

Short communication

Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation

Des Roches A, Paradis L, Knani J, Hejjaoui A, Dhivert H, Chanez P, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation.

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Specific immunotherapy (SIT) using a standardized mite extract is effective and safe when administered under optimal conditions. However, the duration of its effectiveness after cessation of treatment remains unknown. Forty asthmatic subjects who had received SIT with a standardized *Dermatophagoides pteronyssinus* (Der p) extract under the same protocol were studied. All had received SIT for a period of 12–96 months and were not receiving pharmacologic treatment. The FEV₁ was within normal range in all patients. After cessation of treatment, patients were followed for up to 3 years at 6-month intervals. The patient was considered to have relapsed when symptoms of asthma and/or rhinitis occurred and/or when pulmonary function tests were impaired. Skin tests with increasing concentrations of Der p were carried out before and at the end of SIT. Forty-five percent of the patients did not relapse. The duration of efficacy of SIT was related to the duration of SIT itself ($P < 0.04$). Most patients who did not relapse had a decrease in skin test reactivity at the end of SIT, whereas most patients who relapsed did not show any change ($P < 0.003$). The duration of efficacy of SIT after its cessation depends upon the duration of SIT and may be predicted by the effect of SIT on skin tests.

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Specific immunotherapy (SIT) is an effective treatment for allergic diseases under optimal conditions, but the duration of its efficacy after SIT cessation is still a matter of debate. In venom allergy, SIT can be stopped safely after 3–5 years (1, 2). In pollen allergy, the effect of grass pollen SIT lasts several years after its cessation (3–5). Two studies have demonstrated that after 1 year of SIT with perennial allergens, most, if not all, patients exhibited asthmatic relapse within 1 year of discontinuing SIT (6, 7).

Immunotherapy with a standardized extract of *Dermatophagoides pteronyssinus* (Der p) is effective (8), and relatively safe when administered with caution (9). The same protocol used for the past 15 years has been shown to alleviate asthma symp-

toms in children and adults (10). However, the duration of the efficacy of SIT after its cessation remains unknown. Such studies are extremely difficult to conduct since, at the cessation of SIT, patients should be completely symptom-free and should not be receiving pharmacologic treatment which could modify the natural course of the disease.

A controlled prospective study was carried out to assess the duration of efficacy of SIT after its cessation in patients who had received the same standardized Der p extract and the same maintenance dose. Only patients who, at the end of SIT, were symptom-free, were not receiving pharmacologic treatment other than inhaled β_2 -agonists prn, and had a normal pulmonary function test were

enrolled in the study. SIT was stopped after 1–5 years of treatment, and patients were followed-up every 6 months for the next 3 years. The predictive value of the skin test for the duration of efficacy of SIT was also examined by measuring the variation in skin test end point before and at the end of SIT.

Material and methods

Patients

Forty asthmatic patients (7–45 years) were selected by previously published criteria (8) (Table 1). All showed a positive prick test to a Der p standardized extract (Stallergènes Laboratories, Fresnes, France) and the presence of serum Der p IgE (RAST and CAP System®, Pharmacia Diagnostics AB, Sweden). The only perennial allergen to which patients were allergic was house-dust mite, but some patients were also allergic to grass pollens.

Methods

Immunotherapy schedules. Immunotherapy was carried out with a standardized Der p extract (11) and started by an RIT protocol previously published in detail (8, 9). The maintenance dose varied according to the age of the patients, but the protocol remained the same for any given age group. Patients aged 10 years and over received 3000 BU and those under this age 1500 BU. Allergen injections were given weekly for 6 weeks after the end of the RIT protocol, and then bimonthly for the first year and at monthly intervals afterward.

Skin prick tests. Skin prick test end points were carried out as previously described with six three-fold-increasing concentrations of the same Der p extract (8). The size of the skin prick test (SPT) reactions induced by the fourth concentration of allergen was also measured.

Table 1. Demographic characteristics of patients

	Group 1	Group 2
Number	21	19
Age (years) (median)	31.5 (17–42)	27 (16–40)
Sex (% male)	14 M (67%)	11 M (58%)
Rhinitis (%)	9 (43%)	9 (48%)
FEV ₁ end of SIT (% predicted)	87 (80–100)	95 (73–110)
SIT duration (months)	19 (14–24)	40 (36–48)
Total IgE (UI/l)	262 (181–658)	662 (209–1012)
Der p IgE (PRU/ml)	>17.5 (8.49–>17.5)	>17.5 (8.49–>17.5)
Grass pollen allergy (%)	10	31.6
Adverse reaction during SIT (%)	24	26

Group 1: SIT 12–35 months; group 2: SIT >36 months. Results expressed as medians and 25–75th percentiles. Demographic data before immunotherapy.

Serum specific IgE antibodies. Serum Der p-specific IgE was measured by RAST (Pharmacia Diagnostics, Sweden).

Assessment of efficacy of immunotherapy before its cessation. Patients were carefully studied by the use of symptom-medication scores and peak flow. None of them had presented symptoms within the past 3 months, and all were free from antiasthmatic treatment other than inhaled β_2 -agonists prn (less than once a week). A flow-volume loop was performed with a Pneumoscreen (E. Jaeger Laboratories, Würzburg, Germany), and the FEV₁ was always within 80–110% of predicted values (12).

Assessment of efficacy of immunotherapy after its cessation. Patients were followed up every 6 months by symptom-medication scores, and most of them regularly recorded their peak flow. At each visit, we carefully monitored the occurrence of asthma symptoms, recorded any drugs that had been taken, and performed a pulmonary function test. Patients were considered to have relapsed when they presented with asthma symptoms for over 1 week during the same exacerbation and/or they were obliged to take antiasthmatic drugs (regular use of bronchodilators and/or anti-inflammatory drugs) and/or their FEV₁ was under 80% of the values recorded at the end of the allergen injections.

Study design

The patients were divided into two groups according to the duration of SIT: between 12 and 35 months (group 1) and over 36 months (group 2). All patients were followed up for 3 years as described above. Skin tests and IgE measurements were carried out before and at the end of SIT. Statistical analysis was performed by nonparametric tests. The duration of SIT efficacy was estimated with Kaplan Meier's test.

Results

Comparability between groups

The demographic characteristics of the two groups of patients before SIT are presented in Table 1. There was no significant difference for any of the parameters tested including age, sex, presence of asthma and/or rhinitis, and initial FEV₁.

Efficacy of SIT after its cessation

No relapse occurred during the pollen season. Although an alteration in one parameter (symptoms, medication or FEV₁ changes) was sufficient to define a relapse, most patients relapsing had

recurrence of symptoms, need for medications, and altered FEV₁. The rate of relapse after the cessation of SIT was significantly higher in the group who received SIT for under 35 months ($P < 0.04$). Three years after stopping SIT, there was no relapse in 52% of the patients who had received SIT for more than 36 months compared with 38% in the other group who had received SIT for under 35 months. The duration of the efficacy of SIT after its cessation is presented in Fig. 1.

The probability of relapse after SIT as determined by Kaplan Meier's test is shown in Fig. 2. Fifty percent of the patients relapsed in the first 18 months after cessation of SIT. Thereafter, the rate of relapse was decreased, and only an additional 10% of patients had relapsed by 36 months after cessation of treatment.

Parameters involved in the efficacy of SIT after its cessation

The duration of SIT was examined, and it was observed that a longer period of SIT was significantly associated with a lower rate of relapse after cessation ($P < 0.04$). Patients who were younger when SIT was started presented fewer relapses, but

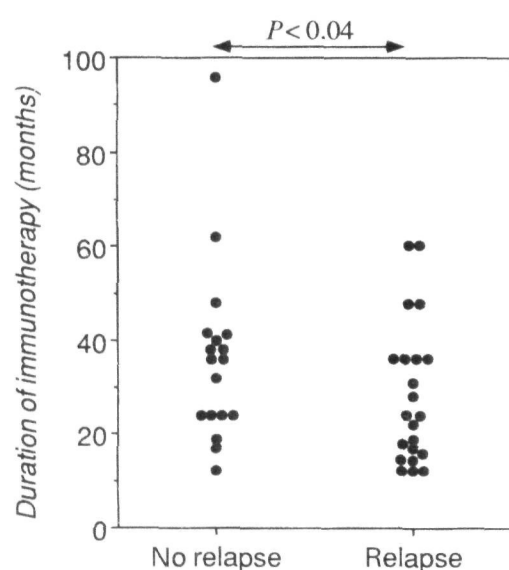


Fig. 1. Relapse of symptoms depending on duration of immunotherapy ($P < 0.04$, Mann-Whitney U test).

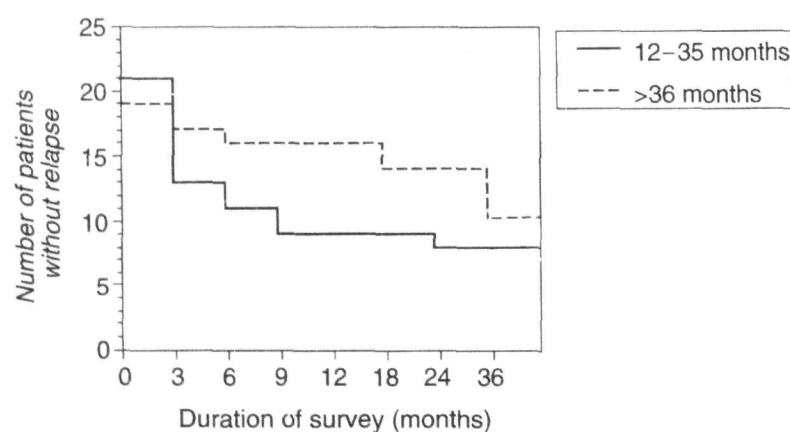


Fig. 2. Rate of relapse of patients depending on duration of immunotherapy ($P < 0.04$, Kaplan Meier's test).

this was not statistically significant. The evolution of skin test titration during SIT was predictive of the duration of efficacy, since the end-point titer at the end of SIT was significantly reduced in the group of patients who did not relapse when compared with those patients who did relapse ($P < 0.003$) (Fig. 3). On the other hand, total and Der p-specific IgE in serum were not predictive of relapse.

Discussion

The data presented in this study demonstrate that the persistence of efficacy of Der p SIT after its cessation is increased in patients who receive a longer period of SIT. Moreover, the persistence of efficacy seems to be related to the reduction of the end-point titration of Der p skin tests.

The methods used in this study have been validated in previous studies by our group. One of the major problems of the present study is that it was not double-blind and placebo-controlled. However, because of the low number of patients eligible for enrollment in the study (symptom-free and without regular pharmacologic treatment), and because we wanted to examine the effect of the duration of SIT, it was not possible to perform the study in a double-blind, placebo-controlled manner.

Only two studies have tried to evaluate the long-term effect of mite SIT after its cessation. In these studies, SIT was administered for 1 year or less and the duration of efficacy after its cessation was lost after 1 year (6, 7). In this study, the group who received a shorter period of treatment (under 35 months) had a higher rate of relapse (62%) than patients who received more than 36 months of SIT (48%). The lower rate of relapse seen in both groups of this study could be explained by the fact that all patients underwent at least 12 months of SIT.

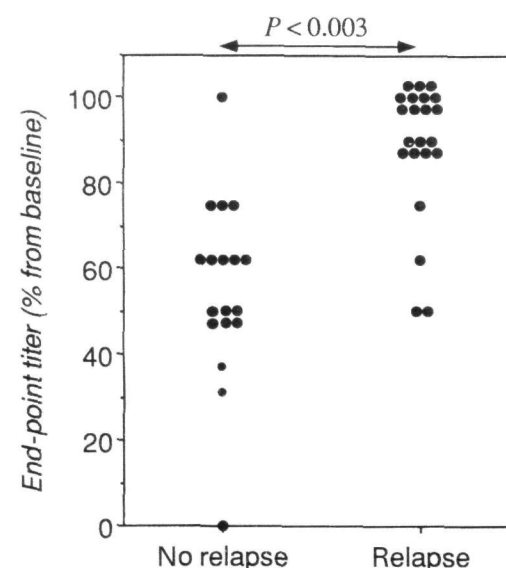


Fig. 3. Evolution of skin test end-point titer measured before and at end of immunotherapy depending on relapse symptoms ($P < 0.003$, Mann-Whitney U test).

Patients receiving a short course of SIT tend to relapse mainly in the first months, while the others show a constant tendency which is more evident after 36 months. A longer period of observation may eliminate any difference between the two groups.

Age may be a confounding factor since patients exposed to long-term allergen exposure are likely to have more pronounced inflammation and airways remodeling (13). The results of the present study only partly confirm this hypothesis because there was a nonsignificant increase in efficacy duration in younger patients. However, these results are not altogether surprising because all patients had improved by the end of SIT and FEV₁ was within normal values, suggesting that, at least in these patients, inflammation and remodeling were not too prominent. Therefore, this study does not contradict previous results from our group (14).

The variation in skin test end-point titers was found to be predictive of the duration of efficacy. This result is of interest since previous studies found clinical efficacy of SIT with grass pollen to be associated with a decrease in the end-point skin test (10, 15). However, in a study involving Der p allergy, no correlation was observed between the end-point titer and the efficacy of SIT (16), probably because inflammation of the airways and non-specific bronchial hyperreactivity are confounding factors in house-dust-mite asthma. However, it seems probable that reduction in the reactivity of patients at the end of SIT to the allergen against which they have been treated is correlated with the outcome after SIT has been stopped.

The levels of total IgE and specific IgE were not significantly different in patients who relapsed and those who did not. This result agrees with another study showing that specific IgE and IgG are not predictors of the duration of efficacy of SIT (5).

In conclusion, the duration of efficacy of SIT with Der p after its cessation can be increased by a longer period of SIT. Two factors appear to be predictive of the efficacy of treatment: diminution of end-point skin test titration at the cessation of therapy and age of the patient at the start of SIT.

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