney U test (for all statistical tests: $\alpha = 0.05$).

Results

Initially, we tried to correlate the duration of asthma symptoms prior to immunotherapy with the changes in FEV_1/VC_p (%) per year before and after immunotherapy in all 43 patients. As shown in figure 1, there was no significant correlation between these two parameters (correlation coefficient -0.26 with $p = 0.09$). There was 1 patient with an asthma duration of 30 years whose FEV_1 changed 23.3% per year by immunotherapy. This patient's exceptionally large change in FEV_1 was approximately 4 times the standard deviation of the mean change in FEV_1 of 43 patients. When this patient was excluded, the correlation

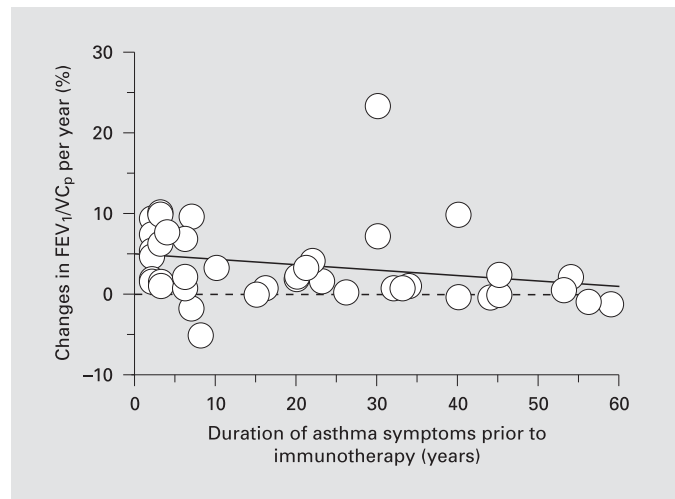


Fig. 1. Correlation between the changes in $FEV_1/VC_p \times 100$ (%) per year by immunotherapy and the duration of asthma prior to immunotherapy in 43 patients.

coefficient was -0.42 with $p = 0.006$. The regression line for the 42 patients was almost identical to that for all 43 patients (not shown). It appears, therefore, that there might be a trend towards a significant correlation between the asthma duration prior to immunotherapy and the changes in FEV_1 after immunotherapy. Indeed, there was a significant correlation (correlation coefficient -0.493 with $p < 0.02$) between these two parameters in 23 patients whose asthma duration was less than 20 years. In figure 1, it was noted that every patient whose asthma duration was less than 5 years showed an increase in FEV_1/VC_p (%) after immunotherapy. Accordingly, 43 patients were divided into a group 1 including 14 patients who began immunotherapy less than 5 years after the onset of the first asthma symptoms and a group 2 including 29 patients who began immunotherapy more than 5 years after the onset of the first asthma symptoms. In group 1, the severity of asthma prior to immunotherapy was mild persistent in 1, moderate persistent in 4 and severe persistent in 9 patients. In group 2, 5 patients had mild persistent, 9 had moderate persistent and 15 had severe persistent asthma prior to immunotherapy. Table 1 shows that there were no significant differences in total serum IgE levels, peripheral blood eosinophil counts or the severity of asthma prior to immunotherapy between groups 1 and 2. The mean age at which immunotherapy was begun was significantly younger in group 1 than in group 2.

In all 14 patients in group 1 and 28 of 29 patients in group 2, the major allergens for immunotherapy were

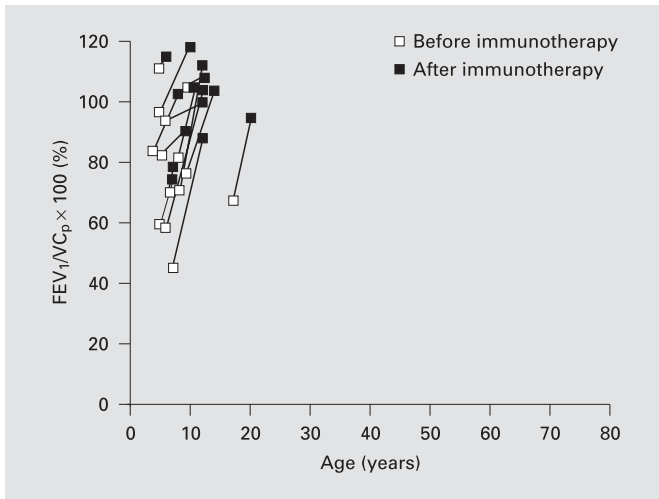


Fig. 2. The 14 patients in group 1 began immunotherapy less than 5 years after the onset of their first asthma symptoms.

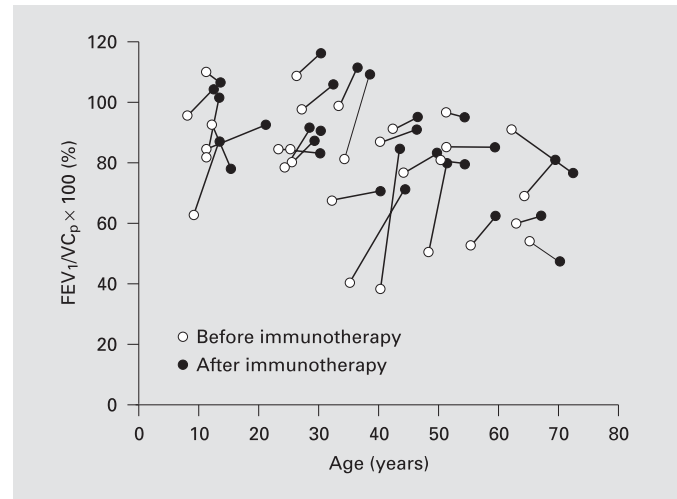


Fig. 3. The 29 patients in group 2 began immunotherapy more than 5 years after the onset of their first asthma symptoms.

Table 1. Comparison of clinical backgrounds between groups 1 and 2

	Group 1	Group 2	p values
Patients	14	29	
Duration of asthma symptoms prior to immunotherapy, years	<5	>5	
Age when immunotherapy was begun, years	7.214 ± 0.866	35.207 ± 3.334	<0.0001
Total serum IgE, IU/ml	728.357 ± 156.411	605.655 ± 132.835	0.5805
Blood eosinophils, %	9.929 ± 1.252	8.207 ± 0.974	0.3031
Asthma severity prior to immunotherapy, arbitrary units	3.571 ± 0.173	3.345 ± 0.143	0.4217

Values represent mean ± standard error of the mean.

D. farinae and *D. pteronyssinus*. In the remaining 1 patient in group 2, the major allergen was cat. Nine of the 28 patients in group 2 who were allergic to mites were also allergic to cats.

Figure 2 shows the initial and final FEV₁/VC_p % of the 14 patients in group 1. The FEV₁/VC_p % increased in every patient. Figure 3 shows the initial and final FEV₁/VC_p % of the 29 patients in group 2. The FEV₁/VC_p % increased in 21 patients, decreased in 7 patients and was unchanged in 1 of the 29 patients. Figure 4 shows average changes in FEV₁/VC_p % per year by immunotherapy. Table 2 shows that there was no significant difference in the mean FEV₁/VC_p % before immunotherapy between groups 1 and 2. After immunotherapy the mean FEV₁/VC % was significantly higher in group 1 than in group 2.

Within each group FEV₁/VC % improved significantly after immunotherapy ($p < 0.0001$ for group 1 and $p < 0.002$ for group 2), but the degree of improvement was significantly greater in group 1 than in group 2 by ANOVA ($p = 0.01$). The mean of average increases in FEV₁/VC_p % per year by immunotherapy was significantly greater in group 1 than in group 2.

Because the mean age at the start of immunotherapy was significantly younger in group 1 than in group 2, it is most likely that the higher increases in FEV₁/VC_p % in group 1 were due to the younger age of these patients.

In an attempt to minimize the age differences between patients of group 1 and 2, we selected only those patients who were 20 years old or younger at the time of the final FEV₁ measurements for comparison between the two

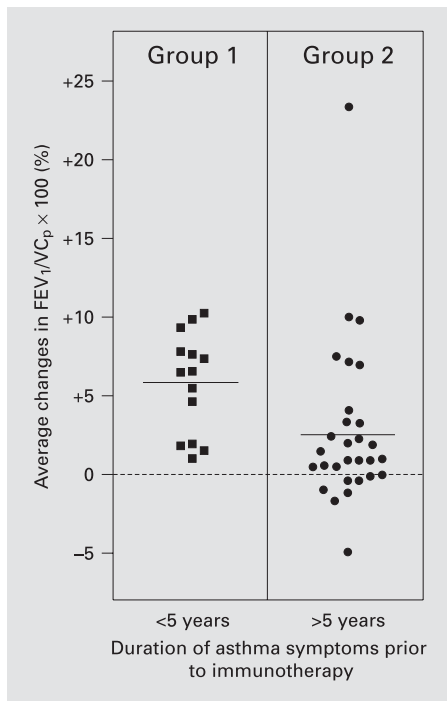


Fig. 4. Average changes in $FEV_1/VC_p \times 100$ (%) per year by immunotherapy are shown for the 14 patients in group 1 and for the 29 patients in group 2.

Table 2. Effect of immunotherapy on $FEV_1/VC_p \times 100$ (%)

	$FEV_1/VC_p \times 100, \%$		
	group 1	group 2	p values
Before immunotherapy	77.936 ± 5.021	79.228 ± 3.468	0.8330
After immunotherapy	99.050 ± 3.364	87.941 ± 2.945	0.0272
Average changes in $FEV_1/VC_p \times 100$ per year by immunotherapy	5.879 ± 0.856	2.641 ± 0.952	0.0367

Values represent mean \pm standard error of the mean.

Table 3. Comparison of beneficial effects of immunotherapy on FEV_1 between groups 1 and 2 in patients who were 20 years old or younger

	Group 1	Group 2	p values
Patients	14	6	
Age at initial FEV_1 , years	7.2 ± 0.87	10.3 ± 0.62	0.039
Duration of asthma prior to immunotherapy, years	2.64 ± 0.17	6.67 ± 0.33	0.0001
Initial $FEV_1/VC_p \times 100, \%$	77.94 ± 5.02	88.25 ± 6.5	0.257
Final $FEV_1/VC_p \times 100, \%$	99.05 ± 3.36	95.22 ± 4.68	0.531
Changes in $FEV_1/VC_p \times 100$ before and after immunotherapy, %	5.88 ± 0.86	2.2 ± 2.21	0.0724

Values represent mean \pm standard error of the mean.

groups. All 14 patients in group 1 were 20 years old or younger, ranging in age from 4 to 20, but there were only 6 patients in group 2 who were 20 years old or younger, ranging in age from 6 to 20 during the study period. Despite the selection, the mean age of the 14 patients in group 1 was significantly younger than the mean age of the 6 patients in group 2 (table 3). There were no significant differences in the initial and final FEV_1 and the changes in FEV_1 before and after immunotherapy between the two groups. Therefore, at least in these small numbers of young patients, slight but significant differences in age and duration of asthma prior to immunotherapy did not result in significant differences in the FEV_1 values between the two groups.

Discussion

Most of the controlled studies of AI proved their beneficial effects on allergic asthma due to a single allergen [2, 16]. In the controlled trial of immunotherapy for asthma due to multiple allergens, injections of up to 7 allergens for over 2 years were of no discernible benefit in allergic children with perennial asthma [17]. Their patients

were selected for compliance during a long run-in period of observation and stabilization. Therefore, 'the participants in their study were not typical of allergic children treated for asthma in routine clinical practice' [17].

In the present study, we attempted to examine whether AI that we use routinely in our clinic is truly beneficial for every patient who improves in clinical symptoms as assessed by the criteria of the 1997 NIH guidelines. In order to substantiate the improvement in clinical symptoms objectively, we obtained FEV₁ since a strong association exists between percent predicted FEV₁ and the risk of an asthma attack over the subsequent year in a pediatric population [8]. Furthermore, we tried to evaluate whether the beneficial effects of successful immunotherapy are influenced by the duration of asthma prior to immunotherapy. An advantage of FEV₁ as a marker of asthma severity is that it is frequently measured in routine clinical practice. Since improvements in FEV₁ parallel improvements in other asthma outcomes such as exacerbations and quality of life [18], objective measures of lung function are necessary in the assessment of the risk for adverse asthma outcomes.

All 43 patients in this study had received our routine immunotherapy against their respective allergens and became asymptomatic. Although there was no significant correlation between the duration of asthma prior to immunotherapy and the changes in FEV₁ before and after immunotherapy in all 43 patients, there was a significant correlation in 23 patients whose asthma duration was less than 20 years. It was also noted that all 14 patients whose asthma duration was less than 5 years prior to immunotherapy showed increases in FEV₁ after immunotherapy. Accordingly, the 43 patients were divided into two groups depending on the duration of asthma symptoms prior to immunotherapy. A beneficial effect of immunotherapy on FEV₁ was greater in group 1 who were younger and began immunotherapy less than 5 years after the onset of the first asthma symptoms.

Currently, AI is considered to be indicated when avoidance of allergens and symptomatic medications fail to relieve allergy symptoms satisfactorily. In a patient with child-onset atopic asthma, it may take several years for a trial of symptomatic medications to be fully evaluated. A belief by some people that childhood asthma may spontaneously remit might further delay a decision to start immunotherapy. As an early intervention ICS have been well documented to be effective. However, when ICS are discontinued FEV₁ decreases and asthma exacerbates [13]. In group 1, 8 of 14 patients (57%) discontinued ICS when they became asymptomatic since their

FEV₁/VC_p exceeded 100% whereas only 9 of 29 patients (31%) of group 2 could discontinue ICS. However, we cannot exclude the potential beneficial effects of early intervention with ICS in group 1 in addition to the beneficial effects of early intervention with AI.

In order to achieve and maintain a higher FEV₁ it may be necessary to start immunotherapy as soon as asthma symptoms appear before irreversible structural changes begin in the airways. Although we could not ascribe the beneficial effects of immunotherapy on FEV₁ to the shorter duration of asthma prior to immunotherapy in our patients of group 1, an early intervention in patients with child-onset asthma means, by necessity, starting the intervention at young ages. This approach is in keeping with the ARIA (Allergic Rhinitis and Its Impact on Asthma) concept of preventing asthma in patients with allergic rhinitis [4, 6]. Immunotherapy should be considered in patients with child-onset atopic asthma at the earliest possible stage of disease since a greater improvement in FEV₁ is more likely to occur if immunotherapy is introduced when they are younger and sooner after the onset of asthma symptoms.

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