

Oral Immunotherapy for Hazelnut Allergy: A Single-Center Retrospective Study on 100 Patients



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What is already known about this topic? Oral immunotherapy raises the allergen threshold in children with IgE-mediated allergy to peanut, cow's milk, and eggs. However, this approach has never been evaluated for hazelnut, a major cause of food allergy in Europe.

What does this article add to our knowledge? This is the first study to show that hazelnut oral immunotherapy may lead to desensitization and increase the allergen threshold safely in IgE-mediated allergic children.

How does this study impact current management guidelines? This study provides initial evidence for the use of hazelnut immunotherapy in IgE-mediated allergic children. These findings may be applied to the design of a randomized controlled clinical trial.

BACKGROUND: Oral immunotherapy (OIT) protects patients with IgE-mediated food allergies from food-induced allergic reactions due to accidental exposure and may improve their quality of life. This approach has never been evaluated for hazelnut, a major cause of food allergy in Europe.

OBJECTIVE: To determine the proportion of hazelnut-desensitized patients after 6 months of OIT and to identify predictors of successful desensitization.

METHODS: In a retrospective single-center study, we included patients younger than 18 years who underwent at least 6 months of hazelnut OIT for IgE-mediated allergy, defined by history of hypersensitivity reaction after hazelnut ingestion, positive hazelnut skin prick test result or specific IgE, and positive double-blind, placebo-controlled food challenge. Patients able to tolerate 1635 mg of hazelnut protein (~8 hazelnuts) were considered to be hazelnut desensitized. We determined the proportion of desensitized patients after 6 months of OIT,

searched for associations between baseline variables and successful desensitization, and estimated the frequency and severity of OIT-related adverse reactions.

RESULTS: One hundred patients were included (64% males; median age, 5 years). History of severe reactions was noted in 7% of cases. At 6 months, the proportion of desensitized patients was 34% (95% CI, 25-44). The median eliciting dose (defined as the amount of hazelnut protein provoking a hypersensitivity reaction during the double-blind, placebo-controlled food challenge) increased from 106 mg (interquartile range, 51-249) at baseline to 523 mg (interquartile range, 190-1635) after 6 months of OIT ($P < .0001$). With longer therapy, the proportion of desensitized patients increased. Using multivariate analysis, successful desensitization was associated with older age (odds ratio [OR], 1.5; 95% CI, 1.2-2.2), smaller hazelnut skin prick test wheal diameter (OR, 0.61; 95% CI, 0.4-0.8), lower hazelnut specific IgE level (OR, 0.86; 95% CI, 0.72-0.98), and absence of cashew allergy (OR, 0.42; 95% CI, 0.12-0.64). Adverse reactions occurred in 30% of patients; none were severe.

CONCLUSIONS: In a cohort of 100 patients aged 3 to 9 years, our results show for the first time that hazelnut OIT is associated with hazelnut desensitization and may be safe in most patients undergoing this therapy. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:704-9)

Key words: Oral immunotherapy; Hazelnut; Tolerance; Desensitization; Food allergy

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INTRODUCTION

In Europe, the prevalence of self-reported food allergy (FA) is up to 5.9%,¹ affecting 17 million people, of whom 3.5 million are younger than 25 years. In children, FA is a major cause of anaphylaxis, a severe life-threatening allergic reaction. Although

Abbreviations used

DBPCFC- Double-blind, placebo-controlled food challenge

ED- Eliciting dose

EoE- Eosinophilic esophagitis

FA- Food allergy

OFC- Open food challenge

OIT- Oral immunotherapy

sIgE- Specific IgE

SPT- Skin prick test

hazelnut is not the most common cause of FA in the United States, it is one of the most frequently implicated in Europe^{2,3} where it is widely consumed in food products. Indeed, hazelnut accounts for 9.3% of FA cases in European adults⁴ and is the third leading cause of early food sensitization in the pediatric population after cow's milk and egg.³ Hazelnut could be responsible for 5% of food-induced anaphylactic events, less commonly than cow's milk (29%) and hen's eggs (25%), and more commonly than peanut (4%).⁵ Moreover, FA is a chronic condition with only 9% of patients outgrowing tree nut allergy.⁶

The current management of FA consists of strict avoidance of the allergenic food, provision of an emergency management plan in the event of an accidental exposure or reaction, and prescription of adrenaline autoinjectors in the case of anaphylaxis.⁷ In some patients, the fear of accidental exposure may lead to impaired health-related quality of life and food neophobia, that is, fear of unfamiliar food.⁸ Despite patient education programs and improvement in food labeling, the rate of accidental ingestion remains high, with 25% to 47% of patients having an allergic reaction.⁹⁻¹¹

Quality of life and safety (protection from severe or life-threatening reactions to unintended exposures) are essential goals for the treatment of patients with FA. The issues of food-related anxiety, dietary restriction, and social limitations must also be addressed.^{12,13} Oral immunotherapy (OIT), developed as a means to achieve desensitization, involves regular ingestion of small amounts of the culprit food. This strategy has been shown to be effective in raising the allergen threshold dose with demonstrated safety in children with IgE-mediated FA to peanut,^{14,15} cow's milk,¹⁶ and eggs.¹⁷ We report here the proportion of hazelnut-desensitized patients and predictors of successful desensitization in children who have undergone an OIT program for hazelnut.

METHODS

Study population

We conducted a single-center retrospective study in an academic hospital center. All patients who received 6 months of hazelnut OIT were considered for inclusion. Inclusion criteria were as follows: (1) age less than 18 years; (2) IgE-mediated hazelnut allergy defined by convincing history of hazelnut hypersensitivity, positive hazelnut skin prick test (SPT) wheal diameter more than 3 mm and/or specific IgE (sIgE) more than 0.35 kUA/L, and a positive double-blind, placebo-controlled food challenge (DBPCFC); (3) participation in at least 6 months of a hazelnut OIT protocol; and (4) performance of an open food challenge (OFC) after 6 months of hazelnut OIT. Exclusion criteria were (1) age more than 18 years, (2) interruption of OIT protocol during the first 6 months, (3) absence of OFC at 6 months, and (4) lack of consent to be included in the study (Figure 1).

The study was approved by our institutional review board and the research and ethics committee of the Catholic Institute of Lille

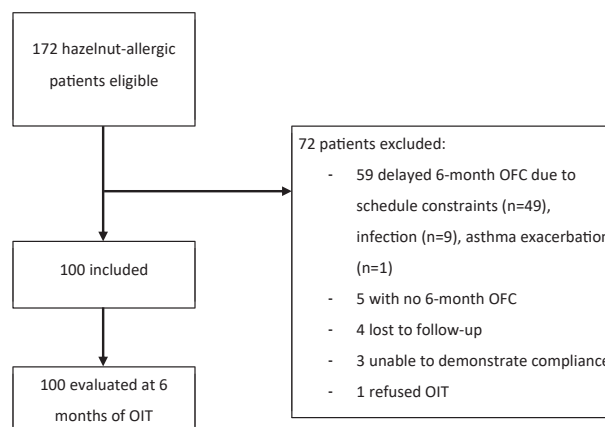


FIGURE 1. Flowchart.

Hospital Group and reported to the National Commission of Informatics and Freedoms. Both parents and children received written information and agreed to the use of their data.

Sociodemographic, clinical, and biological data at baseline and after 6 months of OIT were collected. OIT-related side effects after 6 months of OIT were gathered at the time of inclusion using a standard homemade survey (see this article's Online Repository at www.jaci-inpractice.org).

Procedures

Oral food challenge. A DBPCFC was performed at the time of diagnosis, and an OFC was performed after 6 months of OIT. Except for placebo administration, the protocol was the same for both challenges, with hazelnut or placebo given in boiled apple as a matrix. During the DBPCFC, patients received ground hazelnut or placebo on 2 different days in randomized order. The hazelnut dose escalation protocol is detailed in Table E1 in this article's Online Repository at www.jaci-inpractice.org. In summary, the dose started at 0.7 mg of hazelnut protein. Then, increasing doses (twice the cumulative dose) were administered every 20 minutes to a maximum cumulative dose of 1635 mg or until the occurrence of a hypersensitivity reaction. In the event of an allergic reaction, the DBPCFC was stopped and, if necessary, appropriate treatment was administered. The dose that triggered a hypersensitivity reaction was designated the eliciting dose (ED).

Hazelnut OIT. As part of standard practice in our center, hazelnut OIT was offered to all patients with a proven IgE-mediated hazelnut allergy, unless there was a contraindication (uncontrolled asthma or inability to demonstrate compliance) or unwillingness to follow an OIT protocol. Ground hazelnut was administered daily. The initial dose of hazelnut OIT was one-tenth of the ED; then, the doses were increased monthly without exceeding half the baseline ED. For patients not desensitized at 6 months, a new dose escalation program was initiated on the basis of ED of the 6-month OFC. The same schema was repeated every 6 months until desensitization was achieved. When patients demonstrated tolerance of a cumulative dose of 1635 mg hazelnut with no reaction, they were considered desensitized, and subsequently continued on a maintenance dose of 2 whole hazelnuts (416 mg hazelnut protein) 3 times a week. In case of acute intercurrent illness occurring during OIT, the hazelnut dose was not given for 5 days to prevent adverse reactions. The OIT protocol is detailed in Table E2 in this article's Online Repository at

TABLE I. Baseline clinical and biological characteristics

Variable	n	Value
Age (y), median (IQR)	100	5 (3-9)
Sex: male, n (%)	100	64 (64)
Comorbidities, n (%)	100	
Asthma		56 (56)
Atopic dermatitis		64 (64)
Allergic rhinitis		31 (31)
History of hazelnut hypersensitivity, n (%)	80	80 (80)
Urticaria, n (%)		33 (32.6)
Gastrointestinal, n (%)		5 (4.9)
Angioedema, n (%)		36 (35.5)
Laryngeal edema, n (%)		5 (4.9)
Anaphylaxis, n (%)		2 (1.97)
Atopic dermatitis assessment, n (%)	20	20 (20)
Sensitization to aeroallergens, n (%)	89	
House-dust mites		56 (62.9)
Birch pollen		17 (19.1)
Other pollens		40 (44.9)
Sensitization to trophallergens, n (%)	100	
Peanut		28 (28)
Cashew		31 (31)
Pistachio		24 (24)
Nuts		9 (9)
Pecan nuts		7 (7)
Brazil nuts		3 (3)
Macadamia nuts		3 (3)
Egg		11 (11)
Wheat		1 (1)
Wheal diameter of hazelnut SPT (mm), median (IQR)	94	10 (7-12)
Hazelnut sIgE (kUA/L), median (IQR)	90	5.5 (1.7-20.9)
Cor.a.1 sIgE (kUA/L), median (IQR)	78	0 (0-0.5)
Patients with positive Cor.a.1 IgE (%)		29%
Cor.a.8 sIgE (kUA/L), median (IQR)	75	0 (0-1.52)
Patients with positive Cor.a.8 IgE (%)		32%
Cor.a.9 sIgE (kUA/L), median (IQR)	76	1.75 (0.53-3.9)
Patients with positive Cor.a.9 IgE (%)		83%
Cor.a.14 sIgE (kUA/L), median (IQR)	77	2.53 (0.45-13.4)
Patients with positive Cor.a.14 IgE (%)		83%
ED (mg of hazelnut protein), median (IQR)	100	106 (51-249)

(continued)

TABLE I. (Continued)

Variable	n	Value
Stage of severity of the elicited reaction, n (%)	100	
1		77 (77)
2		22 (22)
3		1 (1)

www.jaci-inpractice.org. Patients and parents received a written protocol, a personalized action plan, and an emergency kit containing an adrenaline autoinjector, the use of which was explained during a therapeutic education session.

Outcome

The primary outcome was the proportion of desensitized patients after 6 months of OIT. Desensitization was defined as no reaction during hazelnut OFC with a cumulative dose of 1635 mg, roughly equal to 8 hazelnuts, and an amount of hazelnut unlikely to be accidentally ingested.

Secondary outcomes were change in ED and SPT wheal diameter after 6 months of OIT, any association between successful desensitization at 6 months and baseline variables, frequency and type of nonsevere and severe adverse reactions, the latter being defined by the need for use of adrenaline, hospitalization, or death.

Desensitization was also recorded in subgroups of patients who continued OIT for 12, 18, or 24 months (see [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org).

Statistical analysis

Characteristics of the study population were described using median and interquartile range (IQR) for quantitative variables, and number (percentage) for qualitative variables. Comparisons between baseline and 6-month values were assessed using a nonparametric Wilcoxon rank sum test.

To assess associations between hazelnut desensitization, as the dependent variable and baseline patient characteristics, univariate and multivariate logistic regression analyses were performed. For multivariate analysis, baseline variables associated with desensitization at 6 months in univariate analysis with a *P* value greater than or equal to 0.2 were introduced into a multivariate logistic regression model. The suitability of the model was checked with both the Hosmer-Lemeshow test and the model's predictive quality. Results are expressed as odds ratio and 95% CI. The threshold for statistical significance was .05. Statistical analyses were performed with R software (version 3.4.2.).

RESULTS

Baseline characteristics

Among the 172 hazelnut-allergic patients referred to our center between January 2012 and January 2017, 168 started a hazelnut OIT program and 100 were included in the study (64% males; median age, 5 years [IQR, 3-9]) ([Figure 1](#)). The main reason for noninclusion was delayed 6-month OFC (*n* = 59) due to schedule constraints (*n* = 49), infection (*n* = 9), and asthma exacerbation (*n* = 1). Baseline characteristics are presented in [Table I](#). Comorbidities included asthma (56%), atopic dermatitis (64%), and allergic rhinitis (31%). Patients' hazelnut-related

TABLE II. Baseline variables associated with hazelnut desensitization at 6 mo of OIT in univariate and multivariate analysis

Variable	Odds ratio (95% CI)	
	Univariate analysis	Multivariate analysis
Age at diagnosis (n = 100)	1.1 (1-1.2)	1.5 (1.2-2.2)
Male (n = 100)	1 (0.44-2.5)	
Severity of hazelnut allergy reaction (n = 100)	1 (0.6-1.9)	
Asthma (n = 100)	0.69 (0.3-1.6)	
Atopic dermatitis (n = 100)	1 (0.44-2.5)	
Allergic rhinitis (n = 100)	1.7 (0.68-4)	
Sensitization to aeroallergens (n = 89)		
House-dust mites	0.85 (0.35-2.1)	
Birch pollens	1.7 (0.56-4.9)	
Other pollens	1 (0.43-2.5)	
Sensitization to trophallergens (n = 100)		
Peanut	1.1 (0.43-2.7)	
Cashew	0.19 (0.053-0.56)	0.42 (0.12-0.64)
Pistachio	0.21 (0.046-0.67)	
Other nuts	0.88 (0.31-2.4)	
Baseline wheal diameter of hazelnut SPT (n = 94)	0.66 (0.53-0.78)	0.61 (0.4-0.8)
Hazelnut sIgE (n = 90)	0.98 (0.97-0.99)	0.86 (0.72-0.098)
Cor a 14 IgE (n = 77)	0.94 (0.87-0.99)	
ED (n = 100)	2.7 (2.7-2.7)	
Grade 1 of severity during the baseline DBPCFC (n = 100)	0.13 (0.021-0.5)	

Bold indicates statistical significance (95% CI, odds ratio excluding 1).

hypersensitivity reactions included urticaria (32.6%), angioedema (35.5%), laryngeal edema (4.9%), anaphylaxis (2%), or gastrointestinal symptoms with vomiting and abdominal pain (4.9%). In 20% of patients, hazelnut allergy was suspected because of hazelnut sensitization discovered during assessment of atopic dermatitis in patients who had never eaten hazelnut and was confirmed by a positive DBPCFC. The median SPT wheal diameter was 10 mm (IQR, 7-12), the median sIgE for hazelnut was 5.5 kUA/L (IQR, 1.7-20.9), for *Cor a 1* was 0 kUA/L (IQR, 0-0.5), for *Cor a 9* was 1.75 kUA/L (IQR, 0.53-3.9), and for *Cor a 14* was 2.53 kUA/L (IQR, 0.45-13.4). The median baseline ED was 106 mg (IQR, 51-249) of hazelnut protein (equivalent to half a hazelnut). According to the Sampson classification,¹⁸ the severity of the allergic reaction occurring during the baseline DBPCFC was grade 1 in 77%, grade 2 in 22%, and grade 3 in 1% of patients.

Aeroallergen sensitization was found in 72 of the 89 patients tested (81%) against house-dust mites (63%), birch pollen (19%), and other pollens (45%). A food allergen cosensitization was found in 61% of the patients including sensitizations to peanut (28%) and to tree nuts, with a predominance of cashew (31%) and pistachio (24%).

Proportion of hazelnut-desensitized patients at 6 months of OIT

After 6 months of OIT, the proportion of desensitized patients (absence of allergic reaction after a cumulative dose of

1635 mg hazelnut protein during OFC) was 34% (95% CI, 25-44). The median ED at 6 months was 523 mg (IQR, 190-1635) hazelnut protein (equivalent to 2.5 hazelnuts), which was an average increase of 417 mg (IQR, 139-1386) from baseline ($P < .0001$). For the 66 nondesensitized patients at 6 months, the median ED was 259 mg (IQR, 106-523) (equivalent to 1 hazelnut). The median SPT wheal diameter was 5.5 mm (IQR, 2-10) after 6 months of OIT, an average decrease of 5 mm (IQR, 2-7) from baseline. Data from the 59 subjects who had a delayed 6-month OFC are available in Table E3 in this article's Online Repository at www.jaci-inpractice.org.

Baseline variables associated with hazelnut desensitization at 6 months

In univariate analysis, desensitization to hazelnut was associated with older age, higher baseline ED, smaller SPT wheal diameter, lower hazelnut and Cor a 14 sIgE, nonsevere hypersensitivity reaction during DBPCFC, no occurrence of side effect, and the absence of allergy to cashew and pistachio. In multivariate analysis, variables associated with desensitization were older age, smaller baseline SPT wheal diameter, lower hazelnut sIgE level, and absence of cashew allergy (Table II).

Side effects

Seventy-six patients answered the survey about OIT side effects. Among them, 70% had no side effects ($n = 53$) and 30% had at least 1 nonsevere side effect (urticaria, 6.6%; oral angioedema, 1.3%; gastrointestinal symptoms including abdominal pain and nausea, 23.7%). No patient developed eosinophilic esophagitis (EoE) or symptoms suggestive of EoE. No serious side effects were reported. The absence of side effects was associated with desensitization at 6 months of OIT in univariate analysis (odds ratio, 1.7; 95% CI, 1.2-1.9) (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

Our results show that in a population of young hazelnut-allergic patients, 6 months of hazelnut OIT was associated with the ability to tolerate 1635 mg of hazelnut protein in one-third of patients. Our findings also show that baseline predictors of successful desensitization were older age, smaller SPT wheal diameter, lower level of hazelnut sIgE, and absence of cashew allergy. Finally, in our study, hazelnut OIT was not associated with severe reactions.

There is currently no cure for FA, and OIT is not intended to be curative. Raising the reactive threshold to the allergenic food is a key outcome of this treatment. Standard prevention of allergic reactions depends on strict avoidance of hazelnut, including hazelnut that may be a hidden ingredient in foods. Avoidance is often complicated by inconsistent food labeling and variable advice from food providers and manufacturers.^{9,11} Fear of accidental ingestion, severe reactions, and death drives down quality of life, limits social activity, and contributes to the development of behavioral disorders.⁸ There is no established threshold for OFC that characterizes desensitization or true tolerance. For evaluation of hazelnut OIT efficacy, we chose a cumulative challenge dose of 1635 mg hazelnut protein, because this quantity is equivalent to 8 whole hazelnuts, which is not an amount that is likely to be ingested inadvertently. A similar definition of desensitization was previously proposed in a randomized controlled trial evaluating the efficacy of OIT in peanut

allergy.¹⁴ In our study, more than one-third of the patients tolerated a challenge with 1635 mg hazelnut protein after 6 months of OIT. Patients who were not considered desensitized (66%) (ie, could not tolerate a challenge with 1635 mg of hazelnut protein) had at least doubled their baseline ED at 6 months (median ED, 259 mg [equivalent to 1 whole hazelnut]; IQR, 106–523). This is a clinically relevant increase in hazelnut tolerance, and may indicate protection from accidental exposures to small amounts of hazelnut that can occur in food products. After the treatment, patients can eat quantities of hazelnuts above the levels present in contaminated meals, allowing them to eat more freely and enjoy a reduction in social restrictions.

Stopping OIT may lead to loss of desensitization and return to the previous threshold dose reactivity.¹⁹ In a study of peanut allergy, 42% of patients lost the tolerance induced by peanut OIT after 8 weeks of a strict elimination diet.⁹ For this reason, we encourage our patients to continue hazelnut consumption indefinitely. It is probable that long-term hazelnut protein ingestion will be needed to provide continued protection from accidental exposure. We found in a subgroup analysis that long-term hazelnut OIT increases the rate of desensitization success, even in patients who were not desensitized after 6 months of OIT (Figure E1).

Several studies have shown that age influences the acquisition of food tolerance during an OIT protocol. In the STOP II study evaluating the effectiveness of peanut OIT, older age was associated with failure of desensitization in a population with a median age of 12.4 years.¹⁴ In contrast, our results found older age to be associated with successful hazelnut OIT in a younger population with a median age of 5 years. Altogether, these results suggest that the ideal age range to start OIT could be between 5 and 12.4 years. This would be consistent with the Burks et al¹⁷ study showing no association between age and successful egg OIT in a population with a median age of 7 years.

Allergic comorbidities such as asthma and atopic dermatitis characterize a particular phenotype of severe FA,²⁰ but are not associated with failure of OIT. Consistently, in our study, there was no association between FA comorbidities and successful desensitization, provided that patients with uncontrolled asthma were not eligible for OIT.²¹ Finally, a small SPT wheal diameter and a low sIgE level are independent biomarkers of successful OIT, as shown in our results and in accordance with results from studies of peanut²² and cow's milk OIT.¹⁶ It was notable that in our study, the profile of sensitization to recombinant hazelnut allergens did not predict the outcome of hazelnut desensitization after 6 months of OIT. In particular, a higher level of Cor a 14 IgE, which is associated with severe anaphylactic reaction,^{23,24} was not associated with desensitization failure. We also found in our study that cashew allergy was related to unsuccessful desensitization after 6 months of OIT. Cashew has been shown to cross-react with hazelnut²⁵ and to produce severe hypersensitivity reactions.²⁶ We therefore assume that the profile of IgE sensitization underlying the hazelnut-cashew cross-allergy is associated with poorer tolerance to OIT, leading to hazelnut desensitization failure.

Finally, although a retrospective design and recall bias may have limited our ability to assess the rate of adverse events, our results show that hazelnut OIT is safe. Reported side effects, which occurred in less than one-third of patients, were benign and easily managed at home. As in our study, long-term buildup protocol for OIT appears to be safe.¹⁹ Although the literature has reported contrasting data on the frequency and severity of food

OIT-related side effects, protocols using slow dose escalation and personalized regimens (doses adjusted on the basis of patient's reactive threshold) are usually associated with benign side effects.^{27–29} Furthermore, patients were carefully selected for their ability to follow the OIT protocol (3 patients were excluded because of their inability to demonstrate compliance) and were systematically enrolled in education programs. Some studies have highlighted the occurrence of chronic gastrointestinal symptoms or EoE during OIT.³⁰ In our study, there were no patients who developed EoE. Educating patients undergoing the OIT protocol to avoid and recognize cofactors for reactions to foods, such as stress, certain medications (nonsteroidal anti-inflammatory drugs, codeine), alcohol, rigorous exercise, and fever, can enhance the safety and tolerability of OIT.^{31,32}

Interpretation of these findings is limited by our single-center study population. In addition, the population included in the study corresponds to 58% of the hazelnut-allergic patients followed in our center. These results therefore may not be generalizable. The main strength of our study is that it provides the first descriptive data on 6-month hazelnut OIT in a large population of children and identifies cashew sensitization as a potential predictor of unsuccessful hazelnut desensitization.

CONCLUSIONS

Our results suggest that hazelnut OIT may be effective and safe in children with IgE-mediated FA to hazelnut. There is a need for randomized trials to confirm the efficacy, safety, feasibility, and ideal protocol of hazelnut OIT and prospective long-term tolerance monitoring studies.

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ONLINE REPOSITORY

Data on adverse reactions were collected retrospectively using a homemade survey, which included 3 questions to the patients' parents:

1. Did the child experience any of these reactions since he started the OIT protocol?

Gastrointestinal symptoms (abdominal pain, nausea, vomiting)
☐ Yes ☐ No

Severe side effect (dysphagia, dysphonia, dyspnea, throat tightness)

☐ Yes ☐ No

Oral pruritus ☐ Yes ☐ No

Oral angioedema ☐ Yes ☐ No

Urticaria ☐ Yes ☐ No

If answered yes, was the child in any of the following situations when he or she experienced adverse reactions?

- taking medication, in particular nonsteroidal anti-inflammatory drugs and aspirin ☐ Yes ☐ No
- infection ☐ Yes ☐ No
- asthma exacerbation ☐ Yes ☐ No
- gastrointestinal disease ☐ Yes ☐ No
- exercise ☐ Yes ☐ No

2. Was the child hospitalized or admitted to the emergency room for any reason since he or she started the OIT protocol?

☐ Yes ☐ No

If answered yes, was he or she admitted for a condition related to his or her food allergy?

☐ Yes ☐ No.

3. Did the parents use the adrenaline autoinjector since the child started the OIT protocol?

☐ Yes ☐ No

If answered yes, how many times was the adrenaline autoinjector used?

TABLE E1. DBPCFC and OFC protocol

Time (min)	Dose (mg of hazelnut*)	Cumulative dose (mg of hazelnut*)	Dose (mg of hazelnut protein)	Cumulative dose (mg of hazelnut protein)
0	5	5	0.7	0.7
20	10	15	1.39	2.2
40	50	65	6.95	9
60	100	165	13.9	23
80	200	365	27.8	50
100	400	765	55.6	106
120	600	1365	83.4	189
140	900	2265	125.1	314
160	1500	3765	208.5	523
180	3000	6765	417	840
200	5000	11765	695	1635

*Or placebo equivalent-dose for DBPCFC.

TABLE E2. OIT protocol

Month	Daily dose
First month	One-tenth of baseline ED If well tolerated after 1 mo, increase the dose
Second month	One-eighth of baseline ED If well tolerated after 1 mo, increase the dose
Third month	One-sixth of baseline ED If well tolerated after 1 mo, increase the dose
Fourth month	One-fourth of baseline ED If well tolerated after 1 mo, increase the dose
Fifth month	One-third of baseline ED If well tolerated after 1 mo, increase the dose
Sixth month	One-half of baseline ED to follow until the next OFC

TABLE E3. Number of desensitized patients beyond 7 mo of OIT in patients with a delayed “6-mo OFC”

	Time of OFC (months after OIT onset)					
	7	8	9	10	11	≥12
No. of patients, n	28	7	10	4	2	8
Cumulative number of patients, n	28	35	45	49	51	59
No. of desensitized patients, n (%)	12 (43)	4 (57)	2 (20)	2 (50)	0 (0)	6 (75)
Cumulative number of desensitized patients, n (%)	12 (43)	16 (46)	18 (40)	20 (41)	20 (39)	26 (44)

A total of 59 patients underwent the “6-mo OFC” with delay (age, 6 y; sex, 52% males; baseline ED, 121 mg [IQR, 54–240]). OFC was performed during a period running from 7 to more than 12 mo after OIT onset. Among them, 26 (44%) became desensitized.

Bold indicates statistical significance (95% CI, odds ratio excluding 1).

TABLE E4. Frequency of OIT side effects

Response to standard homemade survey, n	76
No side effects, n (%)	53 (70)
Gastrointestinal symptoms (abdominal pain, nausea, vomiting), n (%)	18 (23.7)
Severe side effect (dysphagia, dysphonia, dyspnea, throat tightness), N (%)	0 (0)
Oral pruritus, n (%)	8 (10)
Oral angioedema, n (%)	1 (1.3)
Urticaria, n (%)	5 (6.6)

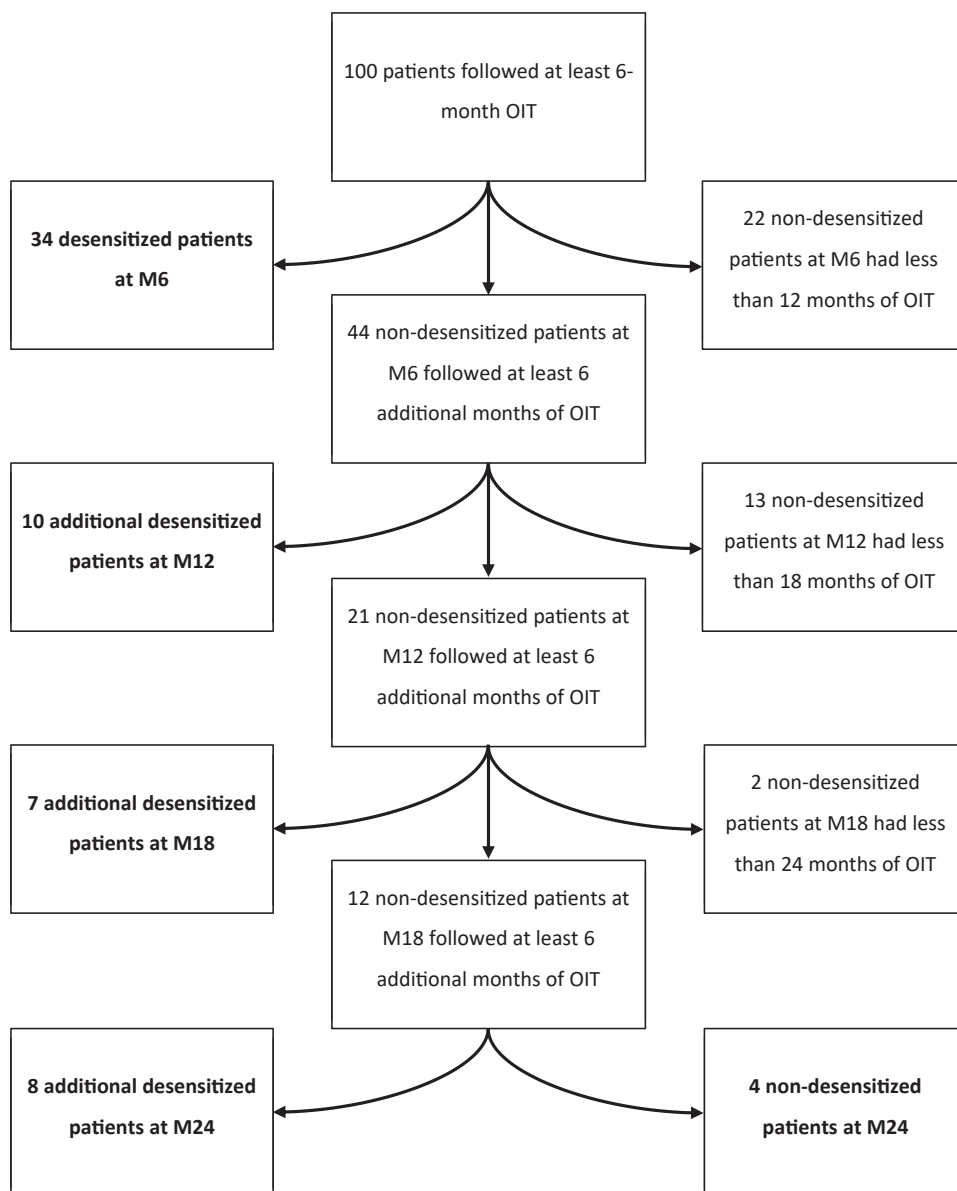


FIGURE E1. Number of desensitized patients after 12, 18, and 24 months of OIT in patients having completed a longer than 6-month OIT. Among the 66 patients who were not desensitized after 6 months of hazelnut OIT, 44 had a longer follow-up of OIT. Of them, 10 were desensitized at 12 months, 7 more at 18 months, and 8 more at 24 months.