

Efficacy of immunotherapy for treatment of allergic asthma in children

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ABSTRACT

Asthma is the most common chronic disease of childhood. Specific immunotherapy is widely used in several countries for managing allergic asthma. Many clinical trials and a meta-analysis of several studies support its efficacy to reduce the symptoms and medical requirements. The purpose of this study was to clarify the efficacy of subcutaneous immunotherapy (SCIT) in improving the symptoms and reducing medication requirements in primary school children with asthma in comparison with pharmacotherapy. A single-blind, drug-controlled clinical trial was performed. A total of 242 primary school children with allergic asthma were included in the study. The patients were recruited from subjects attending the Allergic Center in Mosul City. Their age range was 7–12 years with mean age of 10 ± 2 years. From the total only 197 children (81%) completed the study and were eligible for analysis, of those, 85 children were managed with SCIT and 112 children were managed with pharmacotherapies only. The follow-up after 1 year indicated that the children treated with SCIT show a marked reduction in the clinical symptoms, medication requirements, and the level of serum-specific IgE when compared with children treated with conventional drugs. SCIT was effective treatment and can prevent or decrease the onset of new sensitization to the offending allergen and maintain its beneficial effect for years after discontinuation.

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Key words: Asthma, children, immunotherapy, pharmacotherapy, primary school, subcutaneous immunotherapy

Asthma is a chronic inflammatory disorder of the lower airways. It is associated with substantial morbidity and mortality.¹ Allergic asthma is the most common form of asthma, characterized by symptoms that are often provoked by an identifiable trigger-like environmental allergen to which the patient has been sensitized.²

Specific immunotherapy is widely used in several countries for managing allergic asthma.³ Many clinical trials and a meta-analysis of several studies support its efficacy in reducing the symptoms and medical requirements.^{3–8} The most recent studies have shown that subcutaneous immunotherapy (SCIT) has the potential to affect the immunologic response to allergens.^{3–8}

Allergic asthma is a chronic inflammatory lung disorder and its treatment is based on allergen avoidance, pharmacologic treatment and immunotherapy. Allergen-specific immunotherapy is an important approach in the management of respiratory allergy in both adults and children,⁹ because it may affect the immunologic response toward allergen at its earliest stages.¹⁰ Spe-

cific immunotherapy is the only treatment capable of modifying the natural history of allergic disease.¹⁰

Allergic diseases of the airway, which include seasonal rhinitis, chronic perennial rhinitis, and asthma, are recognized as inflammatory disorders of the airway mucosa,¹¹ but differ in the location of the inflammatory reaction and clinical manifestation of the disease. Thus, the nose and lung should be seen as a continuum.¹² Asthma and allergic rhinitis frequently coexist in the same patient and are thought to share common predisposing genetic factors that interact with the environmental influences. Several studies had revealed that specific allergen injection immunotherapy is a highly effective treatment for IgE-mediated allergic diseases including asthma.^{13,14} Based on these observations, it is reasonable to regard immunotherapy as a particularly advantageous treatment in pediatric patients in whom the natural history of allergy is expected to be in part modifiable.

Although allergic response is, of course, influenced by genetic control, in recent years it has become clear that environment and exposure to allergens are important determinants in the development of the allergic disorders,¹⁵ with no differences between sexes. It has been claimed that SCIT is superior to sublingual immunotherapy since it is capable of modifying the natural history of the disease,^{16,17} of preventing the onset of new sensitization,^{18,19} and of maintaining a long-lasting effect after discontinuation.^{20,21} The relationship between asthma and allergic rhinitis is supported

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by epidemiologic studies; histological, physiological, and immunopathological characteristics; and by the positive effect of various therapies on asthma symptoms in patients with allergic rhinitis.²² All of these additional properties have been confirmed in pediatric patients. However, many of the SCIT effects have also been reported with sublingual immunotherapy.^{17,23,24}

Immunotherapy is usually administered by subcutaneous injection of allergen extract, which is delivered in gradually increasing doses during an up-dosing phase until a maintenance dose is reached and subsequent doses are administered every 1–2 months. None of the current pharmacotherapeutic options have been proved to alter the course of the disease; however, specific immunotherapy could affect the immunologic response toward allergen when given at early stages of the disease.^{17,23–25}

The aim of the present study is to evaluate the efficacy of SCIT in reducing the symptoms, episodes, and the amount of medication requirements in primary school children with allergic asthma.

SUBJECTS AND METHODS

Study Design

A single-blind (physicians were responsible for clinical examinations), drug-controlled clinical trial was performed at the Asthma Allergy Center in Mosul. The study protocol was approved by the Ethical Committee of Aljumhori Hospital and written informed consent was obtained from each child's parent.

Study Population

Primary school children with allergic asthma aged 7–12 years (mean age, 10 ± 2 years) with a specific IgE-mediated sensitization to one or more aeroallergens were eligible for analysis. The children were recruited from the Outpatient Clinic of Asthma and Allergy Center in Mosul. Patients were excluded if they were treated with β -blockers, had any chronic underlying illness, or had severe uncontrolled asthma, *i.e.*, forced expiratory volume in the 1st second (FEV_1) of $<70\%$ of predicted values. Patients were also excluded if they developed local severe adverse effects such as swelling of >5 cm after skin-prick test. Patients were evaluated by medical history, clinical examination, and skin-prick test with common allergens. IgE-mediated sensitization was assigned by determination of specific IgE and skin-prick test to common aeroallergens. The patients were randomized into one of the treatment groups by assignment the odd numbered patients in the immunotherapy group. All data were collected prospectively, including information on exposure, social factors, additional diagnosis, and medication usage, family history of allergic diseases, exposure to house pets, passive smoking, measures of treatment

efficacy, and patient's satisfaction as well as local and systemic reactions to the SCIT shots.

The study included 242 primary school children with allergic asthma, of those children, 127 (53%) patients were associated with allergic rhinitis. The study population was divided randomly in two groups: the first group included 105 children who received SCIT with pharmacotherapy, and the second group included 137 children who received pharmacotherapy only. The pharmacologic therapy included beclomethasone inhaler in doses of 200–300 μ g daily divided into three doses and aminophylline tablet (100 mg) twice daily. Hospital visits for the control group were scheduled at weekly intervals for 2 months, every 2 weeks for a month, and every 4 weeks for 9 months. The adverse reactions to immunotherapy were assessed according to the European Academy of Allergy and Clinical Immunology classification.²⁶

Asthma and Allergic Rhinitis Diagnosis

The diagnosis of asthma and classification were performed by specialist physicians based on the National Heart, Blood, and Lung Institute/World Health Organization workshop on the Global Strategy for Asthma.²⁷ Allergic rhinitis diagnosis was performed according to previously reported guidelines.²⁸

Lung Function Test

A computerized spirometer (Autosphiror, Discom-14; Chest Corp., Japan) was used for measurement of FEV_1 -predicted percent of the patients at their enrollment in the study and when indicated according to studies design.

Skin-Prick Test

The skin-prick tests were performed for all patients and the control group and were evaluated in accordance with European Academy of Allergy and Clinical Immunology subcommittee on allergy standardization and skin tests using the standard allergen panel (Stallergen, France). The panel for skin tests included dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), *Alternaria*, *Cladosporium*, *Penicillium* mixture, *Aspergillus* mixture, grasses mixture, feather mixture, dog hair, horse hair, cat fur, *Fagaceae*, *Oleaceae*, *Betulaceae*, plantain, Bermuda grass, *Chenopodium*, and mugwort. All tests were performed in the Outpatient Clinic of the Asthma and Allergy Center, Mosul, by a physician using commercial allergen extracts (Stallergen, France) and a lancet skin-prick test device. A wheal diameter of ≥ 3 mm in excess of the negative control was considered a positive test result.

Allergen Extracts For SCIT

Therapeutic vaccines containing allergen extracts were purchased from Stallergen. Both aqueous and glycerinated extracts were used to achieve a concentration of 1:100 w/v of the mixed extract. In standardized extracts the stock formulation was prepared by 10-fold dilution. A separate vial was used for allergen extract to reduce proteolysis degradation. All extracts were stored at 8°C. Therapeutic vaccine varied with each individual patient based on specific allergen identified during testing. Most patients received a single allergen (77 patients; mites, 37 patients; grass, 17 patients; trees, 11 patients; mold, 8 patients; pets, 4 patients) and 8 patients received a variety of aeroallergen combinations (3 mite and grass; 2 mite and mold; 3 mold and tree).

SCIT Protocol

The treatment protocol consists of two phases, the induction (build-up) phase and maintenance phase. The induction treatment with gradual increases in dose and concentration of vaccine content were performed weekly for a period of 20 weeks. The vaccine is injected by deep subcutaneous route in the posterior side of the upper arm. The maintenance treatment dose was given in a constant dose every 15 days and then at 4- or 6-week intervals. The interval between two maintenance injections must not exceed 6 weeks. Local reaction size was measured 20 minutes after each injection. Observed large local reactions (>20-mm wheal size) mandated a repeat of the same dose on the next visit, and systemic allergic reactions (skin, respiratory, cardiovascular, and/or gastrointestinal) required a two-fold reduction in vaccine concentration. Maintenance dose was set in most cases at 0.5 of the stock standardized extracts.

Evaluation of Treatment Efficacy

The treatment efficacy was evaluated using symptom score, medications score, FEV₁, specific IgE, and skin-prick test. Visual analog scale was used to calculate symptoms and medication scores at each visit for both active and control groups. A change of two or more points on this scale is considered a clinically significant change with consequent significant changes in the patients quality of life. Symptoms score, medication score, and FEV₁ were recorded at each visit during the attack and maintenance stages. Specific IgE and skin-prick tests were performed after 1 year from starting the vaccination schedule.

Determination of Specific IgE

A commercial enzyme-linked immuosorbant assay kit (Pharmacia Diagnostics, Uppsala, Sweden) was used to determine the allergen-specific IgE antibodies

serum levels of children included in the study. The IgE serum levels were determined at the time of enrollments in the study and after 1 year from starting the vaccine schedule. Values of ≥ 0.35 EU/mL were regarded as a positive response to a specific allergens.

Statistical Analysis

The chi-square test with Yates correction was used to compare the clinical evaluation, skin-prick test, and serum-specific IgE between the two groups.

RESULTS

A total of 242 primary school children aged 7–12 years (mean age, 10 ± 2 years) was included in the study. One hundred ninety-five (81%) patients completed the study protocol. Forty-five (19%) patients were dropped out of the study follow-up, 20 (44.5%) patients from the vaccine group and 25 (55.5%) patients from the conventional therapy group. The dropout rate from the vaccine group was 19% (20/105) and 18% from the group treated with conventional medication. The dropout was mainly caused by logistic difficulties, expense of the vaccine, and bad impression about the efficacy of the SIT that was also addressed by some physicians. Association of allergic rhinitis and asthma was present in 157 (65%) patients, 82 (52%) subjects in the patients group receiving vaccine and 75 (48%) subjects in the group receiving conventional medical treatments (Table 1).

In the patient group receiving the vaccine, there were 47/85 (55%) children sensitive to house-dust mites, 24/85 (28%) children sensitive to grass, 19/85 (22%) children sensitive to trees, 17/85 (20%) children sensitive to molds, and 6/85 (7%) children sensitive to pet dander. A family history of allergic rhinitis was elicited in 48% of patients and asthma in 54% of patients. Passive indoor smoke exposure was reported in 42% of patients.

In the patient group receiving conventional medication therapy there were 54/112 (64%) children sensitive to house-dust mites, 36/112 (32%) children sensitive to grass, 27/112 (24%) children sensitive to molds, 27/112 (24%) children sensitive to trees, and 11/112 (10%) children sensitive to pet dander. A family history of allergic rhinitis was elicited in 52% of patients and asthma in 53% of patients. Passive indoor smoke exposure was reported in 40% of patients.

After 1 year on intervention, there was a significant improvement in the clinical symptoms in 54 (64%) patients receiving immunotherapy, while the corresponding value was 29 (26%) children in the group of patients receiving conventional treatment ($p = 0.000$). In addition, 59 (69%) children in the vaccine group had a history of reduction in asthmatic episode periodicity after 1 year of intervention compared with 23 cases

Table 1 Patient's demographic and clinical characteristics

Variable	Immunotherapy	Pharmacotherapy
No. enrolled	105	137
No. defaulted (%)	20 (19)	25 (18)
No. with allergic rhinitis(%)	82 (78)	75 (55)
No. of patients who completed the trial (%)	85 (81)	112 (82)
No. of boys (%)	47 (55)	67 (60)
Age mean in years (SD)	9.8 (1.7)	10 (1.5)
Age range in years	7–12	7–12
Passive smokers (%)	35 (42)	52 (46)
Family history of allergic rhinitis (%)	41 (48)	39 (52)
Family history of asthma (%)	46 (54)	40 (53)
Sensitization to		
Mite	47 (55)	54 (48)
Grass	24 (28)	36 (32)
Trees	19 (22)	27 (24)
Molds	17 (20)	27 (24)
Pets	6 (7)	11 (10)
Use of medication		
Antihistamines	68 (80%)	95 (85%)
B2-mimetic	36 (42%)	45 (40%)
Mast cell stabilizers	27 (32%)	39 (35%)

Table 2 Therapeutic efficacy of immunotherapy

	Immunotherapy Group Patient No. = 85 No. (%)	Pharmacotherapy Group Patients No. = 112 No. (%)
Reduction in symptoms	54 (64)	29 (26%)
Reduction in specific IgE	64 (75%)	9 (8%)
Skin-prick test is negative or weakly positive	74 (87%)	8 (7%)
Improvement in pulmonary function test	51 (60%)	21 (19%)
Reduction in the need for pharmacotherapies	56 (66%)	13 (12%)

$p = 0.0001$.

(21%) in the conventional treatment group. Pulmonary function test was improved in 51 cases (60%) of the vaccine group compared with 21 cases (19%) in the conventional treatment group ($p = 0.0001$). After 1 year of follow-up, the skin-prick test became negative or weakly positive in 74 cases (87%) in the vaccine group. However, only 8 (7%) cases in medication group had shown such changes ($p = 0.0001$). Furthermore, the serum-specific IgE level became ≤ 0.35 IU/ mL in 64 cases (75%) of the vaccine group, whereas only 9 cases (8%) of children receiving conventional treatment ($p = 0.0001$). Fifty-six children (66%) reported a reduction in medication usage in the vaccine group compared with 13 cases (12%) in the conventional treatment group ($p = 0.0001$; Table 2).

Nine patients (11%) were diagnosed with immediate systemic reactions; of those nine patients, one devel-

oped mild respiratory involvement (grade 2), and eight developed skin rash (grade 1). All reactions were successfully treated in the center and none required additional observation or hospitalization.

DISCUSSION

Allergic asthma is a common chronic inflammatory disorder of the airways in children. It is characterized by episodes of cough, wheezing, and shortness of breath. The symptoms worsen on exposure to an allergen (*e.g.*, dust, mold, pollen, and animal dander) to which the patient has been sensitized. Large longitudinal studies revealed that allergic rhinitis may precede the onset of asthma.^{22,29,30} Although such results have been interpreted to define allergic rhinitis as a risk factor for the development of asthma, rhinitis ap-

pears to be an early stage of combined allergic airways disease. Several potential mechanisms have been proposed to explain the connection between the upper and lower airways in asthma and allergic rhinitis. However, a plausible explanation is that of the loss of nasal protection with a shift from nasal to mouth breathing as a result of nasal congestion. The resulting loss of nasal warming, humidifying, and filtering functions may result in an increased exposure of the lower airways to allergens and rhinitis, leading to inflammation.^{31,32} On the other hand, asthma and allergic rhinitis are associated with a profound immunologic deregulation characterized by an overproduction of Th2 cells in most of the patients.³³

The present study indicated that 65% of children included in the study had asthma and allergic rhinitis. In a recent large-scale study, Iraq provided evidence that asthma and allergic rhinitis are strongly associated with each other.²² The present finding was consistent with that reported for other geographical areas.³⁴

Therapeutic vaccines containing allergen extracts are effective and safe procedures that have been shown to significantly improve symptoms associated with allergic disease.^{6,35} There are only two kinds of treatment capable of modifying the natural history of allergic disease—allergen avoidance and allergy desensitization treatment.¹⁷ Most drug treatments of allergic diseases are very successful in relieving symptoms, but they do little or nothing to modify the natural progression of the disease. Cost-effectiveness studies have shown that when the expenses of long-term allergy drug treatments, lost days at work, and other economic costs are combined, allergy desensitization can be viewed as a cost-effective treatment option.⁸ The results of this study confirm the efficacy and safety of SCIT in the studied primary school children. The adverse systemic reactions reported from 11% of the treated population is comparable with that reported before for other localities,^{36,37} but higher than other.^{38,39} None of the reactions required continued observations or hospitalizations or necessitated the interruption of SCIT. The results of SCIT in reducing symptoms (66%), medication usage (66%), and asthmatic episodes (69%) are highly significant when compared with conventional treatment.

Overall, patient compliance with SCIT in this study was good as or better than general compliance with treatment of these conditions and immediate efficacy was comparable or better than therapeutic options where these results are available long term. Furthermore, SCIT is the only treatment with long-term effects on the immune system and the potential for influencing the natural course of disease. All studies trying to prevent asthma through long-term treatment with anti-inflammatory medications such as inhaled steroids, in

children, have failed in their goal,^{40–42} whereas immunotherapy has been shown to decrease/prevent the development of additional sensitizations⁴³ as well as the development of asthma in patients with allergic rhinitis.^{6,44}

The clinical effects obtained with specific immunotherapy may be explained by several mechanisms⁴⁵: a reduction in specific IgE antibodies, induction of blocking IgG antibodies, alteration of T-cell cytokine production (increase in T-helper 1 [Th1] cytokines), induction of specific T-cell tolerance (T-cell anergy, regulatory T cells),⁴⁶ and induction of anti-inflammatory activity.⁵ An updated meta-analysis of the scientific literature investigating the effectiveness of allergen immunotherapy for patients with asthma reviewing its overall efficacy on symptoms, medication requirement, lung function, and nonspecific and allergen-specific bronchial hyperactivity.^{47–50} They found that allergen immunotherapy significantly reduced the asthma symptoms and medication requirements. In addition, they had found that the pulmonary function test, although it is improved, is not statistically significant.^{48,49} However, in our present study, the improvement in pulmonary function test after 1 year was highly significant in children receiving SCIT.

Abramson and coworkers mentioned in their meta-analysis review that the causative environmental allergens included house-dust mites, pollens (grass and trees), molds, and animal dander.^{48,49} The same aeroallergens were found in children of both groups involved in this study.

One of the main differences between specific immunotherapy and symptomatic therapy is that the benefits of specific immunotherapy can be observed even years after discontinuation of treatment.^{20,50} In addition, specific immunotherapy may prevent the occurrence of new sensitization.^{6,16,51} Furthermore, it was established that specific immunotherapy is able to prevent the extension of upper airway disease to the lower airways.^{6,16} In this study, asthmatic episodes were improved in 69% of patients receiving vaccine, whereas the corresponding value in the conventional medicine-treated group was 21% ($p = 0.0000$). In addition, children with asthma alone showed better improvement with specific immunotherapy if their causative allergens were of the indoor type. In contrast, children with asthma and allergic rhinitis had shown more improvement when their causative allergens were of the outdoor type. This finding may suggest that outdoor allergens are more frequently associated with allergic rhinitis, a result that was consistent with that reported by Boulay and coworkers.⁵² Furthermore, our study reveals that improvement in allergic rhinitis may act as a potentiating factor for improvement in the signs and symptoms of allergic asthma.

In the present study, the follow-up of the involved children after 1 year had shown that the skin-prick test became negative or weakly positive in 87% of the vaccine group, whereas only 7% of the conventional treatment group became negative. Furthermore, immunotherapy induced reduction of specific IgE level in 75%, indicating the ability of immunotherapy in restoring IgE response, an effect that is significantly higher ($p = 0.000$) to that induced by conventional medication treatment.

A Cochrane extensive review showed that specific immunotherapy is beneficial for the treatment of adult asthma.⁴⁷ Compared with placebo, patients treated with specific immunotherapy experienced significant improvements in symptom scores, asthma medication use, and allergen-induced airway responses but had no signs of overall enhanced lung function.⁴⁷ Also, in our present study, we noticed that older children have shown more responsiveness to specific immunotherapy (*i.e.*, more decrease in the symptoms and more decrease in the need for medication therapy); however, the difference is that in our study there is enhancement in the pulmonary function test in 60% after 1 year follow-up in children receiving vaccine. The disadvantage of specific immunotherapy is the long-term duration of the therapy and the developing of adverse reactions in some few cases.

The limitations of this study are its relative small size and short follow-up. Additional long-term benefits such as decreased incidence of asthma could not be evaluated. However, this is the first clinical trial that was conducted in Iraq to evaluate the therapeutic efficacy of immunotherapy in the treatment of allergic asthma in primary school children. Larger, multicenter, real-life studies comparing SCIT with other therapeutic options are needed. In addition, time limitation of the working office environment and parental compliance restricted the use of standardized questionnaires for the assessment of quality of life. Thus, development of simpler tools for the assessment of quality of life in allergic patients, such as a validated visual analog scale score, is suggested.

CONCLUSIONS

Subcutaneous specific immunotherapy was shown to be superior to pharmacologic treatment in asthmatic children because of its efficacy, safety, easy administration, and lower cost, and it appears to be well tolerated with no serious side effects observed and no treatment withdrawals. Thus, it is recommended that SCIT should be started early in the management of allergic asthmatic children to modify the spontaneous long-term progress of the inflammation and disease.

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