

ORIGINAL ARTICLE

Safety of specific immunotherapy using a depigmented and polymerised extract of *Dermatophagoides pteronyssinus* in children under five years of age

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Abstract

Background: Different opinion documents point to a patient age of under five years as a relative contraindication to specific immunotherapy, arguing that this age group has a greater risk of developing anaphylaxis, and that specially trained personnel are needed to deal with the problem if it occurs. However, insufficient evidence exists to support such an affirmation.

Patients and methods: A retrospective follow-up observational study was made of patients aged 60 months or younger who had been subjected to specific immunotherapy. We included 77 children with a diagnosis of extrinsic bronchial asthma (n = 68), extrinsic spasmodic cough (n = 5) and allergic rhinitis (n = 4) confirmed by clinical criteria and prick-test, with specific IgE positivity to *Dermatophagoides pteronyssinus*. All patients received specific immunotherapy with an extract of depigmented *D. pteronyssinus* polymerised with glutaraldehyde, involving an initial cluster protocol of two weeks and monthly maintenance doses. All observed adverse reactions were recorded, and classified according to European Academy of Allergy and Clinical Immunology (EAACI) criteria.

Results: A total of 1837 doses were administered to the 77 patients, with four adverse reactions being observed in three patients. Three reactions (0.16% of the administered doses) were local and immediate, while one was systemic and of grade 2 (0.05% of the administered doses) – consisting of an episode of nocturnal wheezing.

Conclusions: Specific immunotherapy in children under five years of age with the extract used is safe. We consider that further studies are needed, involving other types of extracts, to allow reconsideration of the relative contraindication of patient age for the administration of immunotherapy.

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Introduction

Specific immunotherapy with allergens involves the administration of increasing amounts of an allergen to which the subject is sensitised, with the purpose of suppressing or reducing the symptoms caused by natural exposure to the allergen¹.

Specific immunotherapy with allergens has been shown to be effective in the treatment of bronchial asthma^{2,3}, is allergen-specific, and is presently the only treatment capable of modifying the natural course of allergic diseases^{4,5}. It has also been found to be more effective the earlier it is administered⁴. It is therefore curious that the recommendations of the European Academy of Allergology and Clinical Immunology (EAACI) point to a patient age of under five years as a relative contraindication to the administration of specific immunotherapy^{6,7}, with the argument that this age group has a greater risk of developing anaphylaxis, and that specially trained personnel are needed to deal with the problem if it occurs.

From the tolerance and safety perspective, we have reviewed the experience of our Allergy Unit in a group of children under five years of age who received specific immunotherapy with a biologically standardised extract depigmented and polymerised with glutaraldehyde.

Material and methods

Study design

A retrospective follow-up observational study was made of patients aged 60 months or younger, during the period 2002-2008, with follow-up until June 2009, and who had received specific immunotherapy.

Patients

The study included 77 children with a mean age of 50.32 ± 7.23 months (range 24-60 months), 46 (59.74%) are boys and 31 (40.26%) are girls. Fig. 1 shows the patient age distribution.

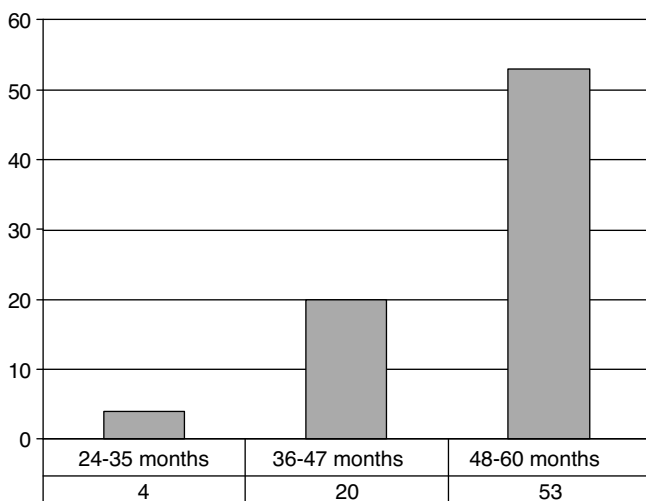


Figure 1 Patient age distribution.

The reason for consultation was bronchial asthma in 68 cases (88.3%), spasmodic cough in five (6.5%), and rhinitis in the remaining four cases (5.2%).

The allergological diagnosis was based on clinical criteria, prick-test and specific IgE positivity to *Dermatophagoides pteronyssinus*. Sixty-seven children were sensitised exclusively to dust mites, while the remaining 10 presented other clinically non-relevant sensitisations to pollen (grasses and olive), animal epithelia (dogs and cats), and fungi (*Alternaria*).

Allergenic vaccine used

All the patients received treatment with an extract of *Dermatophagoides pteronyssinus*, depigmented and polymerised with glutaraldehyde (DEPIGROID®, Laboratorios LETI, S.L. Tres Cantos, Spain). The characteristics of this extract have been described elsewhere⁸.

The native extract of *Dermatophagoides pteronyssinus* contained 20.35 µg of Der p1 and 12.3 µg of Der p2 per mg of dry lyophilised extract. In the modified extract neither Der p1 nor Der p2 could be detected.

Two vials were prepared for each patient, numbered 1 and 2, for the initial cluster protocol. Vial 1 contained 8.5 µg/ml of polymerised and depigmented extract, and vial 2 a 10-fold higher concentration (85 µg/ml). The maintenance doses were prepared with vial number 2.

Immunotherapy regimen

Immunotherapy was initially administered in the hospital setting, using a cluster protocol consisting of the administration of doses of 0.20 ml and 0.30 ml of vial number 1 at intervals of 30 minutes the first day; 0.20 ml and 0.30 ml of vial number 2 one week later; and then maintenance doses of 0.50 ml of vial number 2 at monthly intervals. The patient remained under observation up to 30 minutes after the last administered dose. Once good tolerance of the maintenance dosage was confirmed, we switched to an outpatient administration regimen, with a written registry of the possible incidents using a vaccination card completed by the nurse in charge of administration of the doses.

Safety

A record was kept of all the adverse reactions observed; these were classified according to the criteria of the EAACI into immediate and delayed local reactions, and immediate and delayed systemic reactions. A scale from 0 to 4 proposed by the EAACI was used to assess the severity of the immediate systemic reactions recorded⁷.

Results

A total of 1837 doses were administered to the 77 patients, with the observation of four adverse reactions in three patients. Three reactions (0.16% of the administered doses) were local and immediate, while one was systemic and of grade 2 (0.05% of the administered doses) – consisting of an episode of nocturnal wheezing on the day of administration

of the sixth maintenance dose. This patient has continued to receive the monthly immunotherapy doses without further adverse reactions.

Discussion

A number of different factors can influence the development and severity of systemic reactions in relation to the administration of specific immunotherapy.

Some of these factors are dependent upon the patient: those with unstable asthma or receiving treatment with beta-blockers are at high risk of suffering very serious reactions⁹.

Other factors in turn are dependent upon the allergenic extract. The recommendation of the EAACI to establish a relative contraindication to specific immunotherapy in children under five years of age due to a purported increased risk of anaphylaxis⁷ is based on a single article published in 1990 by the Montpellier group, which observed a 45% systemic reactions rate in this age interval with an aqueous extract of biologically standardised *D. pteronyssinus* administered as a rush Scheme¹⁰. Aqueous extracts are the cause of most of the serious systemic reactions reported in the literature¹¹, and the high rate of systemic reactions found in the article in all age groups is no surprise. In general terms, aqueous extracts produce more reactions than depot extracts. Despite its own indications, seven years later the same group published a study involving the same extract and the same rush administration scheme in a group of 44 children between 2-6 years of age, in which the patients administered specific immunotherapy were not seen to develop new sensitisations with respect to the untreated children – suggesting that such treatment in monosensitised children could alter the natural course of their allergic condition. In this publication they reported no adverse effects in this age group¹².

The initial administration protocol does not seem to influence the appearance of adverse reactions to immunotherapy. Schubert et al.¹³ found no difference in the appearance of adverse effects in children between 6-18 years of age on comparing a "classical" initial immunotherapy regimen with a cluster protocol.

With the purpose of obtaining allergenic extracts inducing fewer systemic effects, extracts polymerised with formaldehyde or glutaraldehyde were developed (i.e., the so-called "allergoids"). These maintain immunogenicity while substantially reducing allergenicity – thereby ensuring good tolerance¹⁴.

In an earlier study⁸ we showed that immunotherapy with a depigmented allergoid of *D. pteronyssinus* administered at high doses in an initial cluster protocol was effective in application to asthmatic children between 8-16 years of age, and that the benefits could be observed in terms of specific bronchial hyperresponsiveness in as little as four months – with a very low systemic reactions rate (2 of 120 administered doses = 1.6%). Two other studies^{15,16} support the safety of this type of extracts in patients over 14 years of age.

A review of the literature yielded a study published by Paniagua et al.¹⁷ in which seven grade 1 and grade 2 systemic reactions were observed in a group of 22 children under five years of age administered immunotherapy with a depot extract of *D. Pteronyssinus* / *D. farinae*, involving a

conventional starting protocol in a period of 16.95 ± 10.12 months.

Systemic reactions due to the administration of specific immunotherapy are rare in our experience, since we have only documented such situations in 0.10% of the last 30,000 administered doses in our department (data not published), using depot extracts and modified extracts of different allergens, and including immunotherapy with insect venom. In no case did patient hospitalisation prove necessary, since the reactions could be controlled at outpatient level with adequate medication. In children under five years of age and with the extract considered in this study, the mentioned percentage is even reduced to by half (0.05%).

Considering the demonstrated benefits of specific immunotherapy in children, such as the non-progression of allergic rhinitis to asthma⁵, and the prevention of the appearance of new sensitisations in monosensitised children^{12,18,19}, as well as the low adverse reactions rate observed with the studied extract, we consider that further studies of this kind are needed, involving other types of extracts, in order to allow reconsideration of the relative contraindication of patient age for the administration of immunotherapy.

Conflict of interest statement

Dr. Nora Hernández has received a grant from Laboratorios LETI, S.L. The rest of the authors have no conflicts of interest to declare.

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