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Original

Safety of grass immunotherapy administered in a specialized unit: study of risk factors

Background: Administration of immunotherapy is not devoid of adverse events. *Aims:* To study the incidence of adverse reactions and the risk factors associated to grass immunotherapy in a specialized unit. *Methods:* 132 patients diagnosed of rhinitis and/or asthma by grass hypersensitivity and receiving perennial grass immunotherapy in our unit were prospectively followed. At the end of the study, we researched the factors associated with systemic reactions. *Results:* Out of 3964 doses administered, only 24 produced systemic reactions (18.2% of patients treated and 0.6% of doses administered). They were all mild except a late anaphylactic reaction related with a warm bath which reverted spontaneously. Only three factors were significantly associated with systemic reactions to grass immunotherapy: hypersensitivity to cat dander (RR = 1.9), immunotherapy administration in the last 30 minutes of visit (RR = 2.1) and treatment with *Phleum* extracts (RR = 0.5). *Conclusions:* The incidence of systemic reactions to grass immunotherapy administered under controlled conditions is low. The use of *Phleum* extracts is associated with a lower incidence of systemic reactions. Cat dander hypersensitivy and immunotherapy injections in the last minutes of visit are associated with a higher incidence of systemic reactions.

Key words: Grass pollen. Immunotherapy. *Phleum*. Safety. Systemic reaction.

Seguridad de la inmunoterapia con gramíneas administrada en una unidad especializada: estudio de los factores de riesgo

Antecedentes: La administración de inmunoterapia produce efectos adversos. *Objetivos:* Estudiar la incidencia de reacciones adversas a la inmunoterapia con extractos de polen de gramíneas en una unidad especializada y los factores de riesgo asociados. *Métodos:* Estudiamos de forma prospectiva a 132 pacientes diagnosticados de rinitis, asma o ambas por hipersensibilidad al polen de gramíneas que recibían inmunoterapia perenne con extractos de gramíneas en nuestra unidad. Al final del estudio, investigamos los factores asociados con las reacciones sistémicas. *Resultados:* De 3.964 dosis administradas, sólo 24 produjeron reacciones sistémicas (18,2% de los pacientes tratados y 0,6% de las dosis administradas). Todas fueron leves excepto una reacción anafiláctica tardía relacionada con un baño caliente que revirtió espontáneamente. Sólo tres factores se asociaron de forma significativa con las reacciones sistémicas a la inmunoterapia con gramíneas: la hipersensibilidad al epitelio de gato (RR = 1,9), la administración de la inmunoterapia en los últimos 30 minutos del ho-

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rario de consulta (RR = 2,1) y el tratamiento con extractos de *Phleum* (RR = 0,5). *Conclusiones:* La incidencia de reacciones sistémicas a la inmunoterapia con gramíneas administrada en condiciones controladas es baja. El uso de extractos de *Phleum* se asocia con una menor incidencia de reacciones sistémicas. La hipersensibilidad al epitelio de gato y la administración de las inyecciones de inmunoterapia en los últimos minutos del horario de consulta se asocian con una mayor incidencia de reacciones sistémicas.

Palabras clave: Inmunoterapia. *Phleum*. Polen de gramíneas. Seguridad. Reacción sistémica.

Specific immunotherapy is the only means of modifying the natural course of allergic diseases, but it carries a risk of inducing systemic side effects. These reactions have mainly been related with dosage errors, symptomatic asthma and exacerbation of allergic disease[1,2]. In order to minimize these events, the EAACI and the AAAAI have published guidelines on how to properly administer immunotherapy and have recommended doing it in units with trained persornel in management of systemic reactions[3,4]. But even when these safety measures are implemented, some patients undergo systemic reactions, in the majority of cases, for unknown reasons.

Our group administers immunotherapy in a controlled unit following the above mentioned published recommended safety measures. We have carried out a prospective study to research the incidence of adverse reactions to grass immunotherapy in these conditions and the possible risk factors associated with them. The results of this study could be of use to modify the administration of immunotherapy in order to reduce systemic reactions.

MATERIAL AND METHODS

Patients

The patients included 132 consecutive subjects [median age 21 (15.29) years, 46.2% females] with rhinoconjunctivitis and/or asthma due to grass hypersensitivity who received grass immunotherapy for a minimum of 2 years in the period 1995-2000. Asthma was diagnosed in 58.3% of them. All the doses were administered in our immunotherapy unit. The diagnosis of grass allergy was made by means of a compatible history and physical examination and a positive skin prick test. In no patients had satisfactory relief been obtained using antiallergic drugs. None suffered from any condition that contraindicated immunotherapy[3]. Patients were informed of the characteristics of the treatment and gave their informed written consent.

Immunotherapy administration

The immunotherapy extracts were commercially available biologically standardized immunotherapy extracts from six differents laboratories (see Table III). Three types of compositions were used: a grass mix extract, a *Phleum* extract and a *Lolium* extract.

All the extracts used were depot. The administration schedule was a conventional, perennial one with weekly doses administered until manufacturer's recommended maintenance dose was reached and then repeated monthly. During the spring, the dose was reduced by half and, afterwards, increased monthly to reach the previous maintenance level again.

During immunotherapy administration, all the EAACI recommendations were followed[3]. Only two allergologists (the authors of the work) prescribed the treatments and only two trained nurses administered all the doses in order to mimimize administration errors. Possible changes in immunotherapy administration due to intercurrent diseases or previous adverse effects were always supervised by one of the allergologists.

Safety assessment

All patients remained under medical supervision 30 minutes after each injection. Then, all systemic and local reactions (immediate or delayed reactions larger than 10 mm diametre) were recorded. Afterwards, the patients were instructed to return to the clinic immediately if a systemic reaction occurred. Before each injection, the patients were asked about adverse local or systemic events occurred in the previous one. The systemic reactions were graded according EAACI guidelines[3].

In the case of an adverse reaction occurrence, the type of reaction, symptomatology, latency period, date and hour of administration and nurse who administered the dose causing the reaction were all recorded. In all cases of systemic adverse reactions, after an initial reduction of the immunotherapy dose, we tried to return to the dose which had caused the reaction and to achieve the normal maintenance dose level. The systemic reactions occured during these second trials of dose build-up were not considered in estimation of incidence of systemic reactions, because they were part of an intent of investigating if the

doses causing them were really the highest doses tolerated by patients.

Analysis of systemic adverse reactions

At the end of the study, we divided the patients into two groups: those who suffered from systemic reactions and those who did not. We first looked for factors which could have caused the systemic reactions in the first group (exercise, warm baths, uncontrolled asthma, infections, etc). Secondly, we looked into the differences found between the two groups of patients at the moment of the initial diagnosis with respect to age, sex, age at the onset of pollinosis, evolution time of pollinosis, type of respiratory disease (rhinitis or asthma), wheal diametre obtained in grass prick test, presence of other inhalant allergies, smoking, sinusitis and oral allergy syndrome with fruits. Also were evaluated differences respect to allergologist prescriptor of the extracts, composition of the extracts and laboratory which manufactured them.

As well as the patients, we also considered all the doses administered at the end of the study and, again, we distinguished doses which produced systemic reactions from those which not. Then, we looked for differences between them with respect to the moment of injection and the nurse who administered them.

Statistical analysis

For comparison of categorical data chi-square or Fisher´s exact test were used. In the case of significant differences, the relative risk for that factor and the 95% confidence interval (CI) were calculated. The distribution of a great deal of continuous data was skewed, so we used non-parametric tests for their comparisons. Results are expressed as median (25th percentile, 75th percentile). Differences were considered significant at the $P < 0.05$ level.

Statistical analysis was performed with a software package (SPSS, v. 5.1, USA).

RESULTS

Incidence and types of adverse reactions from grass immunotherapy

Out of 132 patients, only 24 (18.2%) developed systemic reactions and 46 (34.8%) local ones. The total number of administered doses were 3964; only 24 (0.6%) produced a systemic reaction and 103 (2.6%) a local reaction.

The characteristics of the 24 systemic reactions, grading according with EAACI guideliness, are shown in Table I. The median latency of systemic reactions was 60 (30,60) minutes; 17 systemic reactions (70.8%) developed after more than 30 minutes. Eighty-three point three % of systemic reactions occurred in the dose-increasing phase. Only 3 (12.5%) reactions developed during pollen season. The composition of the extracts responsible for theses systemic reactions were grass mix in 62.5% of cases, *Lolium* in 29.2% and *Phleum* in 8.3%.

Table I. Grading of observed systemic reactions according with EAACI guidelines

Grade*	Number (N)	Percent (%)
Systemic reactions within 30 minutes		
1	0	0
2	2	8,3
3	5	20,8
4	0	0
Systemic reactions after 30 minutes		
1	0	0
2	3	12,5
3	13	54,2
4	1	4,2

*1, unspecific symptoms; 2, mild systemic reactions; 3, non-life-threatening systemic reactions; 4, anaphylactic shock.

In four patients (16.7%), the systemic reactions occurred at the beginning of the summer, after a 50% reduction in the dose administered at the spring, when a build-up was attempted.

All the systemic reactions, except one, were mild and all responded immediately to antihistamines, steroids and/or epinephrine or disappeared spontaneously. The single anaphylactic reaction (grade 4) occurred in a 11-year-old girl two hours after the injection while the patient was having a warm bath and was resolved without treatment.

Continuation of grass immunotherapy

Only two patients (8.4%) decided to stop immunotherapy after the systemic reaction. In 21 patients, after an initial dose reduction, we tried to increase the dose again slowly, but this could not be achieved without a similar systemic reaction to the previous one. So we continued the immunotherapy with a maintenance dose below the one which caused the adverse reaction. In the patient who suffered the anaphylactic reaction, we chose to continue a lower maintenance dose without trying to increase it.

Table II. Characteristics of patients before starting grass immunotherapy, distinguishing between those who suffered systemic reactions and those who not

Initial characteristics of patients	Patients with systemic reactions (n = 24)	Patients without systemic reactions (n = 108)	*p*
Sex	M 41.7% / F 58.3%	M 56.5% / F 43.5%	n s
Age	20 (10, 23.8) years	22 (10,30.8) years	n s
Adults/children	70.8%/29.2%	80.6%/19.4%	n s
Evolution time of pollinosis	4.5 (3,10) years	6 (2,10) years	n s
Age at the onset of pollinosis	12.5 (8,17) years	14 (7.5,20) years	n s
Asthma diagnosis	50%	60,2 %	n s
Smoking	16.7%	11%	n s
Sinusitis	12.5%	19.4%	n s
Oral allergy syndrome to fruits	8.3%	13.0%	n s
Patients monosensibilized to grass pollen	16.7%	18.5%	n s
Wheal diametre in prick test with grass pollen	8 (6.3,11) mm	6 (4,10) mm	n s
Wheal diametre in prick test with grass pollen >10 mm	33.3%	25%	n s
Wheal diametre in prick test with grass pollen ≤ 4 mm	16.6%	31.5%	n s
Hypersensitivity against cat dander (*)	41.6%	22.2%	0.048

*There were not statistically significant differences between the two groups of patients with respect to hypersensitivty to mites, moulds, dog dander, olive, plantain, lamb´s quarter, yellow dock, sycamore and hazelnut (not shown).

Factors associated with immunotherapy systemic reactions

Apparently, there were no identified causal factors related with systemic reactions except the above-mentioned anaphylactic reaction associated with a warm bath. Apart from this, 4 patients (16.8% of those who suffered from systemic reactions) showed local reactions in the doses given before the one which produced the systemic one. But 30% of patients who tolerated grass immunotherapy perfectly also developed local reactions at some point during treatment.

Table II shows all the factors initially identified in patients, prior to immunotherapy, whose association with systemic reactions were analyzed. Only cat dander hypersensitivity was statistically associated with them. Nobody who developed systemic reactions and was allergic to cat dander had cats at home.

The characteristics of immunotherapy extracts and the way they were administered were studied. Compositions of immunotherapy extracts were statistically different in patients who suffered from systemic reactions (62.5% grass mix, 29.2% *Lolium* and 8.3% *Phleum*) and those who did not (45.4% grass mix, 4.8% *Lolium* and 39.8% *Phleum*) ($p = 0.0099$). We further analyzed which one was related with a higher o lowew rate of reactions. As is shown in figure 1, the use of *Phleum* extracts was statistically associated with a fewer number of systemic reactions ($p = 0.032$): only 2 out of 45 patients who received this type of extract suffered from systemic reactions.

There were no significant differences with respect to the manufacturer of the extracts and allergologist who prescribed the immunotherapy (Table III). The nurse who administered the injections did not influence the appearan-

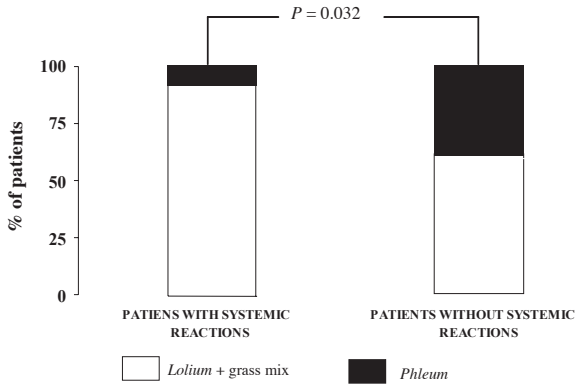

Fig. 1. Composition of grass immunotherapy extracts in patients who suffered from systemic reactions (left) and patients who did not (right). Patients who did not develop systemic reactions received more *Phleum* extracts, and the difference was statistically significant.

Table III. Prescriptor allergologist and manufacturer of the extract in the patients, distinguishing between those who suffered systemic reactions to immunotherapy and those who not

Characteristics of immunotherapy	Patients with systemic reactions (n = 24)	Patients without systemic reactions (n = 108)	*p*
Allergologist prescribing the immunotherapy	Dr. X 41.7% / Dr. Y 58.3%	Dr. X 62% / Dr. Y 38%	n s
Manufacturer of the extract (*)	A 8.3% / B 20.8% / C 4.2% D 4.2% / E 58.3% / F 0%	A 19.4% / B 29.6% / C 1.9% D 5.6% / E 35.2% / F 8.3%	n s

(*) A, ALK-Abelló; B, Bial-Arístegui;C, Bayer ;D, Ipi ;E, Leti ;F, UCB-Stallergenes.

ce of adverse reactions: 0.54% and 0.66% of doses administered by nurses A and B induced systemic reactions, respectively ($p = 0.61$). Neither administering the injections in the morning nor in the afternoon was associated with systemic reactions to immunotherapy (62.5% of injections which induced systemic reactions and 63.9% of injections which did not induce them were administered in the afternoon, $p = 0.89$). By contrast, administering the injections in the last 30 minutes of visit (both in the morning and the afternoon) was significantly associated with systemic reactions (figure 2). We studied this last factor after observing a higher rate of adverse events in the last few minutes of the day, when patients frequently come to the clinic in a hurry.

Finally, we calculated the relative risks of suffering from systemic reactions to grass immunotherapy associated with the previous risk factors found (Table IV).

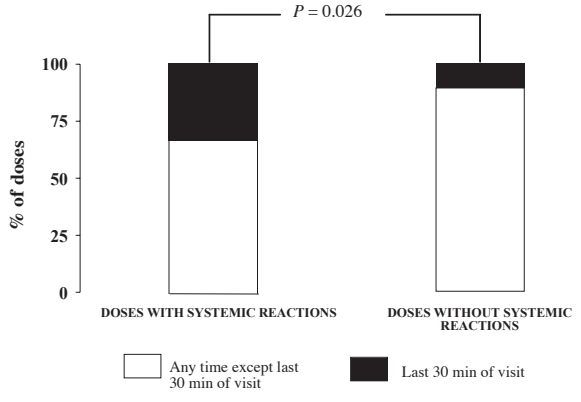

Fig. 2. Moment of administration of the doses of immunotherapy which produced systemic reactions (left) and those which not (right). Twenty-nine % of doses which produced systemic reactions were administered in last 30 minutes of visit vs. only 13.5% of doses which did not cause adverse reactions.

Tabla IV. Risk factors associated with systemic reactions to grass immunotherapy, relative risks an 95 % confidence intervals

Factors associated with systemic reactions	Relative risk	95 % confidence interval
Hypersensitivity to cat dander	1.9	1.03 - 3.4
Phleum immunotherapy extracts	0.5	0.2 - 0.8
Administration in the last 30 minutes of visit	2.1	1.2 - 4.1

DISCUSSION

In this prospective study about the safety of immunotherapy in a specialized unit, we have recorded a low incidence of systemic reactions to grass immunotherapy (18.2% of patients treated and 0.6% of doses administered). All systemic reactions were mild except one related with a warm bath, which reverted spontaneously. Except this clear factor associated with one systemic reaction (the most severe although not life-threatening), no other factors appeared to be involved in the occurrence of these side effects of immunotherapy. But a detailed analysis of our patients revealed that subjects allergic to cat dander and those receiving the injections in the last 30 minutes of visit had a higher risk of suffering from systemic reactions. By contrast, patients treated with *Phleum* extracts developed a lower rate of systemic reactions than those treated with *Lollium* or grass mix extracts.

To our knowledge, no other reports of immunotherapy safety considering only grass pollen extracts have been published, apart from controlled trials. We have evalua-

ted only this type of immunotherapy because factors involved in the occurrence of adverse reactions to grass pollen extracts are different from those involved to moulds, mites, danders or other types of pollen extracts. This makes it difficult to draw comparisons between our study and others. But in spite of these limitations, we have observed a higher incidence of systemic reactions than in other published studies. The incidences reported are between 0.8%[5] and 13%[6,7] of treated patients or between 0.005%[8] and 0.59%[9] of doses administered. These differences may exist because grass extracts trigger more systemic reactions than others[5,6,10], although this is not a consistent finging[11,12]. We have also observed that the larger studies report the lowest incidences of adverse events, perhaps because they do not detect some of these events. Many patients do not report their adverse reactions if they are not specifically asked about them. Our immunotherapy unit does not treat a very high number of patients, which allows us to perform an accurate register of any adverse event.

Although we usually speak about adverse reactions to immunotherapy, perhaps it would be more appropriate to speak about patients who do not tolerate the recommended top dose. When we tried again to administer the dose which induced the systemic reaction (which was attempted in more than 90% of our patients) a similar adverse event occurred. This supports the fact that no incorrect administration was involved in the majority of adverse reactions we observed. In this sense it is also important to point out the lack of association among systemic reactions and the allergologist prescribing immunotherapy, the nurse administering it and the manufacturer of the extracts.

All systemic reactions were mild, responded rapidly and completely to treatment or reversed spontaneously. The only anaphilactic reaction was clearly associated with a warm bath and, in any case, disappeared without treatment. The fact that 70.8% of systemic reactions developed after over 30 minutes leads us to consider, like other authors[6], a more prolonged waiting period. It is important to note that less than 10% of patients suffering from systemic reactions decided to stop immunotherapy. The rest continued the treatment at a lower maintenance dose, perhaps because severity of reactions perceived by patients was not enough to stop immunotherapy. All this data supports the idea that grass immunotherapy, administered in specialized units with trained staff, is a safe procedure.

A part from all th above-mentioned considerations, our real challenge was developing a means of accurately identifying high risk patients to develop systemic reactions to grass immunotherapy. Unfortunately, any demographic or clinical data could forsee this future event. Only cat allergic patients ran a higher risk (relative risk of 1.9) of developing systemic reactions to grass immunotherapy, although this did not seem to be related to a clear cat exposition. Like in other studies[13-15], the presence of local reactions was not helpful in predicting systemic ones. Other authors have defined some risk factors of systemic reactions as female sex[14], asthma diagnose[11,16,17], high nasal sensitivity to allergen[15], high level of serum IgE[17] and atopic dermatitis[17].

Besides the idiosyncratic patient tolerance to the grass extract, at the moment almost impossible to assess, the type of extract and conditions of its administration seem important in defining adverse reactions to immunotherapy. The importance of the phase of immunotherapy is clear: the risk of systemic reactions is higher during the dose-increasing phase than during maintenance phase, an observation made by other authors[6,8,11,16,18]. Furthermore, we have found that *Phleum* extracts developed a lower rate of systemic reactions than *Lollium* or grass mix extracts. From the literature, it seems that *Phleum* extracts are just as effective as other grass extracts[19]. This would be a easily-modifiable aspect to reduce adverse events.

We have observed that many of our patients usually come in a hurry in the last few minutes of visit and that many systemic reactions occurr in this period or even after visit has ended. Indeed, we have showed a significant association between systemic reactions and administration of immunotherapy in last 30 minutes of visit. This is another easily-modifiable factor, and it would be wise to pay more attention to respiration, taquipnea and other signs which signal that the patient is excited or agitated before giving the immunotherapy injection.

In conclusion, this study shows that administration of grass immunotherapy in a specialized unit and using biologically standardized extracts results in a low incidence of systemic reactions, none of which life-threatening. No measurable intrinsic characteristic of patients could identify who had a higher risk of developing systemic reactions to grass immunotherapy (or could not tolerate the recommended top dose). Only cat allergic patients appeared to have a moderate higher risk of systemic reactions. It seems that the extract composition and the conditions in which immunotherapy is administered contribute more to the appearance of systemic reactions.

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