

An Observational Study on Outgrowing Food Allergy during Non-Birch Pollen-Specific, Subcutaneous Immunotherapy

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Key Words

Cross-reactivity · Food allergy · Immunotherapy ·
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Abstract

Background: Birch pollen-specific immunotherapy (SIT) decreases allergy to foods containing birch pollen-homologous allergens. Cross-reactivity was also observed between plane tree pollen and some vegetable foods. **Objective:** The aim of this study was to evaluate the outgrowing of food allergy by patients suffering from vegetable food allergy associated with plane tree pollinosis (rhinoconjunctivitis and/or asthma) during plane tree pollen SIT. **Methods:** An observational and prospective study was conducted in 16 adult patients suffering from vegetable food allergy (hazelnut, walnut, lettuce, peach and cherry) and from plane tree pollinosis receiving plane tree pollen SIT for 1 year. Open oral challenges with the implicated food were performed before and after SIT. Blood samples were drawn for measurement of pollen- and food-specific IgE and IgG4 before and after treatment. **Results:** Plane tree SIT resulted in a significant decrease in food allergy, since the mean food quantity provoking objective symptoms increased from 2.19 to 13.74 g ($p < 0.05$), and 6 of the 11 patients tolerated the highest level (25 g) of the challenged food after plane tree SIT. Laboratory data also showed a decrease in IgE levels and an in-

crease in IgG4 levels after immunotherapy. **Conclusion:** SIT with plane tree pollen has a positive impact on food allergy in plane tree pollen-allergic subjects.

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Introduction

Food allergy is potentially life-threatening, and no curative treatment is known to date. The recommended treatment for individuals with known anaphylactic reactions to foods is avoidance and the use of injected epinephrine as soon as they become aware of an inadvertent ingestion [1, 2].

Allergy to foods of plant origin is frequently caused by pollen-vegetable food cross-reactive IgE. In fact, up to 70% of individuals with pollen allergy experience food allergy symptoms after eating raw fruits and vegetables [3, 4]. These symptoms are referred to as the oral allergy syndrome reflecting a phenomenon based on the cross-reactivity of specific IgE antibodies towards epitopes of certain pollen and food proteins [4, 5].

The plane tree or *Platanus acerifolia* is common in most Western European cities. Plane pollinosis is not generally considered, although high concentrations of its pollen are detected during the flowering season in several cities of the United States and Southern Europe [6–

8]. The association between plane pollinosis and plant-derived food allergy has been reported, but the cross-reactive structure remains unclear [9–11].

Specific immunotherapy (SIT) is an established treatment for pollen allergy [12]. There are some reports and studies suggesting beneficial effects of birch SIT in birch pollen-related food allergy, some of which have been confirmed by double-blind food challenges [13, 14]. Nevertheless, the experience of such studies has not been extended to other cross-reactive food allergies.

The aim of this study was to evaluate the outgrowing of food allergy by patients suffering from plane tree pollen allergy with associated food allergy (a non-birch pollen-food cross-reactivity) during plane tree pollen SIT.

Patients and Methods

Patients and Study Design

This was an observational and prospective study. Patients provided written informed consent. The study was approved by the Ethics Committee of the Institut Universitari Dexeus, Barcelona. Patients were selected on the basis of a clear history of vegetable food allergy and plane tree pollinosis with a positive skin prick test (SPT) and positive oral food challenge to the implicated food and positive SPT to the plane tree pollen extract.

Blood samples were drawn for in vitro studies. All patients were given plane tree pollen SIT for 1 year. Subsequently, after SIT completion, a second open oral food challenge with the same implicated food was performed and blood samples were redrawn.

Pregnancy was a criterion for exclusion, and any asthma had to be under control. Systemic corticosteroids and β -blockers were prohibited before selection and throughout the study, and antihistamines and antidepressants were prohibited for 1 and 2 weeks, respectively, before skin testing and oral food challenge.

Skin Prick Tests

SPT were performed according to the standard procedure with a panel of inhalant allergens containing the main allergens prevalent in the Barcelona area: dust mites, molds, cat and dog dander, latex and pollens such as grass, *Parietaria*, mugwort, olive, hazel and plane tree (Diater Laboratories, Madrid, Spain). SPT with food allergens with commercially available extracts (Diater Laboratories) were also performed with the implicated foods.

Histamine dihydrochloride 10 mg/ml and phosphate-buffered saline solution served as positive and negative controls, respectively. The SPT was considered positive if the wheal area was 3 mm greater than the negative control, 15 min after testing.

Food Challenges

Open food challenge with a modified schedule proposed in a previous study was performed before and after 1 year of plane tree pollen immunotherapy. Briefly, implicated foods were weighed and ground with saline solution, and samples of different concentrations were prepared. SPT were performed with these samples. The starting challenge dose should be that whose wheal area was

lower than that of histamine. Intervals between doses were 20–30 min. After the last concentration intake (400 mg/ml), we continued doubling doses until symptoms appeared or until 25 g of food had been administered in a single dose [15].

Immunotherapy Protocol

All the patients received a standardized aluminum hydroxide-adsorbed plane pollen extract (Diater® Depot®; Diater Laboratories). All patients were given SIT according to a modified cluster schedule, followed by a monthly maintenance injection of 10,000 BU/ml for 1 year without dose reduction during the pollen season. Active SIT consists of a biologically standardized plane tree pollen extract.

Specific IgE and IgG4

Specific IgE and IgG4 against plane pollen and implicated food extracts were measured by an enzyme allergosorbent test following the manufacturer's instructions (Hytec-specific IgE enzyme immunoassay and Hytec-specific IgG4 enzyme immunoassay; Hycor Biomedical, Garden Grove, Calif., USA).

Statistics

Results were expressed as percentages for categorical variables and means for continuous variables. Student's *t* test and the Mann-Whitney U test were used to compare continuous variables before and after SIT. The significance level was 5%, and the statistical program used was APSS 10.0 (1999; SPSS, Chicago, Ill., USA).

Results

Study Population

Sixteen adult patients aged 18–60 years were selected on the basis of a history of plane pollinosis, associated food allergy and open oral food challenge positive to the implicated food. All 16 patients received plane tree pollen SIT. Four of the 16 withdrew their consent for personal reasons before the second oral food challenge. Two female patients were excluded because they became pregnant during the SIT maintenance period. The main patient demographic characteristics and allergy history are summarized in tables 1 and 2.

Evaluation of the Clinical Effect of SIT with Oral Food Challenges

Allergic reactions to foods during oral food challenges were generally well controlled by stopping the challenge and administering treatment with epinephrine, antihistamines and corticosteroids, as appropriate. No patient required overnight hospitalization, and none of those who had anaphylaxis presented severe symptoms or hypotension.

The mean quantity of food provoking objective symptoms increased from 2.19 to 13.74 g ($p < 0.05$; fig. 1).

Table 1. Demographic characteristics and history of allergy of the patients

Characteristics	
Sex	
Male	6 (37%)
Female	10 (63%)
Mean age, years (range)	31 (24–37)
Plane tree-specific IgE, IU/ml	63.31 ± 31.40
Respiratory allergy	
Asthma	0%
Rhinitis or rhinoconjunctivitis	100%
Both asthma and rhinitis or rhinoconjunctivitis	37%
Associated food allergy (implicated food)	
Nuts (hazelnut/walnut)	68.7%
Lettuce	18.7%
Peach/cherry	12.6%
Associated food allergy (allergy symptoms)	
Local reactions	12.5%
Systemic reactions (including anaphylaxis)	87.5%

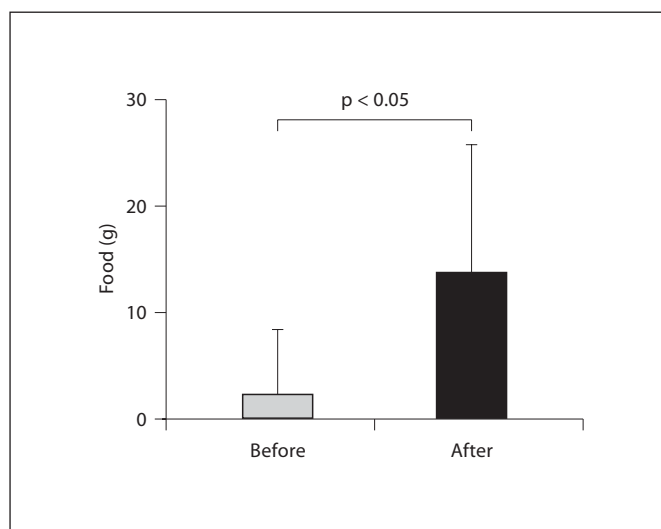


Fig. 1. Oral challenge tests: mean food amounts tolerated before and after immunotherapy.

Table 2. History of food allergy of the patients

Pa-tient	Food allergy		DBPCFC			
	implicated food	symptoms	before SIT		after SIT	
			symptoms	dose, g	symptoms	dose, g
1	hazelnut	angioedema	OAS	0.2	tolerance	25
2	walnut	anaphylaxis	OAS	0.1	tolerance	25
3	hazelnut	angioedema	OAS	0.1	OAS	0.1
4	lettuce	anaphylaxis	OAS	0.2	tolerance	25
5	peach	OAS	OAS	0.2	OAS	0.2
6	lettuce	anaphylaxis	OAS	0.2	OAS	0.4
7	walnut	anaphylaxis	OAS	0.1	OAS	0.4
8	walnut	urticaria	OAS	2	tolerance	25
9	hazelnut	OAS	OAS	1	tolerance	25
10	hazelnut	anaphylaxis	anaphylaxis	20	OAS	0.1
11	hazelnut	urticaria	OAS	0.01	tolerance	25
12	cherry	anaphylaxis	angioedema	0.2	NP	NP
13	walnut	angioedema	OAS	0.2	pregnancy	NP
14	hazelnut	anaphylaxis	OAS	0.1	NP	NP
15	walnut	anaphylaxis	OAS	0.01	pregnancy	NP
16	walnut	anaphylaxis	OAS	0.1	NP	NP

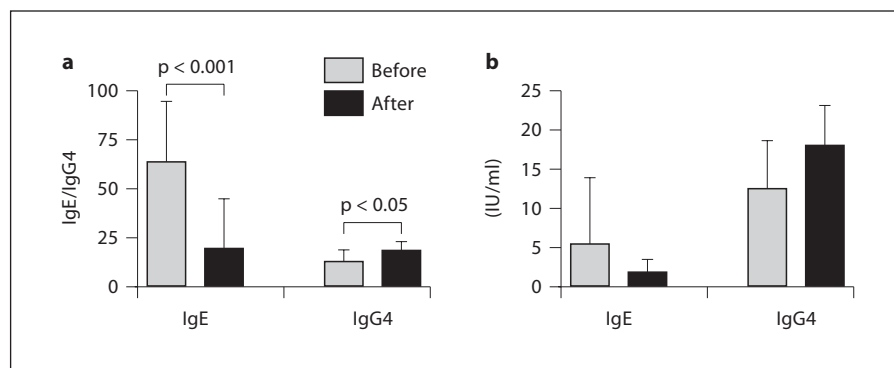
DBPCFC = Double-blind placebo-controlled food challenge; NP = not performed; OAS = oral allergy syndrome.

Moreover, 6 of the 11 patients (54.54%) who underwent oral food challenges after 1 year of plane tree SIT tolerated the highest level, 25 g, providing sufficient protection against most unintended ingestions of the implicated food.

Laboratory Parameters

As expected, lower rates of serum-specific IgE and high levels of plane tree-specific IgG4 were found after 1 year of treatment, both with statistical significance (fig. 2a). The same phenomenon was observed regarding

Fig. 2. a Plane tree pollen-specific IgE and IgG4 levels before and after treatment. **b** Vegetable food-specific IgE and IgG4 levels before and after treatment.



food-specific IgE and IgG4, but with no statistical significance, i.e. a reduction in specific IgE levels, and an increase in IgG4 levels (fig. 2b).

Discussion

Plane tree pollen is a highly common pollen in the atmosphere of many Mediterranean cities. Air concentration of this allergenic pollen peaks in early spring [6, 7]. A strong association has been observed between plane pollinosis and vegetable food allergy, including a great number of systemic reactions [9, 10]. Nevertheless, further studies are required to identify the cross-reacting structures and their importance in eliciting food allergy in patients allergic to plane tree pollen, as neither plane tree profilin nor the two major allergens described (Pla 1 and 2) appear to account for such strong cross-reactivity, and only partial cross-reactivity has been reported between food and plane tree lipid transfer proteins [10].

Although double-blind placebo-controlled food challenges are the 'gold standard' for the diagnosis of food allergy, open food challenges prove useful in the oral allergy syndrome, in which the implicated food must be administered in its natural form – not dried, lyophilized or in capsules – to reproduce the contact between food and the oral mucosa to induce symptoms [1]. Moreover, we decided to perform open oral challenges owing to the high number of patients with plane pollinosis with a history of systemic food allergy reactions [9, 10].

There is a paucity of information on the natural history of food allergy. Nevertheless, food allergy is generally thought to be a lifelong state, and the follow-up of adult patients with food allergy does not typically include routine assessment to determine whether the patient has achieved oral tolerance. Although these management

practices are appropriate given the lack of evidence of these patients' outgrowing food allergy, there might be a substantial number of patients labeled as having food allergy who have in fact outgrown their allergy [16]. Evidently, this natural evolution of food allergy does not explain the results obtained in the current study where more than 50% of patients outgrew their food allergy after plane tree pollen SIT.

Immunotherapy with tree pollen extract is capable of modifying the immunologic response to the offending allergen in the early stages and, as expected, SIT with tree pollen resulted in a significant rise in IgG4 levels. However, no corresponding statistically significant increase in IgG4 to the cross-reactive allergen in foods was observed, thereby suggesting that allergen-specific immunomodulation by SIT with the tree allergens does not affect, or only partially, the immune response to the cross-reactive food allergen [13, 14]. However, in the current study, we observed on the one hand a high positive effect of plane tree pollen SIT on food allergy in patients with plane pollinosis and associated food allergy, and on the other hand a statistically significant increase in pollen-specific IgG4 levels and a non-significant increase in food-specific IgG4 levels, probably due to the lower number of patients participating in the current study, and the possibility that the different foods inducing symptoms (e.g. nuts and lettuce) yield non-homogeneous values that might have masked changes in serum antibodies in a smaller population.

In conclusion, although the mechanisms of cross-reactivity between plane tree pollen and foods are unclear, SIT with plane tree pollen does have a positive effect on food allergy in plane tree pollen-allergic individuals. Further studies are required to clarify the cross-reacting structures for such a strong cross-reactivity.

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