Sublingual immunotherapy for hazelnut food allergy: A randomized, double-blind, placebo-controlled study with a standardized hazelnut extract

Ernesto Enrique, MD, PhD,a Fernando Pineda, PhD, b Tamim Malek, MD, PhD, a Joan Bartra, MD, PhD, c María Basagaña, MD, d Raquel Tella, MD, e José Vicente Castelló, MD, a Rosario Alonso, MD, d José Antonio de Mateo, MD, a Teresa Cerdá-Trias, MD, e Maria del Mar San Miguel-Monc in, MD, d Susana Monzón, MD, d María García, PhD, e Ricardo Palacios, PhD, b and Anna Cisteró-Bahima, MD, PhD d Castellón, Madrid, Girona, and Barcelona, Spain

Background: Food allergy may be life-threatening, and patients affected need to receive accurate diagnoses and treatment. Hazelnut has often been implicated as responsible for allergic reactions, and trace quantities can induce systemic reactions. Objective: The aim of this study was to evaluate the efficacy and tolerance of sublingual immunotherapy with a standardized hazelnut extract in patients allergic to hazelnut. Methods: This was a randomized, double-blind, placebo-controlled study. Inclusion criteria were a history of hazelnut allergy and positive skin prick test and double-blind placebo-controlled food challenge results. Patients were then randomly assigned into 2 treatment groups (hazelnut immunotherapy or placebo). Efficacy was assessed by double-blind, placebo-controlled food challenge results. Patients were then randomly assigned into 2 treatment groups (hazelnut immunotherapy or placebo). Efficacy was assessed by double-blind, placebo-controlled food challenge after 8 to 12 weeks of treatment. Blood samples were drawn for measurement of specific IgE, IgG4, and serum cytokines before and after treatment. Results: Twenty-three patients were enrolled and divided into 2 treatment groups. Twenty-two patients reached the planned maximum dose at 4 days. Systemic reactions were observed in only 0.2% of the total doses administered. Mean hazelnut quantity provoking objective symptoms increased from 2.29 g to 11.56 g (P = .02; active group) versus 3.49 g to 4.14 g (placebo; NS). Moreover, almost 50% of patients who underwent active treatment reached the highest dose (20 g), but only 9% in the placebo. Laboratory data showed an increase in IgG4 and IL-10 levels after immunotherapy in only the active group.

Conclusion: Our data confirm significant increases in tolerance to hazelnut after sublingual immunotherapy as assessed by double-blind, placebo-controlled food challenge, and good tolerance to this treatment. (J Allergy Clin Immunol 2005;116:1073-9.)

Key words: Sublingual immunotherapy, food immunotherapy, hazelnut allergy, biological standardization in mass units, double-blind, placebo-controlled food challenge, Cor a 1, Cor a 8

Food allergy, like other atopic disorders, appears to be on the increase. Moreover, food allergy remains a leading cause of anaphylaxis treated in emergency departments in several countries, and the general public has become increasingly aware of the problem.

In Europe, it has been estimated that hazelnut allergy affects between 0.1% and 0.5% of the population. In the tree nut group, hazelnut (Corylus avellana) is frequently implicated in allergic reactions. In a recent report, Pastorello et al analyzed the allergen profile of patients with hazelnut allergic reactions and positive double-blind, placebo-controlled food challenge (DBPCFC). All sera from patients recognized an 18-kd allergen; other major allergens recognized were at molecular weights of 47, 32, and 35 kd. The 18-kd allergen, Cor a 1, is a protein homologous to Bet v 1 allergen. Patients with severe allergic reactions to hazelnut showed IgE reactivity to a 9-kd allergen. This allergen was shown to be a hazelnut lipid transfer protein, registered as Cor a 8, and it is a major allergen for Spanish patients with allergy to hazelnut without birch pollen allergy.

Peanut and tree nuts are some of the most allergenic foods worldwide. In the United States, peanut and tree nut allergy affects approximately 1.1% of the population. In the United States, peanut and tree nut allergy affects approximately 1.1% of the population.

In the United States, peanut and tree nut allergy affects approximately 1.1% of the population. In the United States, peanut and tree nut allergy affects approximately 1.1% of the population.
possible despite efforts at avoidance in unexpected food products.9

The management of food allergies continues to consist of educating patients on how to avoid relevant allergens, recognize early symptoms of an allergic reaction in cases of accidental ingestion, and initiate the appropriate emergency therapy. Nevertheless, because of the high risk of life-threatening allergic reactions and the difficulty in avoidance of the culprit food, allergen-specific immunotherapy has been studied as a treatment option. However, subcutaneous immunotherapy was accompanied by a high rate of systemic reactions.10,11

The aim of this study was to evaluate the response to sublingual immunotherapy (SLIT) with hazelnut extract standardized in unit masses of major allergens, Cor a 1 and Cor a 8, in a large group of patients allergic to hazelnut. Efficacy was assessed by double-blind, placebo-controlled food challenges with hazelnut before SLIT and after 2 months of immunotherapy maintenance.

METHODS

Patients and study design

This was a randomized, double-blind, placebo-controlled, multicenter study. Patients provided written informed consent. The study was approved by the ethics committees of the participating hospitals. Potential subjects were preselected on the basis of a clear history of hazelnut food allergy and positive skin prick test to hazelnut. Definitive inclusion criteria then also included a positive DBPCFC with hazelnuts. Eligible patients could not be pregnant, and any asthma had to be under control. Systemic corticosteroids and β-blockers were prohibited before screening and throughout the study, and antihistamines and antidepressants were prohibited for 1 week and 2 weeks, respectively, before skin testing and oral food challenge. Patients with systemic diseases and/or oral infection or inflammation not compatible with the correct, easy, and safe administration of the treatment were excluded from the study.

Before the onset of treatment, a titrated skin prick test (SPT) with hazelnut extract was performed, and blood samples were drawn for in vitro standardization of a hazelnut extract in mass units of the hazelnut major allergens Cor a 1 and Cor a 8.5,6

Patients were later randomly assigned to 2 treatment groups (hazelnut extract or placebo). They then underwent a final DBPCFC 8 to 12 weeks later. At that time, a titrated SPT with hazelnut extract was repeated, and blood samples were again drawn for in vitro studies.

SPT

All patients underwent SPT performed according to standard procedure with timothy, parietaria, mugwort, olive, plane tree, birch, and hazel extracts (Diater Laboratorios, Madrid, Spain). A wheal size equal to or larger than the wheal obtained with histamine 10 mg/mL 15 minutes after testing was judged as positive.

Each patient was also skin prick tested in duplicate on the volar surface of the forearm with four 10-fold serial dilutions (10, 1, 0.1, and 0.01 mg/mL) of a raw hazelnut extract (Diater Laboratorios). Wheal areas were marked with a fine-tipped ball-point pen and transferred by transparent adhesive tape onto paper for subsequent planimetric evaluation and statistical analysis. Skin wheal areas were determined by computer scanning (AutoCAD; Autodesk, Inc, San Rafael, Calif) in all patients.

DBPCFC

Double-blind, placebo-controlled food challenges to hazelnut were performed in all patients. A single common protocol, based on a previous European multicenter study, was adhered to in the 3 centers.4 Patients who had systemic reactions or anaphylaxis were also challenged, but they were started with a modified schedule proposed by Alonso et al,12 after which they continued with the normal protocol, always within the double-blind, placebo-controlled schedule.

Allergen sources and extracts

Raw hazelnuts were used for oral challenges and SPT and as source material for production of allergen extracts. The extract was prepared as follows: nuts were defatted with diethyl ether in Soxhlet system and proteins extracted with PBS with 4% Tween 20 at a 50% (wt/vol) ratio by stirring for 1 hour at 4°C. The soluble fraction was separated by centrifugation at 22,000g for 20 minutes at 4°C. The hazelnut extract was then dialyzed against distilled water, filtered, and lyophilized.

The hazelnut extract was used for SPT, IgE, and IgG4 measurements. Recombinant hazelnut allergens recombinant (r) Cor a 1 (Biomay, Vienna) and rCor a 8 (Paul Ehrlich Institut, Langen, Germany) were used to obtain rabbit polyclonal antibodies α-rCor a 1 and α-rCor a 8, and biotinylated antibodies against native (n) Cor a 1 and nCor a 8 by affinity purification.13,14 Protein concentration was determined by the Bradford15 method.

Specific IgE

Specific IgE against hazelnut was measured by an enzyme allergosorbent test (Hyco/Immunomedics, Inc, Garden Grove, Calif) according to the manufacturer’s instructions. Levels higher than 0.35 IU/mL were considered positive (Hytec-specific IgE enzyme immunoassay, Hyco/Immunomedics Inc).

ELISA for specific IgE

nCor a 1 and nCor a 8–specific IgE antibodies were measured by an ELISA experiment similar to that described previously16,17 with some modification. In brief, plates were coated with 0.02 mg/mL of nCor a 1 and nCor a 8. A 50-μL serum sample from each patient (before and after immunotherapy) was incubated for 2 hours at room temperature. The bound IgE were detected by biotinylated mouse monoclonal anti-human IgE antibody (1:1000, 50 μL/well; Operon, Cuarte de Huerva, Zaragoza, Spain) followed by streptavidin–horseradish peroxidase–labeled antirabbit IgG antibody (1:5000, 50 μL/well; Sigma-Aldrich, St Louis, Mo). IgE binding was detected by using a solution of 3,3’5’-tetramethyl-benzidine (50 μL/well; Sigma), and optical densities were read at 450 nm.

Human serum cytokines

Human serum IL-4, IL-5, IL-10, TGF-β, and IFN-γ concentrations were measured by ELISA using reagent kits of BLK (Biolink 2000, Barcelona, Spain), according to the manufacturer’s instructions.
TABLE I. Concentration of vials and build-up treatment schedule*

<table>
<thead>
<tr>
<th>Day</th>
<th>Vial concentration (mg/mL)</th>
<th>Drops</th>
<th>Administered dose (mg)</th>
<th>Cumulative dose (mg)</th>
<th>Daily dose (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(F0) 6.625 × 10^{-11}</td>
<td>1</td>
<td>2 × 10^{-11}</td>
<td>2 × 10^{-11}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>2 × 10^{-10}</td>
<td>2 × 10^{-10}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(F1) 6.625 × 10^{-8}</td>
<td>1</td>
<td>2 × 10^{-8}</td>
<td>2 × 10^{-8}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>2 × 10^{-7}</td>
<td>2 × 10^{-7}</td>
<td>5.68 × 10^{-7}</td>
</tr>
<tr>
<td></td>
<td>(F2) 6.625 × 10^{-5}</td>
<td>1</td>
<td>2 × 10^{-5}</td>
<td>2 × 10^{-5}</td>
<td>3.68 × 10^{-7}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>2 × 10^{-4}</td>
<td>2 × 10^{-4}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(F3) 6.625 × 10^{-2}</td>
<td>1</td>
<td>0.02</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>0.26</td>
<td>0.26</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>(FA) 6.25</td>
<td>1</td>
<td>2.65</td>
<td>2.91</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>5.30</td>
<td>8.21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>7.95</td>
<td>16.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>10.60</td>
<td>26.76</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>10</td>
<td>26.50</td>
<td>53.26</td>
<td>150.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>66.25</td>
<td>119.51</td>
<td>188.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>121.9</td>
</tr>
</tbody>
</table>

*Doses were administered at 15-minute intervals.

SLIT
The active specific immunotherapy consisted of a biologically standardized hazelnut extract, graded in 5 strengths (F0, F1, F2, F3, FA) in glycerosaline solution. The protein concentration of each vial in milligrams per milliliter and the treatment schedule are detailed in Table I.

Placebo was prepared as saline solution in vials with exactly the same appearance, color, and taste, but without allergens, to guarantee the double-blind design of the trial. All vials contained 50% glycerin (vol/vol) and 0.3% phenol (wt/vol).

All doses of the build-up phase were administered in a hospital setting with the availability of complete resuscitation equipment and trained personnel; the patient was kept under constant observation after each administration and for at least 60 minutes after each day’s last administration.

Patients were instructed to keep the allergen solution in the mouth for at least 3 minutes and then to discharge (sublingual-discharge technique). The build-up phase was completed in 4 days according to a rush schedule. During the build-up phase, doses were administered at 15 minutes intervals.\(^{18}\) After the build-up phase, all patients followed the same daily maintenance schedule consisting of 5 drops of the maximum concentration performed at home. SLIT was administered from November 2004 to March 2005 before the birch and hazel pollen season. During the maintenance phase, patients attended the clinic every 21 days.

Statistics
Results were expressed as percentages for categorical variables and as mean or median (quartiles) for continuous variables. Proportions were compared by using the \(\chi^2\) test, and the \(t\) test and Mann-Whitney test were used to compare continuous variables between the 2 treatment groups. The effect of treatment on interleukin levels, TGF-\(\beta\), IFN-\(\gamma\), IgG\(_4\), and IgE was analyzed by generalized linear models (ANOVA) for repeated measurements. Significance level was 5%, and the statistical program used was SPSS 10.0 (1999; SPSS Inc, Chicago, Ill).

RESULTS
Study population
Forty-one adult patients age 18 to 60 were selected on the basis of a history of hazelnut allergy and positive SPT. DBPCFCs to hazelnut were performed in all of the patients and were positive in 29. All of these 29 patients (M/F, 17/12; mean age, 29.4 years; range, 19-53 years) were included to be randomized. Six of the 29 withdrew their consent for personal reasons, and 23 were divided into 2 groups of treatment: active group (n = 12) and placebo (n = 11). One patient of the treatment group withdrew consent for personal reasons on the first day of starting the immunotherapy.

The main demographic characteristics and allergy history of the randomized patients are summarized in Table II and in Fig 1. No statistical differences were found between placebo and active groups for all of the parameters.

Table II and in Fig 1. No statistical differences were found between placebo and active groups for all of the parameters.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Active treatment (n = 12)</th>
<th>Placebo (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 3 (25%)</td>
<td>Female 7 (63.3%)</td>
</tr>
<tr>
<td>Age, y, mean (range)</td>
<td>29.2 (19-53)</td>
<td>29.6 (19-42)</td>
</tr>
<tr>
<td>Hazelnut specific IgE, kU/L, mean (quartiles)</td>
<td>5.34 (0.45-9.10)</td>
<td>6.41 (4.02-9.91)</td>
</tr>
<tr>
<td>Associated pollen allergy</td>
<td>8 (66.6%)</td>
<td>10 (81.8%)</td>
</tr>
<tr>
<td>Grass</td>
<td>5 (41.6%)</td>
<td>5 (44.4%)</td>
</tr>
<tr>
<td>Mugwort</td>
<td>6 (50%)</td>
<td>5 (44.4%)</td>
</tr>
<tr>
<td>Plane tree</td>
<td>5 (41.6%)</td>
<td>4 (36.3%)</td>
</tr>
<tr>
<td>Olea</td>
<td>5 (41.6%)</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td>Parietaria</td>
<td>0 (0%)</td>
<td>4 (36.3%)</td>
</tr>
<tr>
<td>Birch</td>
<td>2 (16.6%)</td>
<td>3 (27.2%)</td>
</tr>
<tr>
<td>Hazel</td>
<td>1 (8.3%)</td>
<td>3 (27.2%)</td>
</tr>
<tr>
<td>Hazelnut allergy symptoms</td>
<td>6 (54.5%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>Oral allergy syndrome</td>
<td>5 (45.5%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0</td>
<td>4 (36.5%)</td>
</tr>
</tbody>
</table>

*No statistical differences were found between placebo and active group for all of the parameters.
hazelnut ingestion; and levels of serum specific IgE to hazelnut, Cor a 1, or2 Cor a 8.

SPT and hazelnut extract standardization

Each patient was also skin prick tested with a raw hazelnut extract to determine the in vivo reactivity of the extract. A concentration of 2.69 mg/mL hazelnut extract was calculated to cause a wheal size equal to that obtained with histamine. For this raw hazelnut extract, 1 mg corresponded to 1.84 mg of the allergen Cor a 8 and 2.88 mg of the allergen Cor a 1 (data not shown).

Oral food challenges: efficacy assessment

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

The mean quantity of hazelnut provoking objective symptoms increased from 2.29 g to 11.56 g (P = .02) in the active group and from 3.49 g to 4.14 g in the placebo group (without statistical significance; Fig 2). Furthermore, almost 50% of patients (5/11) who underwent hazelnut SLIT reached the highest level (20 g) compared with 9% (1/11) of the placebo group (Fig 1). This beneficial effect has been observed in patients with local reactions and also in patients with systemic reactions after hazelnut ingestion.

Tolerance and adverse reactions: safety assessment

All patients reached the planned maximum dose of 25 drops from the most concentrated vial in 4 days. A total of 1466 doses were administered: 309 during the build-up phase and 1157 during maintenance.

Systemic reactions were observed in 0.2% (3 reactions/1466 doses). They appeared only during the build-up phase, and only antihistamines were required for their control. One facial urticaria occurred in the placebo group and 2 reactions in 1 patient of the active group: skin pruritus a few minutes after the last dose of the second day and 1 delayed urticaria several hours after the last dose of the third day, probably associated with exercise (the patient had urticaria after 1 hour of exercise).

Local reactions, mainly in the form of immediate oral itching, were observed in 7.4% (109 reactions/1466 doses). Four patients in the active group reported abdominal pain several hours after the ingestion on 1 occasion each and only during the build-up phase. All local reactions during the maintenance phase were also oral itching, and all were in the same patient.

Laboratory parameters

Hazelnut-specific IgE levels did not differ between groups before treatment but were lower in both groups after treatment, with no statistical significance both between both groups and within the same group (data not shown).

As expected, because patients selected came from birch-free areas, prevalence to Cor a 1–specific IgE was low (22.14%), whereas Cor a 8–specific IgE was present in 50% of the patients selected (Fig 1). Regarding Cor a 1 and Cor a 8 specific IgE, there were no differences between groups before treatment; however, lower rates were observed in both groups after treatment, with no statistical significance within and between both groups (data not shown).

Regarding hazelnut-specific IgG4 levels, no statistical significance was found between the studied groups; however, in the active group, an increase in mean IgG4 levels from 7.34 allergen units (AU)/mL to 9.84 AU/mL (P < .05) was observed (Fig 3).
An increase in IL-10 levels after treatment was found only in the active group, rising from 1.62 pg/mL to 2.24 pg/mL ($P < .05$). No differences were observed between the placebo and active groups (Fig 3).

We were unable to obtain results of the other cytokines because of the low sensitivity of the tests used.

**DISCUSSION**

Food allergy is potentially life-threatening, and there is no known curative treatment to date. The recommended treatment for individuals with known anaphylactic reactions to foods is avoidance and use of injected epinephrine as soon as they become aware of an inadvertent ingestion. However, avoidance of accidental ingestion is difficult when eating away from home, and many people with known food sensitivity do not routinely carry epinephrine with them. Therefore, an improved treatment is needed for anaphylactic reactions to foods.

Previous studies have used subcutaneous peanut-specific immunotherapy and have showed a decrease in SPT reactions and decreased sensitivity to peanut ingestion. However, this therapy was accompanied by a high rate of systemic reactions.

Oral desensitization to foods has been reported in numerous limited series but with varying results. Although oral desensitization is an attractive procedure, well-designed studies are required. Other novel immunotherapeutic approaches have been reported with good results: anti-IgE therapy, Chinese herbal medicines, the uses of subcutaneous birch pollen immunotherapy in patients with oral allergy syndrome, and other laboratory studies with animal models.

Food immunotherapy has recently been suggested again as a food allergy treatment in 2 case report publications: one, oral immunotherapy in patients allergic to peanut, and the other, sublingual immunotherapy in a case of anaphylactic reaction to kiwi. Nevertheless, double-blind, placebo-controlled randomized studies are required to confirm these results.

The aim of this study was to evaluate a large group of patients allergic to hazelnut for their response to a sublingual immunotherapy with a biological extract standardized in unit mass of major allergens. In the current study, efficacy was assessed by DBPCFC with hazelnut performed before and after 2 to 3 months of maintenance immunotherapy.

Our clinical data confirm significant increases in the threshold of sensitivity to hazelnut allergen to a level that should translate into at least partial protection against most unintended ingestion of hazelnuts. Moreover, almost 50% of the patients who underwent active treatment tolerated the highest dose of 20 g, about 15 to 20 hazelnuts, which constitutes a high amount of hazelnuts that should translate into enough protection against most unintended ingestion of hazelnuts.

Surprisingly, 1 patient (Cor a 1 sensitive) who received placebo tolerated the same highest dose of 20 g, and another patient who received placebo, with the same characteristic allergen profile, increased his tolerance from 2 to 10 g hazelnut (Fig 1). These patients presented oral allergy syndrome in the DBPCFC and had hazel pollinosis. Although the second challenge test was performed before hazel pollen season, it is tempting to speculate on the possibility of a seasonal variation in hazelnut pollen–dependent allergy.

Mean provocative dose in a previous study ranged from 1.4 and 2.7 g in patients with hazelnut allergy from Zurich and Copenhagen to 15.3 g in patients from Milan. Nevertheless, the current study is conducted in a birch-free area, contrary to Zurich, Copenhagen, and Milan which are in an area of birch pollen exposure. We found a mean provocative hazelnut dose similar to data observed in Zurich and Copenhagen; however, Cor a 8 was described as a major allergen in Milan and also in the geographical area of the current study.

Regarding safety aspects, in the current study, we observed very good tolerance because the rate of side effects was very low and appeared in both groups of treatment. Although the sublingual-discharge technique seems to lead to better tolerance than the sublingual-swallow
technique, mainly for gastrointestinal symptoms, 4 patients reported abdominal pain. Nevertheless, a relative high rate of gastrointestinal symptoms has been reported with sublingual-swallow immunotherapy with latex, \(^{1,18}\) and also with a high dose of parietaria extract.\(^{30}\)

Our data also confirm regional differences in sensitization pattern reported for other birch pollen–related foods.\(^{5,6}\) In a previous study conducted from Germany in a group of patients with hazelnut allergy and birch pollen allergy, the majority were sensitized to the pollen-related hazelnut allergen Cor a 1.\(^{31}\) In other studies, Cor a 8 (hazelnut lipid transfer protein) was significant for a majority of patients recruited in Spain or Northern Italy.\(^{5,6}\) In this study, we partially repeat the same results. Nevertheless, some patients of the current study with systemic reactions did not react to Cor a 1 or to Cor a 8, suggesting the possible presence of other important pollen-related or nonpollen-related hazelnut allergens, such as Cor a 9, an 11S globulin related to hazelnut-induced systemic reactions.\(^{32}\)

Immunotherapy is capable of modifying the immunologic response to the offending allergen in the earliest stages. The subcutaneous route of administration has been well established, and its mechanisms of action have been extensively investigated.\(^{33}\) However, the clinical use of SLIT is recent. Therefore, some aspects have not been fully investigated, and data on the mechanisms of action are few and contradictory. A recent prospective study of SLIT in children with allergic rhinitis found positive effects on rescue and medication use but observed no significant effects on in vitro T-cell immune responses or immunoglobulins;\(^{34}\) such effects were demonstrated in another double-blind trial\(^{35}\) and in a case report of a patient with severe anaphylaxis caused by kiwi allergy treated with sublingual kiwi immunotherapy with good tolerance and efficacy.\(^{27}\)

In the current study, we observed, on the one hand, a decrease in specific IgE levels in both treatment groups and on the other hand, an increase in specific IgG4 and IL-10 levels only in the active group, suggesting the possibility of immunoregulation through regulatory T cells producing IL-10 and the oral mucosa Langerhans cells.\(^{36-38}\)

In conclusion, this randomized and controlled clinical trial of sublingual immunotherapy performed in patients allergic to hazelnut has found significant increases in the threshold of sensitivity to hazelnut allergen, as assessed by DBPCFC after hazelnut SLIT, and good tolerance to this treatment. This beneficial effect has been observed both in local reactions and in systemic reactions after hazelnut ingestion. Nevertheless, further studies and others on the long-term efficacy of SLIT with food extracts are required.

We thank Dr Stephan Scheurer from the Paul-Ehrlich Institut (Langen, Germany) for providing Cor a 8. We acknowledge Teresa Pitiño, Dolores Sánchez, Inés Saz, Maríoh Aguilar, Josefa Fuentes, and Magdalena Sánchez for technical assistance. We also thank Ms Christine O’Hara for English review of the manuscript.

REFERENCES