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Original Article

Long-term house dust immunotherapy improves pulmonary functions in children and adolescents with bronchial asthma

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Abstract

This study involved long-term analysis of children and adolescents with house dust mite sensitive allergic asthma to investigate the effect of immunotherapy (IT) with a house dust extract containing certain amounts of *Dermatophagoides farinae* (*Der f1*), and *Dermatophagoides pteronyssinus* (*Der p1*, *Der p2*). The medication requirements, peak expiratory flow (PEF) circadian variations, forced expiratory flow between 25 and 75% of the vital capacity (FEF_{25-75}), maximal expiratory flow at 50 and 25% vital capacity (V_{50} and V_{25}), and specific airway resistance (SRaw) were evaluated over a 3-year period in patients treated with IT. When compared with the results for control asthmatic patients who had not been treated with IT, statistically significant amelioration regarding the PEF circadian variations, $\%FEF_{25-75}$, $\%V_{50}$ and $\%V_{25}$ was observed in IT-treated patients during the study. Although the improvement for medication requirement during the study was not different statistically between the two groups, we concluded that long-term house dust IT may result in amelioration of pulmonary functions, which may account for its clinical effectiveness in the treatment of asthmatic patients.

Key words: bronchial asthma, house dust mite, medication usage score, pulmonary function, rush immunotherapy.

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Introduction

Asthma is a multifactorial disease, and many triggering factors have been identified. Among the triggering factors, allergy appears to be more prevalent than previously believed,[1] and house dust mites represent one of the major allergens throughout the world. Immunotherapy (IT) or allergen-specific hyposensitization has been performed for the treatment of allergic diseases since it was introduced by Noon and Cantar in 1911.[2] Although IT with a house dust extract is generally accepted as being efficient in appropriate circumstances,[3–6] it is still debatable whether this treatment affects the natural history of bronchial asthma.[7,8] In most studies, the efficacy of the treatment was judged after relatively short-term observation, and the studies on the mechanisms underlying IT have been focused on the alteration of the immunological status.[9–12] The respiratory physiology of asthmatic individuals is of great practical importance but to date has not been examined fully in IT-treated childhood patients through a long-term study. In this study we conducted a clinical trial of IT over a 3-year period in children and adolescents with bronchial asthma. Multiple indices of the asthma severity, including pulmonary function test results, were recorded.

Methods

Patients

A total of 27 patients, who met the diagnostic criteria of the Guidelines for the Diagnosis and Management of Bronchial Asthma of the Japanese Society of Allergology,[13] participated in this study. All the patients were sensitive to house dust mites, according to the skin prick test reactivity and mite-specific IgE serum level. Before

Table 1. Patient characteristics

	With immunotherapy	Without immunotherapy
Male/female	7/4	7/4
Age (years)	11.5 ± 4.0*	10.5 ± 3.9
IgE (IU/mL)	794, 316–1, 995**	631, 316–1, 259
Dp-IgE (UA/mL)	79, 40–158	50, 16–158
Control medication		
Inhaled beclomethasone	5	5
Cromolyn and theophylline	6	6

*Mean ± 1 standard deviation. **Geometric means and 1 SD range.

the study informed consent was obtained from the subjects and/or their parents. A total of 13 patients were started on IT with a house dust extract, the others being treated symptomatically. Two of the 13 IT-treated patients and three of the 14 IT-nontreated patients were eliminated from the study because of their failure to complete the protocol. The characteristics of the 11 IT-treated patients, aged 6–18 years, and the 11 IT-nontreated patients, aged 8–19 years, who completed the study over the 3-year period are summarized in Table 1.

Immunotherapy

We used a standardized extract of house dust containing certain amounts of *Der f1*, *Der p1* and *Der p2* (Torii Pharmaceutical Co., Tokyo, Japan).[14] Immunotherapy was performed according to the rush protocol, originally described by Miller and Mansmann,[15] as shown in Table 2. During the rush IT, each patient was hospitalized and given ketotifen twice a day, with inhalation of sodium cromoglycate plus procaterol four times a day together with their controller medications for asthma. While patients were being given injections, peak expiratory flow (PEF) was determined 30 min after each shot for all the patients. The dosage increment was not made when the local induration exceeded 3 cm in diameter, or when the PEF result was less than 50% of the personal best value. No major problems were encountered in any patient, with the exception of one who developed chest tightness, wheezy coughing, bloody sputum and generalized urticaria within 20 min of receiving an injection of 0.1 mL of 1:10 w/v house dust extract. After the rush IT, an injection of the maintenance dose was given every second week for 1 year, and then every month over the next 2 years at the outpatient clinic of Kumamoto University Hospital, Kumamoto. The adverse reactions and the maintenance dosages are summarized in Table 3.

Table 2. Rush injection protocol with a house dust extract

Dose (w/v)	Day	Dosage (mL)	Time (h)
1–100 000	1	0.05	11:00
		0.10	13:00
		0.20	15:00
		0.35	17:00
	2	0.50	09:00
1–10 000		0.05	11:00
		0.10	13:00
		0.20	15:00
		0.35	17:00
	3	0.50	09:00
1–1000		0.05	11:00
		0.10	13:00
		0.20	15:00
		0.35	17:00
	4	0.50	09:00
1–100		0.05	11:00
		0.10	13:00
		0.20	15:00
		0.35	17:00
	5	0.50	09:00
1–10		0.05	11:00
		0.10	13:00
		0.15	15:00
		0.20	17:00

Clinic visits

Clinic visits were designed to facilitate optimal asthma control and close follow-up over an extended period of time. Patient compliance with the prescribed medication regimens was assessed by performing periodic pill counts, and canister weight and serum theophylline measurements. Medication was adjusted with the use of an algorithm based on the clinical symptoms and daily PEF values. The algorithm was designed to reduce medication use to the lowest level that maintained stability. Thus, the asthma disease activity was evaluated using daily medication usage scores (Table 4) as described by Gern *et al.*[16]

Table 3. The adverse reactions and maintenance dosages for rush immunotherapy with a house dust extract in patients with bronchial asthma

Case	age/sex	Final dose/adverse reaction	Maintenance dosage
KM	14/F	10^{-2}*, 0.5 cc/induration > 3 cm	10^{-2}, 0.3 cc
OK	17/F	10^{-2}, 0.5 cc/local urticaria	10^{-2}, 0.2 cc
KS	15/M	10^{-1}, 0.2 cc/systemic reaction	10^{-2}, 0.2 cc
TK	14/M	10^{-1}, 0.2cc	10^{-1}, 0.2 cc
IA	9/F	10^{-3}, 0.5 cc/induration > 3 cm	10^{-3}, 0.3 cc
YU	10/M	10^{-2}, 0.35 cc/induration > 3 cm	10^{-2}, 0.2 cc
MU	8/M	10^{-2}, 0.25 cc/induration > 3 cm	10^{-2}, 0.15 cc
MN	6/M	10^{-2}, 0.25 cc/induration > 3 cm	10^{-2}, 0.15 cc
HN	8/M	10^{-1}, 0.15 cc/local urticaria	10^{-1}, 0.1 cc
UY	8/M	10^{-1}, 0.25 cc/decreased PEF	10^{-1}, 0.1 cc
IA	18/F	10^{-2}, 0.35 cc/induration > 3 cm	10^{-2}, 0.2 cc

*weight by volume; PEF, peak expiratory flow.

Pulmonary function testing

Peak expiratory flow was measured by patients at home with an Assess Peakflow Meter (Healthscan Products Inc., Cedar Grove, NJ, USA). The best of three attempts was recorded in a diary twice daily, once in the morning before the use of any bronchodilator and once in the evening before bedtime medications were taken. The mean diurnal variation was calculated with the following formula (highest – lowest reading/mean reading of the day) × 100. The FEF_{25-75}, V_{50}, V_{25} and SRaw were measured with a body plethysmograph (Minato-Ikagaku, Osaka, Japan). FEF_{25-75}, V_{50} and V_{25} data were expressed as percentages predicted for age and height of Japanese people.[17]

Statistical analysis

Serum total IgE (IU/mL) and *Der p*-specific IgE (D.p-IgE, UA/mL) were analyzed as exponential values. The data were expressed as geometric means and 1 standard deviation (SD) range. Statistical analysis was performed by means of Student's *t*-test for paired and unpaired comparisons. A probability (*P*) value of less than 0.05 was considered significant.

RESULTS

The patients included in the two groups were similar in terms of mean age, sex, IgE, Dp-specific IgE and requirement for control medication (Table 1). The daily medication usage scores before the study were 4.3 ± 1.5 for the IT-treated group and 3.6 ± 1.6 for the IT-nontreated group, these two scores not being different statistically ($P > 0.3$). After the 3-year study, a statistically significant decrease was observed

Table 4. Daily medication usage scores

Medication	Consumption	Score
Cromolyn		1
Ketotifen		1
Theophylline		2
Inhaled β-agonist		2
Inhaled beclomethasone	< 400 μg	2
	< 400 μg	3
Oral steroids		4

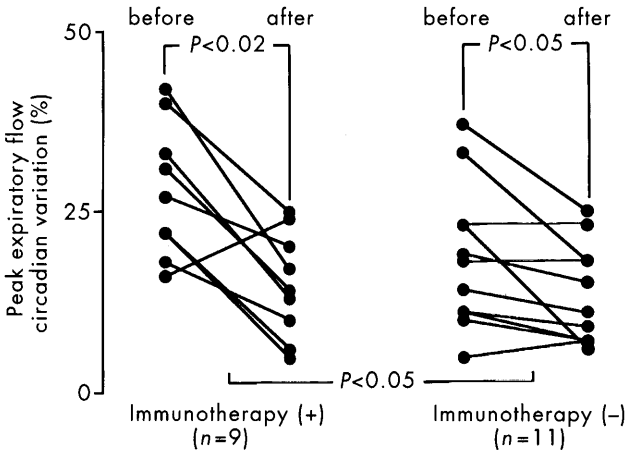

Fig. 1 Changes in peak expiratory flow (PEF) circadian variation (%) after 3-year treatment period with or without immunotherapy (IT) in patients with bronchial asthma. The PEF circadian variations in a 4-week period were improved significantly in both groups; however, the improvement rates in the IT-treated group were significantly better than in the IT-nontreated group.

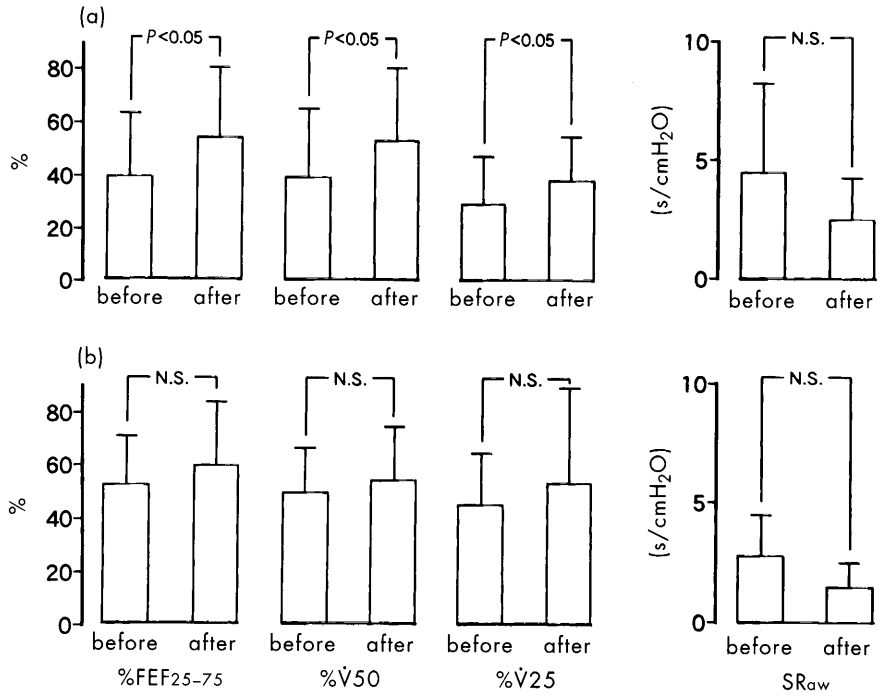

Fig. 2 Changes in percentage predicted FEF_{25-75}, V_{50}, V_{25} and SRaw after 3-year treatment period (a) with ($n=8$) or (b) without ($n=8$) immunotherapy in patients with bronchial asthma. *NS, not significant.

in both groups (i.e. improvement to 3.1 ± 3.4 ($P < 0.05$) in the IT-treated group and to 2.5 ± 2.3 ($P < 0.02$) in the IT-nontreated group). However, these improvements were almost the same in the two groups ($P > 0.5$).

The PEF data for 2 patients in the IT-treated group were omitted in this study, because their daily records were not of sufficient quality to be analyzed. The means and 1 SD of the PEF circadian variations for 4 weeks before the protocol began were 27.9 ± 8.8% in the IT-treated group and 18.6 ± 9.4% in the IT-nontreated group, these two values being different statistically ($P < 0.01$). Although the PEF variations in a 4-week period in the IT-treated group had decreased to 23.7 ± 10.9% after the 1-year therapy and to 22.0 ± 9.9% after the 2-year therapy, the ameliorations were not significant statistically when compared with the PEF variations before the therapy ($P > 0.05$ for both groups). The PEF variations had also decreased to 17.5 ± 8.5% after the 1-year study and to 15.5 ± 6.8% after the 2-year study in the IT-nontreated group. However, the improvements were not significant statistically when compared with the PEF variations before the protocol began ($P > 0.5$ after 1 year of the study and $P > 0.1$ after 2 years of the study). After the 3-year study had been completed, the PEF circadian variations in a 4-week period were improved significantly in both groups, becoming 14.9 ± 6.8% ($P < 0.02$) in the IT-treated group and 13.3 ± 6.6% ($P < 0.05$) in the IT-nontreated group. As shown in Fig. 1, the improvement rates in the IT-treated group were significantly better than those in the IT-nontreated group ($P < 0.05$).

The data obtained using a body plethysmograph in the subjects younger than 8 years were not always constant; therefore, 3 of the IT-treated group and 3 of the IT-nontreated group were excluded from the analysis. The $\%FEF_{25-75}$, $\%V_{50}$, $\%V_{25}$ and SRaw for the two groups were not different statistically before the study ($\%FEF_{25-75}$, $P > 0.2$; $\%V_{50}$, $P > 0.3$; $\%V_{25}$, $P > 0.1$; and SRaw, $P > 0.2$). Significant ameliorations in $\%FEF_{25-75}$, $\%V_{50}$, $\%V_{25}$ and SRaw were not found in either group after the 1-year study or after the 2-year study. However, after 3 years of the study, $\%FEF_{25-75}$, $\%V_{50}$ and $\%V_{25}$ were significantly improved in the IT-treated group, as shown in Fig. 2. In comparison, after 3 years of the study these values slightly, but not significantly, improved in the IT-nontreated group ($\%FEF_{25-75}$, $P > 0.05$; $\%V_{50}$, $P > 0.2$; and $\%V_{25}$, $P > 0.05$). When SRaw was compared between the baseline and after the 3-year study, differences were not observed statistically in either group ($P > 0.05$ for both groups) (Fig. 2).

Discussion

Allergen avoidance is always the first recommendation in the management of allergic asthma. However, avoidance is sometimes not practical for patients who are sensitive to house dust mite, and the control of bronchial inflammation induced by the mite allergens often requires long-term pharmacotherapy including inhaled steroids.[1]

The purpose of this study was to investigate the effect of IT in asthmatic patients allergic to house dust mite. A random, double-blind clinical trial would have been the best investigational approach to this problem. However, we could not enrol patients in such a trial due to the long follow-up period and nature of the disease. The clinical assessment by diary cards was hampered by poor compliance among the children, and most patients reported few symptoms of asthma exacerbation. Therefore, a major concern in our open study was to include objective measurements that were not based on knowledge of the patient's treatment status.

Pulmonary function test results are an accepted objective measure of airflow limitation and might be expected to reflect the clinical status of asthmatic patients. It has long been known that some pulmonary function abnormalities may persist after an acute asthmatic attack, and may be present in cases of asymptomatic asthma. However, it is not fully known why pulmonary function abnormalities persist in some patients with asthma who are otherwise free of symptoms. In some of these patients, PEF circadian variation has been proposed as a useful index of asthma stability and clinical control.[16] We were unable to state authoritatively why PEF circadian variation decreased with time in most patients from both groups. Although we suspected that close clinical follow-up, pharmacotherapy and aging contributed to this trend, we speculated that specific IT might additionally contribute to lower PEF circadian variation.

Haugaard *et al.* reported that mite-allergic patients with bronchial asthma who had undergone 2 years of IT exhibited decreases in both medication and PEF scores.[5] Costa *et al.* observed the improvement of PEF circadian variation in patients with bronchial asthma after 1 year of IT together with inhaled steroids treatment, although the clinical symptoms were not different from those of patients treated with inhaled steroids alone.[8] On the contrary, no amelioration of PEF values was observed in mite-allergic patients with bronchial asthma who had undergone specific IT for either 12 months[3] or 15 months.[7] Unfortunately, however, the circadian variations of PEF were not analyzed in either study. Although the improvements in medication requirements were not different statistically between IT-treated patients and control patients who had not been treated with IT in this study, Gern *et al.*[16] reported after the 3 year analysis that, in group studies of asthma, medication usage scores were a less useful indicator of disease severity than PEF circadian variations.

The improvement of forced expiratory volume in 1 second and FEF_{25-75} has been reported in mite-allergic patients with bronchial asthma after 1 year of IT.[4] However, long-term follow-up of the relationship between specific IT and V_{50}, V_{25} or airway resistance has not been performed. The present study showed amelioration of V_{50} and V_{25} after 3 years of IT in patients with bronchial asthma. Since V_{50} and V_{25} are expected to reflect a smaller airway function to some degree, it might be speculated that specific IT makes a therapeutic contribution to inflammatory lesions observed in the smaller bronchi in patients with bronchial asthma.[18,19]

A study of the microscopic structure of lobar bronchial specimens taken from asthmatic patients revealed airway inflammation with increased numbers of immunomodulating cells, including eosinophils, mononuclear phagocytes and T-helper lymphocytes.[18–20] Various immunological changes have been reported in mite-allergic patients receiving specific IT,[9–12] but the mechanism underlying its beneficial effect remains largely unknown. However, several possibilities have been proposed, including the suppression of an eosinophil chemotactic factor,[9] and monocyte chemotactic and activating factors produced by mononuclear cells.[10] Furthermore, IT has been shown to induce preferential activation of type 1 T-helper lymphocytes,[12] which downregulate the release of allergic inflammatory cytokines from type 2 T-helper lymphocytes. Because long-term studies have not proven that pharmacotherapy with inhaled steroids can impede the decrease in pulmonary function observed in adult asthmatic patients, the combination of pharmacotherapy and IT is likely to be more efficacious than pharmacotherapy alone due to the likely synergistic interference in the inflammatory cascade in the bronchi.[21]

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