

Short communication

A prospective safety-monitoring study of immunotherapy in mite-allergy patients with mass-units-standardized extract

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To determine the tolerance of an allergen extract standardized in mass units, we closely monitored the side-effects, during the buildup phase of immunotherapy treatment, in 88 patients with well-documented respiratory allergy to house-dust mite (*Dermatophagoides pteronyssinus*). Thirty-four patients (38.6%) suffered from moderate perennial rhinitis, and 54 had mild to moderate bronchial asthma (61.4%). For the desensitizing treatment, we used a depot extract adsorbed in aluminum hydroxide of *D. pteronyssinus* (Pangramin® Depot UM), biologically standardized and having the major allergens Der p 1 and Der p 2 quantified in micrograms. A total of 1244 doses were administered. All patients except one (98.9%) reached the expected maximum dose of 4 µg Der p 1. Only five patients suffered mild adverse reactions (5.7%). All adverse reactions except one appeared to be related to the vial of maximum concentration: vial III (4 µg Der p 1). Considering the number of patients who had adverse reactions and the frequency of adverse reactions per dose, we found no significant differences between rhinitis and asthma sufferers. We think that immunotherapy in doses of 4 µg Der p 1 and 2 µg Der p 2 is well tolerated and should not be avoided in mildly to moderately asthmatic patients when treating house-dust mite allergy.

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Since its introduction by Noon in 1911 (1), immunotherapy (IT) has been frequently used as an etiologic treatment of respiratory allergic patients. Nevertheless, the use of this therapeutic method to treat asthmatic patients has been questioned by the Committee on Safety of Medicines in the UK (2). It is believed that its adverse effects may outweigh any therapeutic benefits obtained.

Many well-designed studies, using high-quality allergen extracts and following accepted methodology, have shown the efficacy of this treatment (3). However, IT is not free of risk. Adverse reactions occasionally occur, and these are more frequent during the initial phase of treatment than the maintenance period. They are also more frequent in asthmatic patients than in patients with upper respiratory tract disorders (3, 4).

The efficacy of desensitizing treatment as well as the rate of adverse reactions arising from IT are dose related; a higher dose leads to greater efficacy but also to a higher rate of adverse reactions (3, 5). A few years ago, it was considered advisable to reach the maximum tolerated dose by each patient, thereby forcing virtually every patient to present at least one adverse reaction. Nowadays, it is believed to be preferable to reduce the patient's risk while aiming at an optimal dose; i.e., that which produces clinical improvement in most patients while incurring a low rate of adverse effects (3).

The objective for the next few years should be to have high-quality extracts available (11), preferably with the main allergens quantified in mass units, and to establish optimal doses of IT for each clinical case.

In our study, we have closely monitored the appearance of adverse reactions during the buildup phase of IT when biologically standardized extracts were used. The patients studied had clinical sensitivity to house-dust mite, and major allergens were quantified in mass units. The doses chosen were those with clinical effectiveness on asthmatic patients (5, 6).

Material and methods

Patients

We studied 88 patients with well-documented respiratory allergy to house-dust mite (*Dermatophagoides pteronyssinus*). Fifty-seven patients (64.8%) presented sensitivity to other allergens. Their mean age was 22.9 ± 13 years, and there were 45 women and 43 men.

Thirty-four patients (38.6%) suffered from moderate perennial rhinitis, and 54 had bronchial asthma (61.4%). Of these, 23 presented mild asthma (all presented moderate associated rhinitis) and the rest moderate asthma. Asthma severity was measured according to the NIH Asthma International Consensus classification (7). The mean duration of their illness was 7.0 ± 6.2 years. All patients had *D. pteronyssinus*-positive skin prick test (mean largest diameter of 7.9 ± 3.1 mm) and high specific IgE levels (51.4 ± 45 KU/l, Pharmacia CAP System).

They received appropriate symptomatic medical treatment. This treatment was continued during the entire period of IT in order to keep patients asymptomatic. Antihistamines and topical budesonide were administered in cases of nasal symptoms, β_2 -agonists in mild asthma cases when necessary, and daily inhaled budesonide, together with β_2 -agonists on demand when the diagnosis was moderate bronchial asthma.

Immunotherapy

The criteria for prescribing and administering specific IT followed the recommendations of the IT subcommittee of the European Academy of Allergology and Clinical Immunology (EAACI) (3).

For the desensitizing treatment, we used *D. pteronyssinus* Pangramin® Depot UM (Alergia e Inmunología Abelló, SA), an aluminum hydroxide-adsorbed extract, biologically standardized with the major allergens Der p 1 and Der p 2 quantified in micrograms (8, 9).

We followed a treatment schedule consisting of weekly injections up to a total of 14, as recommended by the manufacturers, with an additional dose of 1 ml to reach the maximum dose of 10 BU,

equivalent to 4 µg of Der p 1 and 2 µg of Der p 2 (Table 1).

The mean theoretic accumulated dose at the end of the buildup phase was 13.06 µg of Der p 1 and 6.53 µg of Der p 2.

Safety monitoring

Treatment was always administered in the IT unit of the hospital, by the same experienced and specially trained nurse, under the direct supervision of an allergologist. Patients remained in the unit for 30 min after administration of the treatment, as required by Spanish law (10). Each event was carefully registered.

Only immediate (equal to or larger than 5 cm diameter during the 30-min wait) or delayed (equal to or larger than 8 cm in diameter after the 30-min wait) local reactions were considered. Systemic reactions were graded according to EAACI guidelines (3).

Statistical analysis

Statistical analysis was done with the SIGMA-PLUS statistical package from Horus Hardware (Madrid, Spain). Group comparisons were performed with Fisher's exact test.

Results

A total of 1244 doses were administered. Only five patients suffered adverse reactions (5.7%) (Table 2). All adverse reactions, except one, appeared when the maximal dose vial was administered: vial III (4 µg Der p 1).

All patients except one (98.9%) reached the maximum expected dose of 4 µg Der p 1. The exception was a woman diagnosed with moderate bronchial asthma, who presented bronchospasm after administration of 0.4 µg Der p 1, and was thus maintained on 0.32 µg Der p 1.

No significant immediate local reaction (≥ 5 cm) was reported. Four out of five patients who presented adverse reactions (one rhinitic and three asthmatic patients) suffered delayed local reactions (≥ 8 cm). This accounted for 4.5% of patients under IT, and for 0.32% of the total number of doses administered.

Table 1. Immunotherapy schedule

Vial (Der p 1)	Doses (ml)					
I (0.04 µg/ml)	0.1	0.2	0.4	0.8		
II (0.4 µg/ml)	0.1	0.2	0.4	0.8		
III (4 µg/ml)	0.1	0.2	0.4	0.6	0.8	1

Table 2. Frequency of appearance of adverse reaction according to diagnosis

	Rhinitis	Asthma	P ^a
Systemic reaction			
Per patient	0/34 (0%)	1/54 (1.85%)	1.00
Per dose	0/478 (0%)	3/766 (0.39%)	0.29
Local reaction			
Per patient	1/34 (2.9%)	3/54 (5.55%)	1.00
Per dose	1/478 (0.21%)	3/766 (0.39%)	1.00

^a Fisher's exact test (two-tailed).

No anaphylactic shocks or systemic delayed reactions were reported. Only one patient experienced three systemic grade 2 reactions, consisting of mild intensity bronchospasms, which disappeared with β -mimetic inhalers. These reactions occurred with 0.4 μ g of Der p 1 after an attempt to increase the dose above 0.32 μ g Der p 1. The latter was subsequently defined as the maximum tolerated dose for this patient.

There were no statistical differences in local and systemic reactions between rhinitic and asthmatic patients, taking into account both the number of patients and the number of doses administered in each group (Table 2).

Discussion

In this prospective study of IT, we found good tolerance of IT, using biologically standardized extracts, with 4 μ g Der p 1 and 2 μ g Der p 2, in patients with respiratory allergy to house-dust mites. Most (98.9%) reached the maximum dose of 4 μ g Der p 1 with an expected rate of adverse reactions. We must note that house-dust mite allergen levels in this region of Spain are very high. This is due to the high atmospheric humidity, and for much of the year humidity levels are favorable to the growth of these arachnids.

All adverse reactions were mild. We registered no anaphylactic shocks. Most patients who experienced adverse reactions presented delayed local reactions, with one exception. We did not find significant differences in the rate of systemic reactions or in the number of doses which produced such adverse reactions between rhinitic and asthmatic patients. This is probably explained by the small number of patients included in the study but also by the mild to moderate severity of the asthmatic patients studied.

All patients were stabilized before starting IT and followed personalized preventive treatment, including antihistamines in the case of nasal symptoms, according to the severity of their clinical

profile in order to maintain their asymptomatic state. We believe that this fact contributed to the good tolerance of the treatment.

Several studies have attempted to estimate IT tolerance in clinical practice with commercial extracts (4–6, 11–15). Tolerance varied depending on the extract used, treatment protocol followed, patient environment, and the method of monitoring adverse reactions.

Tabar et al. (4) carried out a prospective safety study of this same extract in 419 patients (9482 doses, of which 5120 were with *D. pteronyssinus*), always administered in the IT unit. In this study, 0.37% of doses resulted in systemic reactions, which corresponded to 4.8% of the patients. Systemic reactions were reported in 0.54% of mite extract injections. Such reactions were also more frequent in the buildup phase, when using the highest concentration vial, and in asthmatic patients.

Olaguibel et al. (6), carried out a maximum tolerance research study on asthmatic, mite-sensitized patients, using the same extract that we used, but introducing an additional higher concentration vial. They attempted to reach a maximum dose of 16 μ g of Der p 1, achieving a maximum tolerated dose of 3.2 μ g of Der p 1, which was reached by more than 90% of these patients. The study concludes that the optimal *D. pteronyssinus* IT dose for asthmatics appears to be between 0.8 and 3.2 μ g Der p 1. We found higher tolerance levels, since 98.15% of our asthmatic patients tolerated 4 μ g Der p 1 without adverse reactions.

Most of the studies cited before tabulated the tolerance during the initial and maintenance phases of the treatment. The adverse reactions rate that we obtained was equal to, or lower than, those of these studies. However, it must be noted that we considered the tolerance only during the buildup phase of treatment; therefore, the rate of adverse reactions was higher than when both phases – initial and maintenance – are tabulated (3, 4).

In conclusion, IT in doses of 4 μ g Der p 1 and 2 μ g Der p 2 is well tolerated and should not be avoided in mildly to moderately asthmatic patients when treating house-dust mite allergy.

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