ABSTRACT

Background: Despite its clinical effectiveness, allergen immunotherapy (AIT) remains controversial because serious systemic reactions can occur during its administration. Most of the studies on the safety of AIT are retrospective and use different methods, which frequently depart from daily clinical practice.

Objective: The aim of this study was to determine risk factors for adverse reactions, especially systemic adverse reactions, produced during routine AIT administration.

Methods: We registered 5,768 consecutive doses of standardized extracts administered to 273 patients in conventional schedules, following the recommendations on safety and data collection of the European Academy of Allergology and Clinical Immunology. Of the 273 patients, 236 were asthmatics, 28 had rhinitis and 9 received immunotherapy due to Hymenoptera anaphylaxis.

Results: We examined 143 local reactions (2.48% of the doses) and 145 systemic reactions (78 immediate and 67 delayed). Risk factors for developing an immediate systemic reaction were asthma severity, sensitization to molds, the most concentrated vials and a fall in peak expiratory flow of more than 15% or an immediate systemic reaction in the previous dose. Late systemic reactions were significantly more frequent with less concentrated vials and in patients with late local reactions in the previous dose. No serious reactions were registered.

Conclusions: We believe that AIT is reliable when used with strict safety protocols and administered by specialized staff. Risk factors for adverse reactions to this type of treatment can be identified and reduced by systematic data collection.


RESUMEN

Antecedentes: La inmunoterapia con alergenos es aún controvertida para algunos grupos, a pesar de su eficacia clínica, porque puede provocar reacciones sistémicas graves durante su administración. La mayoría de estudios sobre la seguridad de la inmunoterapia con alergenos son retrospectivos y emplean diferentes metodologías, muchas veces apartadas de la realidad clínica diaria.

Objetivos: El ánimo de este estudio fue conocer los factores de riesgo de las reacciones adversas, especialmente sistémicas, producidas durante la administración rutinaria de inmunoterapia.

Métodos: Registramos 5,768 dosis consecutivas de extractos estandarizados administrados a 273 pa-
cientes con pautas convencionales, siguiendo las recomendaciones de seguridad y recogida de datos de la EAACI (European Academy of Allergology and Clinical Immunology). De todos los pacientes 236 eran asmáticos, 28 riniticos y 9 recibieron inmunoterapia por anafilaxia por Himenópteros.

**Resultados:** Registramos 143 reacciones locales (2,48 % de las dosis), y 145 reacciones sistémicas (78 inmediatas y 67 tardías). Encontramos como factores de riesgo para el desarrollo de reacciones inmediatas sistémicas: la gravedad del asma, la sensibilización a hongos, los viales más concentrados, la caída del PEF superior al 15 % en la dosis previa y la presencia de otra reacción sistémica inmediata en la dosis anterior. Las reacciones sistémicas tardías fueron significativamente más frecuentes con los viales menos concentrados y en los pacientes con reacciones locales tardías en la dosis previa. No se produjo ninguna reacción grave.

**Conclusiones:** Creemos que la IT es segura cuando se emplean protocolos de seguridad estrictos y es administrada por personal especializado. La reco-gida sistemática de datos permite conocer y reducir los factores de riesgo relacionados con las reacciones adversas a este tipo de tratamiento.


**INTRODUCTION**

Allergen immunotherapy (AIT) is still a controversial point for some groups 1-7, in spite of many researches that guarantee its clinical effectiveness in case of respiratory allergy due to of pollens8,9, mites8,10, moulds8,8, animal dander8,11, and in hymenoptera anaphylaxis12,13. The consensus documents14,15, or metaanalyis16 locate it already in an evidence-based medicine level17.

However, and this is one of the arguments that can be used against, the AIT, as any other therapeutic form, it is not risk free and serious systemic reactions can occur during its administration. The majority of studies about safety with the AIT are retrospective18 and they use different methods, frequently far from clinical daily practice19. That is the reason why we decided to carry out a prospective study that let us know and reduce risk factors concerning adverse reactions, especially systemic, produced during the routine procedure of AIT administration in our Immunotherapy Unit. In this unit we work with a very well trained nursery staff (more than 3000 doses administered per year), we use only standardized extracts and we dispose of an appropriate training or allergists, immunotherapy clinic support staff and a computerized data recollection20, as well as necessary material to treat an eventual anaphylactic reaction, according to the European Academy of Allergology and Clinical Immunology (EAACI)11 recommendations.

**METHODS**

**Patients**

We evaluated 273 consecutive patients between 4 and 65 years of age, both included an average of 23.42 ± 15.79 years old, with indication of immunotherapy: 264 for respiratory pathology and 9 for hymenoptera anaphylaxis. 28 of the patients (10 % of the sum) with respiratory allergy exclusively showed rhinoconjunctivitis and the rest were asthmatic (85.2 %), 33.3 % of these with intermittent asthma, 43.7 % with persistent mild asthma and 22.9 % with persistent moderate asthma according to NHLBI/WHO consensus22. Patients maintain the necessary symptomatic treatment for their clinical stability during the course of the IT. The following patients’ variables were analysed: age, sex, diagnostic and severity in asthmatic, sensitizing allergens, PD20 methacholine and environmental conditions (origin of the population, presence of pets at home, kind of house and level of antigen exposition).

**Immunotherapy**

The vaccines used were all standardized in accordance to the International Consensus23,24 and following conventional schedules. In every patient we tried to reach the maximum dose recommended by different manufacturers. The vaccines with modified extracts or allergoids were administered in a presessional regimen (from September to March), being all the rest administered following a continuous schedule. Of the total of administered vaccines 74.4 % were of pollens, 7.8 % of mites, 11 % of moulds (Alternaria alternata), 3.8 % animal dander (cat, dog or horse) and 3.2 % hymenoptera venom (Vespula or Polistes).

**Doses – Safety monitoring**

Every dose was administered in our AIT unit following the recommendations of the AIT committee of...
Immediate systemic reactions 78 (1,3) 47 (17,0)
Late local reactions 83 (1,4) 45 (16,2)
Immediate local reactions 60 (1,0) 40 (14,4)
Late systemic reactions 67 (1,1) 55 (20,2)

Moulds (alternaria alternata) 476 345 821 14,23
Epithelia cats, dogs or horse 227 87 314 5,44
Hymenoptera (vespula and/or polistes) 98 79 177 3,07
Total 3,371 2,397 5,768 100,0

Table II

<table>
<thead>
<tr>
<th>Composition</th>
<th>Increase</th>
<th>Maintenance</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollens (graminea and/or trees, no cupressaceae)</td>
<td>1,761</td>
<td>705</td>
<td>2,466</td>
<td>43,1</td>
</tr>
<tr>
<td>Pollens (with cupressaceae)</td>
<td>174</td>
<td>378</td>
<td>552</td>
<td>9,57</td>
</tr>
<tr>
<td>Pollens (with weeds)</td>
<td>381</td>
<td>437</td>
<td>818</td>
<td>14,18</td>
</tr>
<tr>
<td>Mites (D. pteronissinus and/or D. farinae)</td>
<td>234</td>
<td>366</td>
<td>600</td>
<td>10,4</td>
</tr>
<tr>
<td>Moulds (alternaria alternata)</td>
<td>476</td>
<td>345</td>
<td>821</td>
<td>14,23</td>
</tr>
<tr>
<td>Epithelia cats, dogs or horse</td>
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<td>314</td>
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</tr>
<tr>
<td>Hymenoptera (vespula and/or polistes)</td>
<td>98</td>
<td>79</td>
<td>177</td>
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<tr>
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<td>5,768</td>
<td>100,0</td>
</tr>
</tbody>
</table>

A total of 5,768 administered doses to 273 patients (122 men and 151 women) were analysed. 27,07 % (75 patients) were younger than 10 years old and they received 1469 doses. 3371 doses belong to the build-up phase and 2,397 to the maintenance therapy (table I). 177 were aqueous extracts (hymenoptera venom), 3,973 adsorbed vaccines in aluminium hydroxide, and 1,618 allergoids. All patients but 9 (5 due to local reactions and 4 to systemic reactions) reached the maximum preestablished dose. The number and type of registered adverse reactions are exposed in table II. Only 1 patient presented both types of systemic reaction (immediate and late) after different doses of an Alternaria alternata extract. Most of the immediate systemic reaction (ISR) occurred significantly with the most concentrated vials, in more severe asthmatic patients, in those sensitized to moulds and in children younger than 10 years old (p < 0,05) (fig. 1). As an interesting fact we found, according to age, that children younger than 10 years old sensitized to animal dander or with an > 15 % fall in PEF in the previous dose, highly increased the risk of ISR. In relation to the late systemic reactions (LSR), the higher risk was related to the least concentrated vials (increasing dose regimen), and to the presence of another LSR (p = 0.07) or a late local reaction (LLR) in the previous dose.

The collected data were processed in a data base (Access® data base Microsoft®), SPSS (Superior Performing Software Systems 10.0) was used for statistical analysis. Comparative analysis of groups was carried out by the chi-square nonparametric test and the exact Fisher’s test. For the multivariable research we followed every step of the logistic method. A P value of < 0.05 was considered statistically significant.

RESULTS

A total of 5,768 administered doses to 273 patients (122 men and 151 women) were analysed. 27,07 % (75 patients) were younger than 10 years old and they received 1469 doses. 3371 doses belong to the build-up phase and 2,397 to the maintenance therapy (table I). 177 were aqueous extracts (hymenoptera venom), 3,973 adsorbed vaccines in aluminium hydroxide, and 1,618 allergoids. All patients but 9 (5 due to local reactions and 4 to systemic reactions) reached the maximum preestablished dose. The number and type of registered adverse reactions are exposed in table II. Only 1 patient presented both types of systemic reaction (immediate and late) after different doses of an Alternaria alternata extract. Most of the immediate systemic reaction (ISR) occurred significantly with the most concentrated vial, in more severe asthmatic patients, in those sensitized to moulds and in children younger than 10 years old. Otherwise, we found that an asymptomatic decrease of more than 15 % in PEF 30 minutes after a dose, showed a significative higher risk of suffering an ISR in the following dose (table III). Also, the presence of an ISR in a previous dose highly increased the probability of being repeated. Polisensitized patients (to more than 3 antigens) showed a higher probability of developing an ISR (p < 0.05) (fig. 1). As an interesting fact we found, according to age, that children younger than 10 years old sensitized to animal dander or with a > 15 % fall in PEF in the previous dose, highly increased the risk of ISR. In relation to the late systemic reactions (LSR), the higher risk was related to the least concentrated vials (increasing dose regimen), and to the presence of another LSR (p = 0.07) or a late local reaction (LLR) in the previous dose.
DISCUSSION

In some researches that employ similar doses regimen and method to ours the RS incidence is smaller than the one we found (2.53 % of the doses)\textsuperscript{29,30}. This fact could be due to, among other factors, that our series include many mould vaccines that have demonstrated, especially in children, to be worse tolerated\textsuperscript{31}. On the other hand it is possible that asthma severity in our asthmatic patients was as a whole greater than in another studies. The use of maximum doses with some extracts in which the optimum doses adapted to the patient are not defined could also collaborate to the increase of SR\textsuperscript{32}. However the percentage of patients (38.6 %) who show some SR to conventional treatment so that we consider that the AIT was safe in our patients.

The risk factors to suffer from RS found in our population, as asthma severity or patients’ pol sensitization grade, are in agreement with those found by other authors\textsuperscript{33}. The population that we attend comes from a residential area nearby Madrid, with a continental climate that stands out two pollination sharp points (February for cupressaceae and May-June for grass and olive tree pollen), as well as a great proportion of one family-houses and the presence of pets in 50 % of these residences. This could explain that the collective that suffers more from systemic reactions have been housekeepers, exposed more often to house dust mites, moulds and animal dander. This collective is frequently immunized population that fulfil the treatments worse, and, particularly for asthma, this is usually worse controlled.

We have found that a decrease of more than 15 % in PEF after a dose is a risk factor to present an ISR in the following dose. This fact supports the PEF monitoring recommendations of the EAACI and it can be of great profit in children and other patients, that don’t express their symptoms properly, which preclude possible modifications in the dose schedule that would not work otherwise.

As well as in previous studies the local reactions didn’t predict the ISR, but they predicted the LSR, what allows us to warn patients about it. In that sense the use of premedication, that we don’t employ, but that some other authors do\textsuperscript{34}, could hide the warning that suppose to present a LLR, although further researches are needed to clear up this aspect.

According to our safety medical records we don’t consider the administration mistakes as a risk factor of patients (38.6 %) who show some RS to conventional treatment...
ACKNOWLEDGMENTS

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