

A prospective safety-monitoring study of immunotherapy with biologically standardized extracts

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We evaluated the safety of immunotherapy in 419 patients who attended our allergy department for treatment. They were suffering from rhinitis and asthma caused by sensitization to grass pollen or *Dermatophagoides pteronyssinus*. Immunotherapy was given by biologically standardized aluminum hydroxide adsorbed extracts according to a conventional schedule. Local reactions were recorded in 10.5% of the patients and systemic reactions in 4.8%. Only 0.37% of the doses administered were associated with systemic side-effects. We found that 84% of the patients who showed systemic reactions were asthmatic subjects ($P < 0.01$), and most of them were sensitized to *D. pteronyssinus* (71%). Side-effects occurred more frequently during the dose-increase period ($P < 0.05$). After 9482 doses had been administered, no anaphylactic shock or life-threatening reactions were registered. We believe the risk associated with immunotherapy to be drastically reduced when treatment is carefully monitored by skilled personnel. In such conditions, as shown by our study, immunotherapy is safe.

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It is well known that specific immunotherapy for allergic diseases is not without risk (4, 8, 10). However, there are few prospective studies that assess this risk when immunotherapy is given to allergic patients who are controlled in a hospital immunotherapy unit. Usually, the analyses reported are retrospective, generally trying to detect serious side-effects, including fatal reactions (7, 12, 19), and using nonstandardized extracts or experimental schedules that are very different from those applied in daily practice (4, 6). It is also common for the side-effects considered, as well as the method used to record them, to show important differences according to each clinical protocol (10, 16). Sometimes these studies are performed in collaboration with general practitioners who, if they have not participated in a special education program, are not familiar with this type of treatment (11, 17).

As all our patients were receiving immunotherapy in a hospital and in accordance with the guidelines published by the Immunotherapy Subcommittee of the European Academy of Allergology and Clinical Immunology (EAACI) (8), we decided to undertake a prospective study of the safety of immunotherapy.

Our data relate to the administration of biologically standardized aluminum hydroxide adsorbed extracts according to a conventional schedule. Approximately 10 000 doses were administered from 1989 to 1990.

Material and methods

Patients

A total of 419 consecutive patients who had been diagnosed in our department as having rhinitis or asthma caused by *Dermatophagoides pteronyssinus* or grass pollen (*Dactylis glomerata*, *Festuca pratensis*, *Lolium perenne*, *Phleum pratense*, and *Poa pratense*), and who were receiving immunotherapy took part in our study.

The mean age of the patients was 19.5 ± 11 years. Asthma was diagnosed in 57.3% (240 patients), 70.4% of them (169 patients) because of sensitization to *D. pteronyssinus*. Patients suffering from rhinitis (179) were sensitized to grass pollen in 68.1% of the cases (122 patients). The clinical severity of asthmatic patients was graduated according to the method of Aas (1).

None of the patients presented any condition or

situation that contraindicated immunotherapy (2, 8, 9). All patients were told about the details of the treatment and gave their informed written consent before the study started.

Immunotherapy

Both *D. pteronyssinus* and grass pollen extracts were biologically standardized and adsorbed in aluminum hydroxide (Pangramin Depot, Alergia e Inmunología Abelló, SA, Madrid, Spain). Biologic standardization was performed according to the method of Brighton (5, 13). The measurement of the biologic activity comprised two steps: 1) preparation of a reference extract and determination of *in vivo* activity by a quantitative skin prick test in a sample of at least 30 allergic patients, and 2) evaluation of the total allergenic activity of extracts for clinical use by RAST inhibition, as compared with the corresponding reference extract. The allergenic analysis of the extract comprised the separation of the components by isoelectric focusing (IEF) and electrophoresis (SDS-PAGE) and the identification by immunoblotting of the components that bind specific human IgE.

A conventional and perennial schedule was used, and doses were increased weekly to reach the manufacturer's recommended maintenance dose. The planned maintenance dose, based on previous data (3) was the 0.8-ml vial III (1000 STU/ml), which corresponded to 20 BU for grass pollen and 8 BU for *D. pteronyssinus*. This dose was given monthly (Table 1).

The first dose with a new treatment set was half of the corresponding dose to be administered. Immunotherapy with grass pollen was not interrupted during the pollen season; nevertheless, during this period, the dose administered was halved.

Safety monitoring

The administration of treatment was performed by four specially trained nurses of our allergy department with extensive experience in this field. A physician supervised the administration, determined whether the immunotherapy protocol had to be modified because of special conditions (respiratory infection, exacerbations of rhinitis and asthma in the last 3 days, a 20% decrease in PEF in asthmatic

patients, etc.), evaluated possible reactions produced by the last dose, treated any side-effects, and ensured that each patient remained under observation for at least 30 min after each allergen injection. All data were carefully recorded on registration forms.

We defined an immediate large local reaction as one greater than 5 cm in adults and greater than 3 cm in children under 12 years; a delayed large local reaction was defined as either one greater than 8 cm or one smaller if it was inconvenient to the patient.

Modifications of treatment schedule, grading of systemic reactions within 30 min, and determination of types of systemic reactions after from 30 min to 48 h of any treatment followed the EAACI's recommendations (8). We never recommended premedication with antihistamines before administering treatment.

Statistical analysis

The data were analyzed by a Compaq Deskpro 386 personal computer, with the Statgraphics 4.0 statistical package. The following descriptive parameters were determined: mean, standard deviation, and range for the quantitative variables, and absolute frequency, together with the corresponding percentage, for the qualitative variables. The relation between two variables was determined by the z test to compare two proportions; the chi-square test; and, if there were few cases, Fisher's exact test. The level of probability accepted was $P < 0.05$.

Results

The total number of allergen doses given was 9482, 60.5% of them corresponding to the dose-increase period. With regard to the allergen extract, we administered 4362 doses with grass pollen and 5120 with *D. pteronyssinus*. Asthmatic patients received 5501 doses (58.1%); patients with rhinitis, 3981 (Table 2).

The maintenance dose was reached in 13 ± 2.74 weeks. In 13 of the 419 patients studied (3.1%), the recommended top dose (the 0.8-ml vial III: 1000 STU/ml) could not be administered, and a lower maintenance dose was established. Large local

Table 1. Treatment schedule

Vial	Doses (ml)				
I (10 STU/ml)	0.1	0.2	0.4	0.8	
II (100 STU/ml)	0.1	0.2	0.4	0.8	
III (1000 STU/ml)	0.1	0.2	0.4	0.6	0.8

Table 2. Number of doses administered in relation to allergen extract, treatment steps, and diagnosis

	Pollen		<i>D. pteronyssinus</i>		Total
	Rhinitis	Asthma	Rhinitis	Asthma	
Increase	1658	986	763	2332	5739
Maintenance	1086	632	474	1551	3743
Total	2744	1618	1237	3883	9482

reactions were recorded in 10.5% of patients and systemic reactions in 4.8%. Of the total number of doses administered, 35 (0.37%) were associated with systemic side-effects, 83% of which appeared after administration of a dose corresponding to vial III (Fig. 1). The number of systemic reactions was significantly greater on the dose-increase phase (67%) than during administration of the maintenance dose ($P < 0.05$). On 12 occasions, this was the first dose administered with a new treatment set.

With respect to the type of pathology, we found that 84% (21/25) of the patients that presented systemic reactions were asthmatic ($P < 0.01$). However, the rate of local reactions was very similar in asthmatic and rhinitic sufferers, and there were no significant differences.

Of the 69 patients who exhibited adverse reactions, 44 were sensitized to *D. pteronyssinus*, and 25 to grass pollen. Systemic reactions were significantly more frequent (80%) in the group of patients on immunotherapy with *D. pteronyssinus* ($P < 0.05$). There were no differences with respect to local reactions.

During the pollen season no side-effects were recorded in grass-pollen-allergic patients.

No patient suffered from anaphylactic shock. The severity of systemic reactions recorded in the 25 patients affected is shown in Table 3 according to type of pathology, allergen administered, and time of onset (latency). Late reactions represented 82.8% of the total systemic reactions, although these were mild. On five occasions, it was necessary to treat systemic reactions with epinephrine, while on 18 occasions they were treated exclusively with β_2 agonists. Eighty-six percent of the patients with systemic reactions had a slight to moderate graduation of asthma and normal respiratory function in basal conditions. We randomly chose a group of 30 pa-

Table 3. Grading of systemic reactions according to the EAACI Immunotherapy Subcommittee

	Pollen		<i>D. pteronyssinus</i>	
	Rhinitis	Asthma	Rhinitis	Asthma
Systemic reactions within 30 min				
1 (Slight feeling of illness, headache, arthralgia, etc.)	0	0	0	0
2 (Mild rhinitis or asthma)	0	0	0	2
3 (Urticaria, angioedema, or severe asthma)	0	1	1	2
4 (Anaphylactic shock)	0	0	0	0
Systemic reactions after 30 min–48 h				
Unspecific symptoms	0	0	0	0
Urticaria	0	0	0	1
Eczema	0	0	0	0
Rhinoconjunctivitis	1	0	2	1
Angioedema	0	0	0	0
Asthma	0	5	0	19

tients with bronchial asthma caused by mites and with complete tolerance of *D. pteronyssinus* extract and compared them with the patients who had bronchial asthma caused by mites and systemic reactions in the course of immunotherapy. No differences were found in any of the indicators evaluated: age, sex, score of medication and symptoms, respiratory function, and total and specific IgE.

Discussion

In the reported prospective studies on the safety of immunotherapy by aqueous extracts, the proportion of patients showing systemic reactions is greater than in our study (10, 15, 18). Administering the same type of extract as ours, Horak (11) found only 1.2% of patients with systemic reactions, even though in some cases doses greater than those recommended by the manufacturer were administered.

The fact that 4.8% of our patients showed a systemic reaction that responded rapidly and fully to treatment led us to consider the overall tolerance to be very good. Surely, the fact that patients under treatment with mold extracts were not included in this study may have influenced the result, because the percentage of adverse reactions with these allergens seems to be greater (14, 17).

In correspondence with the prevalence of allergic diseases in our region, most of our patients were asthmatic as a result of sensitization to *D. pteronyssinus*. Unfortunately, as our study shows, this was the group with the higher risk of systemic reactions during immunotherapy ($P < 0.01$). Most of the systemic reactions in this group were late and consisted of mild asthma attacks which occurred 4–8 h after the allergen injection was given; such attacks rapidly remitted with inhaled beta-mimetics. This led us to

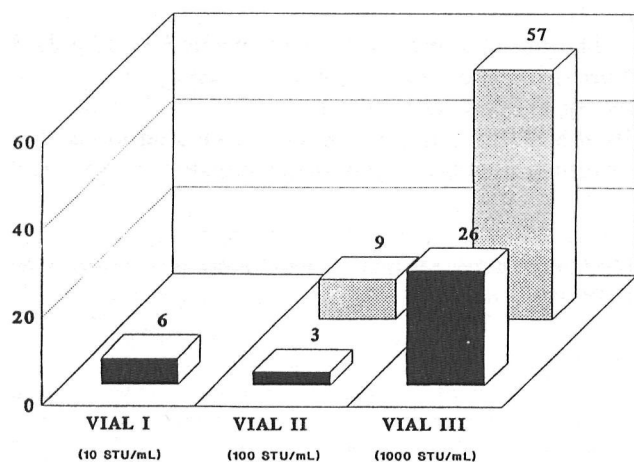


Fig. 1. Number and type of side-effects according to vial administered. Local reactions (light gray). Systemic reactions (dark gray).

take special care with these patients during treatment and made us consider the possible influence of the levels of allergen exposure at home and the value that allergen-avoidance measures could have on the development of these late systemic reactions during immunotherapy. Current studies are being performed in our department to determine the possible influence of these factors on the safety of immunotherapy.

One of the most frequent causes of adverse reactions, incorrect administration (12, 19, 21), did not play any part in our study.

The use of a perennial schedule with grass pollen extracts was well tolerated in our patients, as shown by the absence of side-effects associated with administration during the pollen season. Possibly, the characteristics of pollination in our region greatly influenced this result; thus, our results should not be extrapolated to different environmental conditions.

This is the first prospective study to follow the EAACI's recommendations dealing with safety monitoring in immunotherapy. In our opinion, this type of information should constitute one of the first objectives in every allergy department. Thus, not only would we understand the exact risk of immunotherapy as used in our population (and therefore the safest way to use it), but we could also inform our patients of its possible risk in realistic terms.

We consider that the alarm caused in the UK by the publication of the Committee on Safety of Medicines (CSM) report (7) is unwarranted when we look at immunotherapy administered by trained personnel under the supervision of specialists.

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