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ORIGINAL ARTICLE

Clinical Efficacy of House Dust Mite-specific Immunotherapy in Asthmatic Children

Tzu-Chun Tsai, Jen-Her Lu, Shu-Jen Chen, Ren-Bin Tang*

Department of Pediatrics, Taipei Veterans General Hospital and School of Medicine,
National Yang-Ming University, Taipei, Taiwan

Received: Mar 3, 2009
Revised: Apr 23, 2009
Accepted: May 22, 2009

KEY WORDS:

asthma;
children;
house dust mite;
immunotherapy

Background: Immunotherapy has been widely used in the treatment of allergic diseases. We evaluated the clinical efficacy of specific immunotherapy with extracts of *Dermatophagoides pteronyssinus* (*Dp*) and *Dermatophagoides farinae* (*Df*) in children with asthma.

Methods: All 40 children had moderate-to-severe asthma and positive allergen tests for *Dp* and *Df*. All required daily medication. They were randomly assigned to two groups: Half of them received immunotherapy with subcutaneous injections of *Dp* and *Df* extracts, while the other half were not given immunotherapy. Participants were followed up for more than 6 months.

Results: Children in both groups had apparent improvements in medication use and symptoms after 6 months. The mean medication scores declined from 3.6 ± 1.14 to 1.7 ± 0.66 in the immunotherapy group ($p < 0.01$) and from 3.35 ± 0.87 to 2.4 ± 1.09 in the control group ($p < 0.01$). There was a significant difference between the two groups (mean difference 0.95; $p < 0.01$). The symptom score improved in the immunotherapy group from 2.65 ± 0.98 to 1.20 ± 1.00 ($p < 0.01$) and in the control group from 2.55 ± 0.99 to 1.40 ± 0.88 ($p < 0.01$), with a significant difference between the two groups (mean difference 0.3; $p < 0.01$). The number of office visits in the immunotherapy group was greater than that of the controls, but the frequencies of emergency room visits and hospitalization decreased.

Conclusion: Our study showed that specific immunotherapy with *Dp* and *Df* was beneficial for asthmatic children.

1. Introduction

Immunotherapy using injected aeroallergen extracts was first evaluated for the treatment of seasonal pollinosis in 1911¹ and has been widely used as a treatment for respiratory allergies, especially allergic rhinitis and asthma.² Controlled trials have shown that immunotherapy, using high-quality extracts in sufficient doses, relieves the symptoms of allergic rhinoconjunctivitis with minimal side

effects.^{3,4} Studies of immunotherapy for allergic asthma have shown that single-allergen immunotherapy reduces airway sensitivity to allergens, decreases symptoms and signs, and improves basal pulmonary function in some cases.^{5,6}

Immunotherapy with crude extract or partially purified allergen has been used in adults with allergic asthma,^{7–9} however, controlled clinical trials in children with allergic asthma have revealed no discernible benefits of multiple-antigen immunotherapy.¹⁰

*Corresponding author. Department of Pediatrics, Taipei Veterans General Hospital, 201 Shih-Pai Road, Section 2, Taipei 11217, Taiwan.
E-mail: rbtang@vghtpe.gov.tw

Nevertheless, although specific immunotherapy (SIT) is recommended for adults with asthma in the Global Initiative for Asthma (GINA) guidelines, its therapeutic role in children with asthma is still uncertain.¹¹

House dust mites, especially *Dermatophagoides pteronyssinus* (*Dp*) and *Dermatophagoides farinae* (*Df*), have been shown to comprise the most important allergens in airway hypersensitivity,¹² and are well known inhalant allergens responsible for certain Immunoglobulin E (IgE)-mediated disorders, such as allergic rhinitis and asthma.¹³ Available tests, including the skin prick test and specific antibody tests, can precisely detect reactions to *Dp* and *Df* in allergic children.¹⁴

The current study aims to evaluate the additive benefits of SIT using the specific injected allergens, *Dp* and *Df*, in allergic children with asthma who were receiving satisfactory medical care, including asthma pharmacotherapy.

2. Materials and Methods

2.1. Patients

We recruited 40 children (21 boys and 19 girls). All eligible children underwent an initial period of observation and had medical records for more than 1 year with a diagnosis of moderate persistent to severe persistent asthma, according to the severity classification of the GINA guidelines.¹¹ During the year of observation, the children had daytime or nocturnal asthma symptoms and suffered from frequent exacerbations. They also used daily asthma medications, including rapid-acting β_2 agonists, either for prophylaxis or rescue use. The children and their parents were instructed on how to manage their asthma and were evaluated for medical compliance. All enrolled children were monosensitized to house dust mites, as demonstrated by a skin prick test or specific antibody test. Enrolled children and their parents were informed about the details and risks of treatment, and guardians of all the children provided signed informed consent.

2.2. Management of asthma

At each visit, a team of clinical pediatricians, who were unaware of the treatment assignments, reviewed the patients' daily diaries, including records of symptom scores, diurnal peak-flow readings, and medications. They administered the medical treatment to the children according to their individual conditions of asthma control. The medication was increased or reduced by stepping up or down to gain control of clinical symptoms and/or lung function. Asthma medications were provided by

national health insurance and adjusted in a stepwise fashion as follows: step 0, no need for medication; step 1, use of rapid-acting inhaled β_2 agonist as needed; step 2, regular use of single medication such as low-dose inhaled corticosteroids (ICS), sustained-release theophylline, or leukotriene modifier; step 3, regular combined use of two drugs, such as low-to-medium dose ICS plus long-acting β_2 agonist, or medium-dose ICS plus sustained release theophylline or leukotriene modifier; step 4, regular use of high-dose ICS plus long-acting β_2 agonist, and additional sustained release theophylline or leukotriene modifier; step 5, the use of oral corticosteroids such as prednisolone. Acute exacerbations of asthma were treated by prescriptions from the children's physicians. Emergency room care and inpatient treatment were provided at the physicians' discretion.

2.3. Specific immunotherapy (SIT)

Allergies to *Dp* and *Df* were confirmed by skin prick or specific antibody tests prior to randomization. Children were divided randomly into two groups: an immunotherapy group and a control group. Children in the immunotherapy group received subcutaneous injections of extracts of *Dp* and *Df* (10,000AU/mL, Allered Laboratories Inc., San Diego, CA, USA), respectively, at an initial dose of 0.5AU/mL once a week. The dosage was increased weekly by 25–100% to reach an optimal maintenance dose. A large local reaction has previously been shown to predict a systemic reaction.¹⁵ If a dose produced a systemic reaction, the next dose was adjusted to 1/5 of the previous dose and was used as the optimal maintenance dose. Maintenance therapy was given every 2 weeks for at least 3 months. Dosage adjustments and safety procedures were based on large local reactions or systemic reactions combined with the authors' long-term experience and systematic attempts to rationalize the treatment by identifying risk factors and improving safety, while balancing time consumption, patient inconvenience, and the risk of inducing systemic reactions.¹⁶

2.4. Outcome variables

The principal outcome measure was the amount of medication required to control symptoms and maintain peak flows within acceptable limits. We used a 5-point ordinal scale of daily medication usage scores, modified according to the management of the GINA guideline.¹¹ Briefly, a score of 0 indicated no medication; scores 1–4 reflected the respective steps 1–4 of the medical algorithm; and score 5 reflected the use of systemic prednisolone.

Secondary outcome measures included the daily peak expiratory flow rate, asthma symptom score,¹⁷ and number of contacts with health care providers.

2.5. Statistical analysis

Nonparametric statistics were used to determine *p* values for group comparisons of all outcome measures. In the subgroup analysis of daily medication use, we used rank transformation and two-way analysis of variance to determine if the effect of immunotherapy differed among subgroups of children. All *p* values reported were two-sided and were calculated using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA) and Excel software for the signed-rank test, rank-sum test, and analysis of variance.

3. Results

3.1. Patients

A total of 40 children (21 boys and 19 girls) were enrolled in the study. Their average age at randomization was 8.5 years, ranging from 5 to 14 years. The baseline characteristics did not differ significantly between the two treatment groups (Table 1).

3.2. Primary outcomes

The mean daily medication scores before randomization (baseline) and 6 months later (last follow-up

visit) are listed in Table 2. The mean score declined significantly from randomization to the last follow-up visit in both groups ($p < 0.01$). However, there were no significant between-group differences at baseline or at the last follow-up visit.

We compared the mean change in medication scores between baseline and the last follow-up visit to identify any treatment-related changes in daily medication use. The magnitude of the changes was significant in the two groups (mean difference 0.95, 95% CI -0.92 to -0.97 ; $p < 0.01$) (Table 2).

3.3. Other outcomes

Other clinical outcomes are shown in Table 2. Both groups had significant reductions in symptom scores. The changes in both groups were significantly different and were related to the different treatments

Table 1 Characteristics of 40 children with allergic asthma randomly assigned to specific immunotherapy or control group

Characteristics	Immunotherapy (n=20)	Control (n=20)
Mean age (yr)	8.6±2.99	8.35±2.43
Sex (M/F)	14/6	7/13
Symptom score	2.65±0.98	2.55±0.99
Medication score	3.60±1.14	3.35±0.87
Peak flow (% of predicted value)	83.15±7.49	84.98±5.50

Table 2 Changes in outcome measures from baseline to the last follow-up visit

Measure	Immunotherapy (n=20)	Control (n=20)	Mean difference	<i>p</i>
Medication score				
Baseline	3.6±1.14	3.35±0.87	0.25	0.44
Last follow-up	1.7±0.66	2.4±1.09	-0.7	0.02
Change	-1.90	-0.95	0.95	<0.01
<i>p</i>	<0.01	<0.01		
Symptom score				
Baseline	2.65±0.98	2.55±0.99	0.1	0.75
Last follow-up	1.20±1.00	1.40±0.88	-0.2	0.51
Change	-1.45	-1.15	0.3	<0.01
<i>p</i>	<0.001	<0.01		
PEFR (% of predicted value)				
Baseline	83.15±7.49	84.98±5.50	-1.83	0.39
Last follow-up	84.3±5.56	84.12±4.72	0.18	0.92
Change	1.15	-0.86	-2.01	-
<i>p</i>	0.056	0.099		
Medical contact (no. in 6 mo)				
Clinic visit	17.25±4.6	12.4±5.87	4.8	0.006
Emergency room or hospitalization	0.76±0.17	0.95±0.21	-0.19	0.267

PEFR = peak expiratory flow rate.

(mean difference 0.3, 95% CI 10.29 to -0.31; $p < 0.01$). The peak expiratory flow rate increased in the immunotherapy group but declined slightly in the control group, though the difference was not significant. In summary, the immunotherapy group had a significantly greater improvement in symptoms than the control group. The immunotherapy group had a higher peak expiratory flow rate than the control group after treatment, but neither the differences before and after treatment, nor between groups were significant (Table 2).

3.4. Treatment-related adverse events

The most common adverse effect was local, reddish swelling at the injection site, which was experienced by eight children in the immunotherapy group. There was no apparent systemic reaction to the injections in our study.

4. Discussion

In this study, children with allergic asthma specific to *Dp* and *Df* were treated according to a protocol designed to approximate current standards for immunotherapy and pharmacotherapy. Immunotherapy using injections of specific allergen or allergens affected the course of asthma in children during the 6-month follow-up period, by decreasing their daily medication use and relieving symptoms.

These results are contrary to those of a previous study, where no discernible benefit of immunotherapy with injections of allergens in children with asthma already receiving pharmacotherapy was reported.⁷ Studies of subcutaneous SIT in children have not been as numerous as those in adults, and their results have usually assigned this therapy a controversial role in pediatric asthma treatment. However, Adkinson et al⁷ used therapeutic extracts containing mixtures of up to seven allergens, including pollen, molds, and dust mites. They presumed that dilution of multiple allergens may result in suboptimal doses of individual allergens, or mixtures with other allergens may reduce the potency of individual allergens. As a result, they suggested that the use of allergen mixtures be avoided. The current study showed beneficial results by utilizing mite-specific immunotherapy, but not allergen mixtures, indicating that SIT may be more appropriate for treating asthma in children than immunotherapy using mixtures of multiple allergens. Thus, our conclusions are different from those of the Adkinson et al study,⁷ but consistent with those from other recent reports.¹⁸

Although SIT has been used in the treatment of childhood asthma, the recommendations of this

therapy have varied from cautious acceptance to outright dismissal. Both the European Academy of Allergy and Clinical Immunology and the British Society for Allergy and Clinical Immunology advised against its use in patients under 5 years of age, and raised doubts about its use for the treatment of pediatric asthma.^{4,19} Moreover, the National Heart, Lung, and Blood Institute Working Group and the World Health Organization stressed that SIT should be considered only in cases where exposure to allergens cannot be avoided, or when a suitable pharmacological therapy has proved unable to control the disease.²⁰ Immunotherapy was omitted from the recommended asthma treatment for children, although it remains a choice of standard asthma treatment for adults.¹¹ In our study, SIT had additive benefits and produced no marked side effects in the children, who were all above 5 years old and receiving suitable medical care. However, investigations and observations in larger populations are needed to further demonstrate the effectiveness of SIT.

In our study, SIT effectively reduced the medication requirements and symptoms in children with allergic asthma. However, while a trend towards better performance was observed in the SIT group, the improvement in peak flow rate failed to reach statistical significance. Some reports suggested that SIT may improve bronchial reactivity,⁶ while others remained controversial. Immunotherapy provides the potential to downregulate the inflammatory cascade,²¹ reduce IgE antibody production,^{22,23} and attenuate symptoms in patients with asthma.²⁴ If these patients are left untreated, they would undergo airway remodeling and eventually progress to permanent abnormalities of the bronchial wall. Such remodeling processes are likely to play a considerable role in lung function decline and bronchial obstruction.^{25,26} Conceptually, early intervention in allergic disease is the most promising strategy for arresting disease progression, altering its severity, and preventing the development of the respiratory disease process.²⁷⁻²⁹ It could be reasonably supposed that early management with SIT in children with asthma may alleviate bronchial reactivity and even reverse bronchial obstruction before the natural progression to airway remodeling. Recent studies of SIT might support this possibility by demonstrating its long-term efficacy³⁰ and its preventive effect in reducing the onset of new sensitizations.³¹

A few children in our study experienced side effects of SIT with *Dp* and *Df*; eight children had local reddish swelling in injection site. It cannot be overemphasized that immunotherapy should be performed carefully because of the risk of side effects, which include itching, flushing, erythema, local swelling, urticaria, rhinitis, conjunctivitis, bronchospasm, and anaphylactic shock.³²

In conclusion, our results further support the idea that SIT using individual injections of extracts of house dust mites is effective in children with allergic asthma, and can reduce medication use and alleviate asthma symptoms.

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