Effects of specific immunotherapy on the development of new sensitisations in monosensitised patients

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ABSTRACT

Background: Specific immunotherapy (SIT) is the only treatment that interferes with the basic pathophysiological mechanisms of allergic disease and is widely used in the management of clinically significant respiratory IgE-mediated diseases. Nevertheless, until recently, information on the influence of SIT on the development of new allergic sensitisations has been scant.

Methods: One hundred consecutive patients (45 males and 55 females, aged 6 to 69 years) with respiratory allergic diseases and attending the allergy unit of a general hospital were selected. All had been diagnosed by clinical history and skin prick tests of allergic rhinitis and/or asthma, were monosensitised (71 to *Dermatophagoides spp*, 22 to *Parietaria judaica* pollen and 7 to grass pollen) and had been followed up as outpatients between 1990-98. Sixty-six patients had been treated with conventional SIT for at least 3 years, while thirty-four followed only environmental measures and drug treatment. Family atopy status (first-degree relatives), smoking, family pets (cat and/or dog), rhinitis and/or asthma symptom score and inhalant skin prick tests to the same aeroallergens were compared between baseline and after 3 to 5 years of treatment.

Results: No statistically-significant differences in the development of new sensitisations were observed between the two groups (36.4% of SIT-treated patients versus 38.2% in control group, RR = 0.97, CI 95%: 0.72-1.3). Smoking, family atopy history and pets did not appear to be risk factors for the development of neosensitisations ($p < 0.05$). Nevertheless, SIT-treated patients presented a better clinical score than the control group, with improvements of 89.4% and 61.8%, respectively ($p = 0.007$).

Conclusions: Three-year SIT did not protect against development of new sensitisations in monosensitised allergic rhinitis or asthma. Smoking, family atopy history and pets were not associated with development of new sensitisations. Clinical score improved significantly in the SIT-treated group compared with drug-treated patients.

Key words: Allergy. Monosensitisation. New sensitisations. Prevention. Specific immunotherapy.

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RESUMEN

Introducción: La inmunoterapia específica es el único tratamiento que actúa sobre los mecanismos fisiopatológicos de las enfermedades alérgicas y se utiliza frecuentemente en el manejo clínico de los pacientes con enfermedades respiratorias mediadas por IgE. Recientemente se ha sugerido que la inmunoterapia podría tener un efecto protector sobre el desarrollo de nuevas sensibilizaciones, siendo el objetivo de este estudio analizar este posible efecto.

Pacientes y métodos: Se seleccionaron 100 pacientes consecutivos (45 hombres y 55 mujeres, con

edades comprendidas entre los 6 y 69 años) con alergia respiratoria que consultaron en una unidad de alergia de un hospital general durante el período comprendido entre 1990 y 1998. Estos pacientes se diagnosticaron de rinitis y/o asma por historia clínica y prick test, siendo todos ellos monosensibles (71 a *Dermatophagoides spp*, 22 al polen de *Parietaria judaica* y 7 al polen de gramíneas). Sesenta y seis pacientes se trataron con inmunoterapia convencional durante un mínimo de 3 años (grupo inmunoterapia) y treinta y cuatro realizaron únicamente medidas ambientales y tratamiento farmacológico (grupo control). Al inicio del estudio y después de 3 a 5 años de tratamiento se realizó todos ellos un estudio que incluía la realización de pruebas cutáneas con la misma batería de aeroalergenos, valoración de la gravedad de la rinitis y/o asma mediante un baremo de síntomas e interrogatorio sobre la presencia de ciertos factores que pudieran influir en su evolución o en la aparición de nuevas sensibilizaciones (antecedentes familiares de atopia de primer grado, tabaquismo y exposición a los animales domésticos perro y/o gato).

Resultados: No se observaron diferencias estadísticamente significativas en el desarrollo de nuevas sensibilizaciones entre los dos grupos (el 36,4 % en el grupo tratado con inmunoterapia frente el 38,2 % en el grupo control, RR = 0,97; IC 95 %: 0,72-1,3). La presencia de antecedentes familiares de atopia, el tabaquismo o la exposición a animales no fueron factores de riesgo para el desarrollo de nuevas sensibilizaciones ($p < 0,05$). Sin embargo, los pacientes tratados con inmunoterapia presentaron una mejor evolución clínica que el grupo control, con mejorías del 89,4 % y del 61,8 % respectivamente ($p = 0,007$).

Conclusiones: La inmunoterapia específica durante un período mínimo de 3 años no protegió de la aparición de nuevas sensibilizaciones en pacientes monosensibles con rinitis y/o asma. Tampoco influyeron en la aparición de nuevas sensibilizaciones los antecedentes familiares de atopia, el tabaquismo o a la exposición a animales domésticos. El baremo clínico mejoró significativamente en el grupo tratado con inmunoterapia en relación al grupo control.

Palabras clave: Alergia. Inmunoterapia específica. Monosensibilización. Nuevas sensibilizaciones. Prevención.

INTRODUCTION

Specific immunotherapy (SIT) is the only treatment that interferes with the basic pathophysiological mechanisms of allergic disease[1] and is widely used in the management of clinically-significant IgE-mediated respiratory allergic diseases. SIT has been used since 1911[2] proving efficacious both in allergic rhinoconjunctivitis and bronchial asthma[3,4]. As SIT is able to modify the immune response in early stages, it may also be effective in the prevention of new allergic sensitisations. Prior to the present study, only one group of researchers had addressed this topic, drawing different conclusions depending on whether patients were mono or polysensitised[5,6] being both referred to paediatric populations. Recently, it has been published another paediatric study showing a lower development of new sensitizations in the SIT group compared to the control group[7]. Moreover, the European multi-center Preventive Allergy Treatment study show that after 3-year SIT and 5-year follow-up, the risk for onset of asthma is reduced in children 5 to 13 years old suffering from allergic rhinoconjunctivitis, but no results on development of new sensitizations are available[8,9].

The aim of the present study was to assess the ability of SIT to prevent the development of new sensitisations in monosensitised patients. The influence of other factors (age, sex, atopy background, family pets and smoking) on the development of new sensitisations was analysed and the clinical outcome compared in patients treated with or without SIT.

PATIENTS AND METHODS

Patient population

The first 100 consecutive patients attending for the first time an allergy outpatient clinic of a general hospital after 1990 and meeting the following inclusion criteria were selected:

1. Diagnosis of allergic rhinitis and/or asthma established after a conventional work-up study and evaluated by symptom score. Rhinitis was expressed as absent, mild, moderate or severe, and asthma was evaluated by the four degrees of the Global Initiative for Asthma[10].
2. Monosensitisation to one of the three more prevalent allergens in the area (*Dermatophagoides spp*, *Parietaria judaica* pollen and grass pollen).
3. Complete follow-up in the same allergy outpatient clinic for 3 to 5 years.

The selected patients were offered a comprehensive interview covering recent data on family atopy

history (first-degree relatives), smoking habits, having pets at home (cat and/or dog) and the same symptom score used for the initial diagnosis by a blinded investigator who also performed prick tests with the same aeroallergen battery as that used at the time of the initial diagnosis. The patients were divided in a SIT-treated group (group A) and a group treated with conventional drugs and environmental measures alone (group B).

Skin prick test

The skin prick tests were performed with biologically-standardised extracts, if possible, and of the same commercial brand. The extracts included house dust mites *(Dermatophagoides farinae, Dermatophagoides pteronyssinus)*, cat and dog dander, main pollens in the area (*Cupressus arizonica, Corylus avellana, Platanus acerifolia, Olea europea*, *Parietaria judaica, Artemisia vulgaris, Plantago lanceolata, Mercurialis annua, Salsola kali, Phleum pratense, Cynodon dactylon* and *Phragmites communis*), common moulds (*Alternaria alternata, Cladosporium herbarum, Aspergillus spp,* and *Penicillium spp*) and latex. Positive (histamine chloride 10 mg/ml) and negative (saline) controls were used. Skin prick tests were performed in the same order and on the same volar surface of the forearm in both evaluations. A mean diameter greater than 3 mm was considered positive if no dermographism and/or positivity of negative control were recorded.

Immunotherapy

SIT was performed using commercial extracts of biologically-standardised extracts of *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus*, (whatever the greater skin test area), *Parietaria judaica* and grass mix pollen, according to the usual protocol in the unit and consisted of an initiation phase of gradually increasing doses in which the injections were administered weekly, and a maintenance phase with the standard commercial dose (or the highest dose tolerated by the patient) was administered at 4-week intervals until at least 3 years of treatment had been completed.

Statistics

Descriptive analysis was performed using absolute and relative frequencies for categorical variables and medians and ranges for quantitative variables. The occurrence of new sensitisations in SIT-treated and untreated patients was compared with the chi-square test. A parametric test (*t*-test) was used for quantitative variables, calculated as relative risk (RR) with 95% confidence interval (95% CI). P values ≤ 0.05 were considered statistically significant. All analyses were performed with the SPSS 6.1 statistical software package.

RESULTS

Forty-five males and fifty-five females aged 6 to 69 were recruited. Seventy-one were monosensitised at baseline to *Dermatophagoides*, twenty-two to *Parietaria judaica* pollen and seven to grass pollen. Of the 100 patients, 66 were treated with SIT (group A) and 34 with avoidance of allergen and conventional drugs alone (whatever the inhaled corticosteroids, bronchodilators, local or oral antihistamines or nasal corticosteroids).

Age and sex of both groups were comparable at baseline. Prevalence of asthma was higher in the SIT-treated than in the non-SIT-treated group (table I).

No statistically-significant differences were observed between the groups in the rate of new sensitisations (RR = 0.97, CI 95%: 0.72-1.3), since 36.4% of SIT-treated patients showed new sensitisations, compared with 38.2% of the control group (table II). Smoking, family atopy history and pets did not appear to be a risk for developing new sensitisations ($p < 0.05$). Nevertheless, the SIT-treated group showed better clinical outcome compared to the control group, with an improvement of 89.4% *versus* 61.8% ($p = 0.007$).

Table I

Descriptive clinical characteristics of patients

	SIT group	Control group
Mean age (SD)	28.79 (13.02)	26.03 (16.84)
Sex (male/female)	31/35	14/20
Symptoms:		
Rhinoconjunctivitis and asthma	34 (51.5%)	9 (26.5%)
Rhinoconjuntivitis	14 (21.2%)	16 (47.1%)
Asthma	18 (27.3%)	9 (26.5%)
Sensitisation:		
House dust mites	45	26
Parietaria pollen	16	6
Grass pollen	5	2
Smoking (yes/no)	9/57	6/28
Family atopy (yes/no)	39/27	16/18
Pets (yes/no)	19/47	17/17
Clinical evolution good/poor	59/7	21/13

Table II

Effects of specific immunotherapy on the development of new sensitisations in SIT-group and control group

	SIT-group		Control group		Total
	New sensitisations	No new sensitisations	New sensitisations	No new sensitisations	
Monosensitisation to grass pollen	3	2	1	1	7
Monosensitisation to *Parietaria judaica* pollen	6	10	5	1	22
Monosensitisation to *Dermatophagoides sp*	15	30	7	19	71
Total	24	42	13	21	100

DISCUSSION

The present study, which evaluated 100 consecutive monosensitised patients aged between 6 and 69, showed no differences in the development of new sensitisations between patients treated by 3 to 5-year SIT and patients not treated with SIT. Prior to the start of the study, only two published reports had analysed the effect of SIT on the rate of new sensitisations and both referred to paediatric populations. One included polysensitised patients and concluded that SIT did not prevent the development of new sensitisations[5]. The other, a prospective case-control of 44 asthmatic children aged 2 to 6 years, showed that all children in the control group developed new sensitisations, versus only 12/22 of the 3-year SIT-treated group[6]. Preliminary data of another paediatric study, the ongoing European multi-centre Preventive Allergy Treatment (PAT)[8,9], clearly show that after 3-year SIT and 5-year follow-up, the risk for onset of asthma is reduced in children 5 to 13 years old suffering from allergic rhinoconjunctivitis, but no results on development of new sensitisations are available to date.

Table III

Rate of new sensitisations reported in different studies

	Total	SIT-treated group	Control group
Silvestri (10)	43.6% (72/165)	NC*	NC*
Purello-D'Ambrosio (11)	30.2% (2532/8396)	23.8% (1706/7182)	68% (826/1214)
Pajno (12)	43.1% (53/123)	24.6% (17/69)	66.7% (36/54)
Tella	37% (37/100)	36.4% (24/66)	38.2% (13/34)

* Not considered.

Other articles on development of new sensitisations have recently been published[7,11,12]. In the two studies conducted in the south of Italy, the development of new sensitisations was found to be statistically lower in the SIT group compared to the control group. However, when the total number of patients in each study is considered, the rate of new sensitisations ranges from 30 to 43% with the highest percentages being in paediatric series (table III). These studies were planned as retrospective and observational and did not define medical judgement to prescribe SIT, thereby slanting the results obtained. Therefore, new randomised studies are required to draw definitive conclusions regarding the effect of SIT on preventing new sensitisations in monosensitised patients.

A family history of atopy did not influence the development of new sensitisations in our patients, probably due to the selection of monosensitised patients, since a background of atopy is usually more prevalent in polysensitised patients. In our study, neither smoking nor pet exposure influenced the development of new sensitisations. In this respect, recent information casks some doubt on the role of smoking and exposure to pets in the development of allergic sensitisation[13-21].

From a clinical point of view, the degree of reduction in symptoms and/or drug intake was significant when the SIT-treated group and non-treated group were compared, thereby reflecting the efficacy of SIT.

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