

Oral Immunotherapy for Egg Allergy: A Double-Blind Placebo-Controlled Study, with Postdesensitization Follow-Up

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What is already known about this topic? Oral immunotherapy is a promising route for the active treatment of food allergy. There are few data on hen egg allergy, especially about the maintenance of acquired tolerance after desensitization.

What does this article add to our knowledge? This study confirms that oral desensitization to egg is effective and safe, but only 1/3 of children maintain tolerance after 3 months of food withdrawal.

How does this study impact current management guidelines? This study underlines the need for more data about desensitization and tolerance induction for food, and its usefulness in clinical practice.

BACKGROUND: Oral immunotherapy (OIT) may be an effective treatment for food allergy in children. It is not clear if the OIT-induced effect is achieved by desensitization (transient state dependent on regular antigen exposure), or by tolerance (persistent condition where the ability to consume the food is retained even after a period of withdrawal).

OBJECTIVE: The aim of this study was to investigate the efficacy of OIT-egg desensitization in a double-blind placebo-controlled study, and to evaluate if, after desensitization, tolerance can be maintained.

METHODS: Children with egg allergy were randomized to OIT or placebo for 4 months. At the end of the controlled phase, a double-blind food challenge was repeated to confirm the achieved desensitization. Those subjects found to be desensitized were placed on an egg-containing diet for 6 months, followed by

an egg avoidance phase for 3 months, when the food challenge was repeated to determine the maintained tolerance.

RESULTS: A total of 31 children were randomized to OIT with dehydrated egg white ($n = 17$) or placebo ($n = 14$). Of the 17 active patients (1 dropout), 16 achieved desensitization and started the 6-month egg-containing diet. After 3-month of egg avoidance, 31% remained tolerant. In the control group, only 1 passed the final food challenge. Egg-specific IgG4 increased only in the active group. Five active OIT patients had side effects.

CONCLUSION: Egg OIT results in desensitization in almost all subjects, although tolerance was maintained in only 1/3 of them after a 3-month period of withdrawal. Side effects were encountered, but the procedure appeared safe. In hen egg allergy, OIT is effective for desensitization. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:532-9)

Key words: Egg allergy; Dehydrated egg white; Oral immunotherapy; Tolerance; Follow-up

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts.

Received for publication July 17, 2014; revised January 20, 2015; accepted for publication January 23, 2015.

Available online February 25, 2015.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2015.01.017>

Food allergy is a serious disorder with life-altering implications for the affected subjects and their families. Second only to cow's milk, egg represents the most frequent cause of food allergy in infants and young children.^{1,2} The spectrum of allergic reactions to hen's eggs (HE), as with other food-induced allergies, may vary in severity, which range from atopic dermatitis and urticaria, to more severe systemic reactions and anaphylaxis. Recent studies suggest that oral immunotherapy (OIT) may offer an effective modality for the management of many children with food allergy. It is not clear, however, if the OIT-induced unresponsiveness is achieved by desensitization, a type of "transient tolerant" status dependent on the regular antigen exposure to a more sustained condition where the ability to consume the food is retained even after a period of its withdrawal from the diet. The occurrence of spontaneous tolerance in children with egg

Abbreviations used

DBPCFC- Double-blind placebo-controlled food challenge

DEW- Dehydrated egg white

HE- Hen's egg

OIT- Oral immunotherapy

SPT- Skin prick test

allergy is not uncommon, but it is usually delayed, in comparison with the tolerance that develops in cow's milk allergy.³

Based on evidence derived from birth cohort and epidemiologic studies, it is likely that in the future, the prevalence of atopy will increase.⁴ In addition, across all ages, food allergy still remains one of the most common causes of anaphylaxis seen in emergency departments, associated with an increased rate of hospitalization and mortality.⁵ Currently, the standard care in food allergy is nutritional counselling, strict food avoidance, and education to the use of self-administered epinephrine when an accidental exposure occurs. However, because neither fully effective therapeutic strategies nor truly curative approaches are currently available, several treatments using OIT are being explored with encouraging results. Following the oral administration of increasing doses of the offending food, a mechanism of desensitization (and possibly tolerance) has been repeatedly suggested to explain the encouraging results seen for cow's milk, HE, and peanut allergy.⁶⁻¹²

Currently, it is still unclear whether desensitization is the first step toward a permanent tolerance. As with other types of immunotherapy (eg, for aeroallergens), the duration of desensitization may be crucial in achieving permanent tolerance. Although the clinical efficacy of OIT and an induced immune modulation have been demonstrated, the strength of current evidence from clinical trials is considered insufficient, and it is hypothesized that when ingestion is discontinued, the protective effect is progressively lost. Based on these considerations, the present study was performed to assess the efficacy of OIT for HE allergy and the degree to which tolerance is maintained after HE withdrawal.

METHODS

Overall design

This study was designed as randomized, double blind, placebo controlled, with 2 parallel arms. Children aged ≥ 4 years, with ascertained IgE-mediated HE allergy, were enrolled and randomized (by a computer-generated list) to receive either dehydrated egg white (DEW, Lofarma SpA, Milan, Italy) or placebo. Seventeen children were assigned to OIT, and 14 to placebo. A double-blind placebo-controlled food challenge (DBPCFC) was performed at baseline, and after 4 months, to verify the establishment of desensitization, at which time the code was broken. Those patients who were found to be desensitized by the DBPCFC were placed on an HE-containing diet for 6 months. This was then followed by an HE-avoidance phase for additional 3 months, after which the DBPCFC was repeated to determine the state of tolerance. Those patients who passed again the challenge were considered tolerant. The primary endpoint was the achievement of desensitization after the 4-month randomized period of OIT with DEW. Secondary endpoints were the maintenance of tolerance to HE after the 3-month period of withdrawal, together with selected immunological parameters (IgE, IgG4, wheal diameter). The overall study design and patients'

disposition is summarized in Figure 1. The study was approved by the Ethical Committee of the Messina University, and all parents provided their informed consent.

Patients and diagnosis

Children of both sexes aged 4-11 years were enrolled at the Pediatric Allergy Units of Department of Pediatrics of Messina University Hospital and at the Children Hospital G. Di Cristina, Palermo, Italy. The diagnosis of HE allergy was based on (a) clinical history, (b) skin prick test (SPT) and specific IgE positive assay for HE, and (c) positive DBPCFC. According to clinical history, none of the children had previously consumed baked eggs.

The SPT was performed on the volar surface of the forearm using commercial extracts of HE white, yolk, ovalbumin, ovomucoid, cow's milk, lactalbumin, lactoglobulin, casein, wheat, peanut, tree nuts, and codfish (Lofarma Spa, Milan, Italy). SPTs for inhalant allergens were also performed using mite grass, *Parietaria*, olive, tree mix, and *Alternaria alternata*. Saline and histamine were the controls, and a wheal of 3 mm was considered positive. Serum HE white-specific IgE and IgG4 were measured by ImmunoCap 100 (Thermo-Fisher Scientific, Waltham, Mass). The lower detection limit of the Cap-System was 0.35 kU/L for specific IgE and 0.0 mcg/mL for specific IgG4. The DBPCFC was conducted according to current guidelines. Briefly, the challenge started with a dose of 0.12 g egg white.¹³ The dose was then doubled (0.24, 0.48, 0.96, 1.9 g) at hourly intervals, until objective clinical manifestations appeared.^{13,14} The cumulative dose was 3.7 g egg white, approximately equivalent to one boiled egg. If this dose could be tolerated, one fresh egg was given openly on the next day. Vegetable puree or mashed potatoes were used for masking. Reaction severity was evaluated according to "Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms" by Sampson.¹⁵ Criteria for anaphylaxis were those reported in the EAACI position paper: multisystem involvement including cardiovascular, lower respiratory tract or persistent gastrointestinal symptoms.¹⁶

Oral immunotherapy and protocol

DEW was obtained from eggs of *Gallus domesticus*. Briefly an egg was pasteurized and then passed through a spray tower where it was dried. The resulting DEW was approximately 4 g, equivalent to the egg white contained in a fresh egg. Sodium dodecyl sulfate polyacrylamide gel electrophoresis was carried out, according to Laemmli,¹⁷ using a Hoefer SE 600 electrophoresis system (GE Healthcare, Little Chalfont, Buckinghamshire, UK). Gels were stained with PageBlue Protein Staining solution (Fermentas International Inc., Burlington, Canada) to ensure proper protein separation and visualization. The inclusion of electrophoresis of DEW allowed a better standardization of HE dosing.

The OIT procedure consisted of weekly administration, at the hospital clinic, of increasing dosages of DEW, diluted in sterile saline, starting with 0.1 mg. The dose was doubled every week until week 16, to achieve a cumulative dose of 4 g in approximately 4 months. The placebo (corn flour, indistinguishable from active) was administered following the same protocol. The doses were prepared separately by a trained nurse according to the randomization list, so that the physicians remained blinded to the treatment. All doses were administered at the hospital. The protocol is summarized in Table I. After each dose, children were kept under strict observation. Adverse reactions were defined as the occurrence of one or more of the following: urticaria, exacerbation of eczema (>10 point increase in SCORING Atopic Dermatitis), angioedema, vomiting, diarrhea,

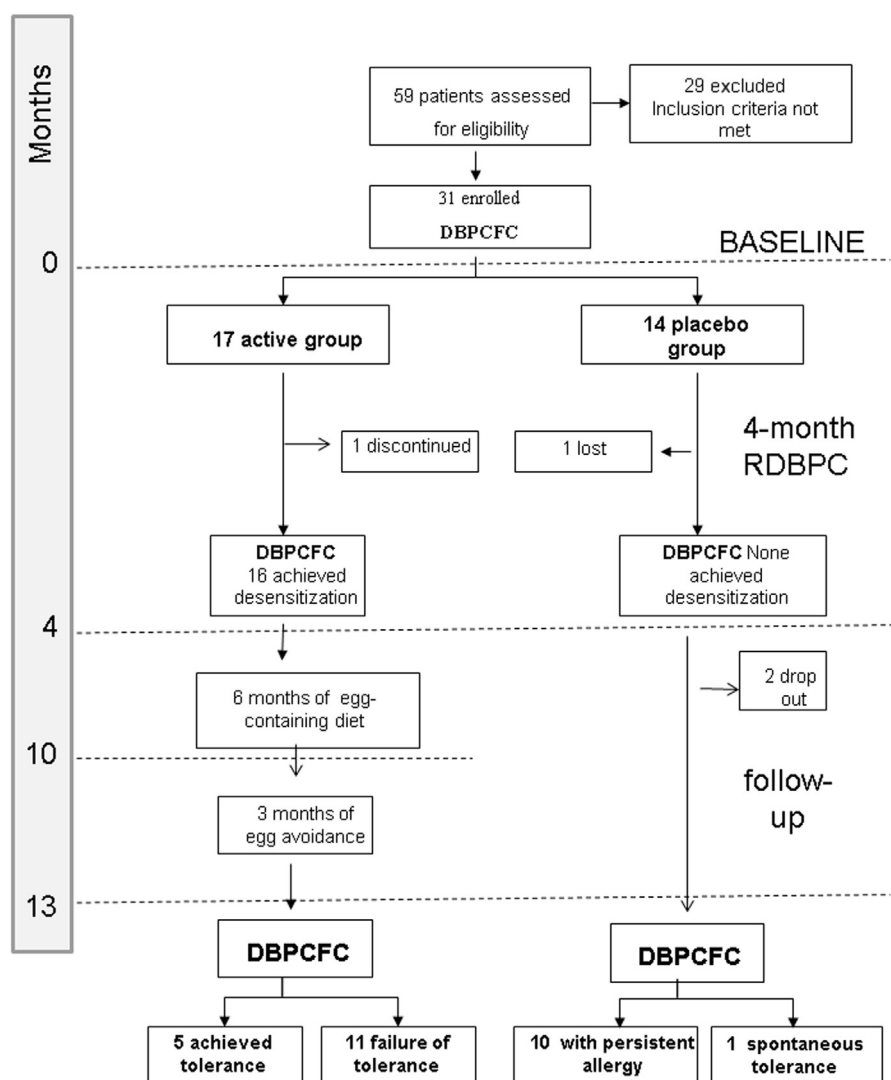


FIGURE 1. Study design, patients' disposition and clinical results. *DBPCFC*, Double blind placebo controlled food challenge; *RDBPC*, randomized, double blind placebo controlled.

rhinitis, wheezing, conjunctivitis, or hypotension. If symptoms were judged as mild (abdominal pain, erythema, throat itching, gritty eyes), no action was taken and OIT continued. When moderate or severe symptoms appeared, an appropriate medical treatment was given. If a concurrent illness ensued (eg, common cold) during desensitization, an adequate therapy was given, and the dose increase was postponed. Those children who tolerated the maximum dose of 4 g DEW received 1 cooked or 1 boiled egg (according to the child's choice).

Evaluated parameters

After completing the randomized, double blind placebo controlled phase, the DBPCFC was repeated (the achieved desensitization represented the primary endpoint), and the blinding was broken. Those children who passed the DBPCFC were placed on a 6-month egg-containing diet, including 1 cooked or boiled egg at least 2 times a week, and then on a 3-month egg-avoidance diet. At the end of this phase (13 months from baseline), the DBPCFC was repeated again.

On this occasion, the opportunity to repeat the challenge was given also to those children who had not been desensitized to HE.

Immunological parameters SPT, IgE, and IgG4 assay were evaluated at baseline, and at the end of OIT (4 months) in all children (active and placebo). The assays were repeated again only in those children who had achieved desensitization, and at the end of the egg-containing diet follow-up (10 months from baseline).

Statistical analysis

All clinical outcomes were assessed by intention to treat analysis. The Fischer exact test was used to compare the clinical characteristics of the 2 groups at baseline, except for age that was analyzed by the *t*-test. Immunological changes from baseline in the OIT group and immunoglobulin levels were analyzed using the Wilcoxon and Mann-Whitney signed rank tests for intragroup and intergroup comparisons, respectively. All the tests were 2-tailed and $P < .05$ was considered significant. Logistic regression was used to evaluate the association of selected immune variable with clinical outcomes.

TABLE I. Oral immunotherapy protocol

Day/ Week	Dose no.	Dehydrated egg white (DEW) powder single dose (mg)*
1/1	1	0.1
7/2	2	0.2
14/3	3	0.4
21/4	4	0.8
28/5	5	1.5
35/6	6	3
42/7	7	6
49/8	8	12
56/9	9	25
63/10	10	50
70/11	11	100
77/12	12	200
84/13	13	500
91/14	14	1000
98/15	15	2000
105/16	16	4000

*Increasing doses were given weekly; when the dose of 4 g was tolerated, the protocol was continued with the cooked egg or the boiled egg at home.

RESULTS

Clinical results

A total of 31 children with HE allergy (median age 6 years, age range 4-11 years) were enrolled. Of them, 17 were randomized to active DEW OIT and 14 to placebo. Of the 31 participants, 9 had at least 1 additional allergy to inhalants (mostly house dust mite), but no other food allergy. The clinical and demographic characteristics of the study population at randomization are summarized in Table II.

The clinical results of the OIT are shown in Figure 1. Among children who received OIT ($n = 17$), 16 were successfully desensitized and tolerated the dose of 4 g. One subject experienced generalized urticaria, rhinitis, cough, throat pruritus, vomiting at a dose of 3 mg, requiring epinephrine, and OIT cessation. The remaining 16 subjects passed the oral food challenge without symptoms. One of the placebo subjects relocated from the geographical area and was lost at the beginning of the study. Although none of the remaining 13 control subjects had symptoms during the study, none of them passed the DBPCFC after the randomized phase ($P < .001$ vs active). There was no difference in age, sex, and demography between the 2 groups at the end of the randomized phase (not shown).

When desensitization and food challenges were completed, the 16 patients who had achieved desensitization were placed on an egg-containing diet with 2-3 eggs per week for a 6-month period, following which egg avoidance was re-instituted for 3 months, followed by another DBPCFC. Of these 16 children, 5 (31%) appeared to have achieved a sustained tolerance and 11 (69%) lost their desensitization and reacted again to HE ($P = .05$). Among those patients who were no longer tolerant, the median cumulative dose HE that caused symptoms was 0.84 g (range 0.36-3.7 g). There were no statistical differences in demographic or clinical characteristics between those subjects who achieved tolerance and those who did not manifest tolerance. The children who belonged to the former placebo group obviously avoided HE for 9 months. Of them, at the final

TABLE II. Characteristics of the enrolled patients

	Active OIT ($n = 17$)	Placebo ($n = 14$)	<i>P</i> value
Years of age: median (range)	6 (4-10)	6 (4-11)	NS
Years of age at first reaction: median (range)	1.2 (0.4-5)	1.4 (0.5-6)	NS
Sex (male/female)	10/7	8/6	NS
Egg-specific IgE (kU/L): median (range)	36.6 (5.2-110)	38.4 (4.6-98.3)	NS
Egg-specific IgG4 (mcg/mL): median (range)	0.9 (0-6.8)	0.7 (0-4.6)	NS
Wheal diameter SPT (mm): median (range)	11 (6.5-18)	9 (6-16)	NS
Clinical presentation: N (%)			NS
Urticaria+angioedema	5 (29)	4 (29)	
Urticaria+atopic dermatitis	2 (11)	2 (14)	
Atopic dermatitis	4 (24)	3 (21)	
Asthma and/or rhinitis	1 (6)	0 (0)	
Anaphylaxis	2 (11)	1 (7)	
Multiple (more than one of the above)	3 (19)	4 (29)	
Concomitant allergies: N (%)			NS
Dust mite	4 (24)	3 (21)	
Dust mite+grass	1 (6)	0 (0)	
Dust mite+parietaria	0 (0)	1 (7)	

OIT, Oral immunotherapy; NS, nonsignificant.

DBPCFC, 10 (77%) had symptoms at the cumulative dose HE of 0.36 g (range 0.12-1.8 g) and 2 were lost to follow up. One boy (10-year-old, with atopic dermatitis and dust mite allergy) passed the DBPCFC, although he was not eating egg. An egg-containing diet was then allowed, and the subsequent clinical follow-up confirmed that he had spontaneously achieved tolerance.

Immunological parameters

The mean egg-specific IgG4 level after desensitization was higher in the active group (29.2 mcg/mL) than in the placebo group (1.5 mcg/mL; $P = .001$). The difference of the mean IgG4 level after desensitization versus the baseline level was significant only in the active group (29.2 mcg/mL vs 0.9 mcg/mL, $P = .001$) (Figure 2). The logistic correlation analysis confirmed that egg-specific IgG4 at 14 weeks correlated with desensitization (data not shown). The IgE antibody mean level after desensitization was 34.2 kU/L in the active group and 38.9 kU/L in the placebo group with no statistical difference between groups and versus baseline (Figure 3). The mean SPT wheal size after desensitization was not different between groups (9.2 mm vs 10 mm; $P = .88$), whereas a significant change was seen versus baseline only in the active group (9.2 mm vs 11.0; $P = .05$) (Figure 4). Of note, in the formerly active OIT children, who ate eggs for 6 months, specific IgG4 remained significantly higher than baseline values (32.4 mcg/mL vs 0.9 mcg/mL; $P = .001$), with IgE significantly lower than at baseline (37.6 to 12.2 kU/L, $P = .02$), and the wheal size smaller ($P = .03$) (Figures 2-4). After egg's avoidance for 3 months, in the 5 children who achieved tolerance, the mean specific IgG4 level was 34.0 mcg/mL ($P = .001$ vs baseline), specific IgE 1.94 kU/L ($P = .001$ vs baseline), and wheal size 3.2 mm ($P = .001$ vs baseline). In the 11 children who lost the previously achieved desensitization, the mean IgG4 level

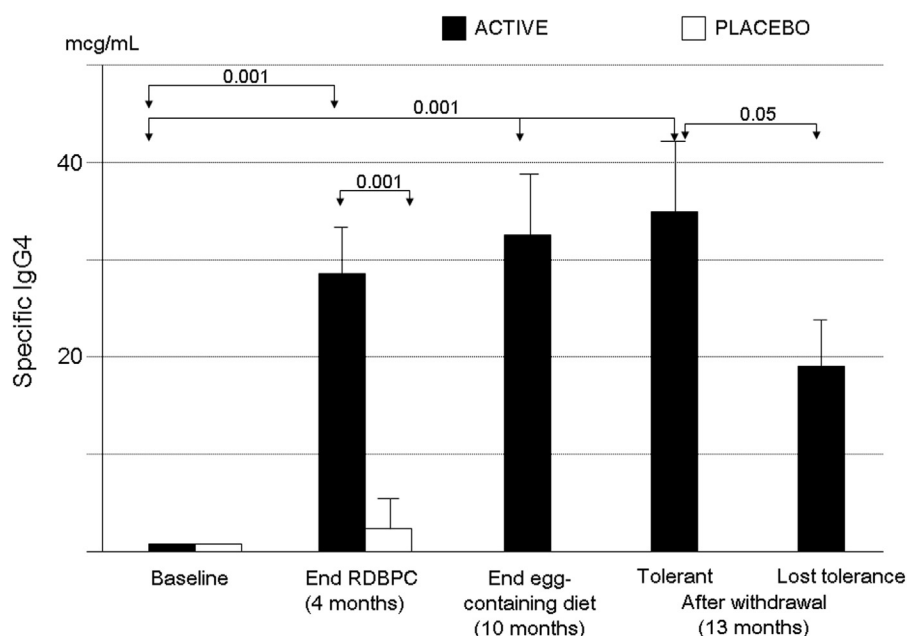


FIGURE 2. Egg-specific IgG₄ (mcg/mL, mean $\pm$ SD) during the randomized, double blind placebo controlled phase, and during follow-up phases in patients who achieved desensitization. Only the significant intragroup and intergroup differences are shown above the bars. *RDBPC*, Randomized, double blind placebo controlled.

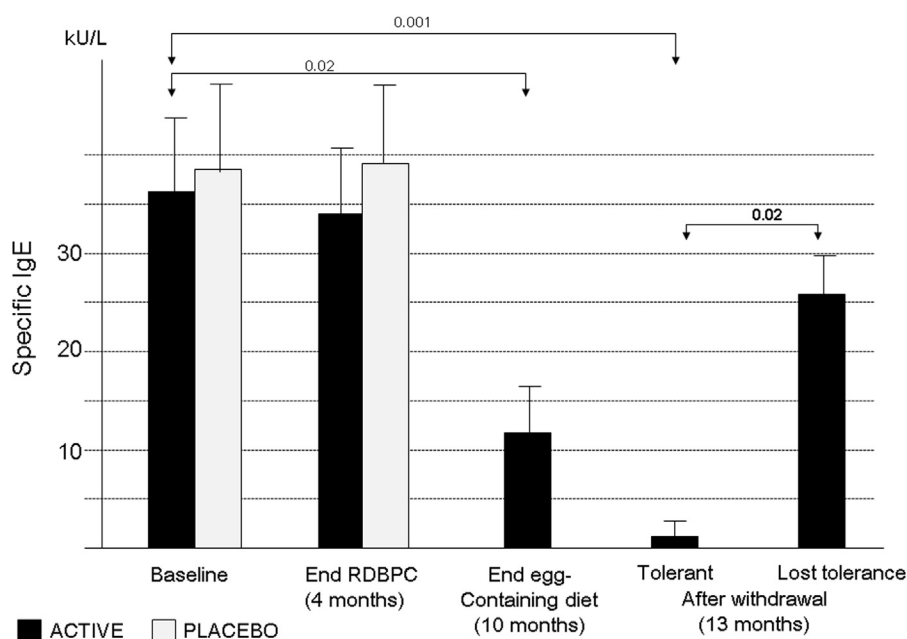


FIGURE 3. Egg-specific IgE (kU/L, mean $\pm$ SD) during the randomized, double blind placebo controlled phase, and during follow-up in patients who achieved desensitization. Only the significant intragroup and intergroup differences are shown above the bars. *RDBPC*, Randomized, double blind placebo controlled.

was 17.4 mcg/mL ($P = .05$ vs the tolerant patients), specific IgE 25.6 kU/L ($P = .02$) and wheal diameter 7.3 mm ($P = .04$).

Safety

The safety data during the double-blind treatment and the egg-containing dietary period in the active group are summarized in

Table III. Adverse events were seen in 3 subjects during the desensitization procedure, 1 of whom had to discontinue OIT. During the egg-containing diet, 1 patient had abdominal pain with urticaria after exercise, and 1 had rhinitis and/or asthma during a respiratory tract infection. No adverse effects were observed in the control group.

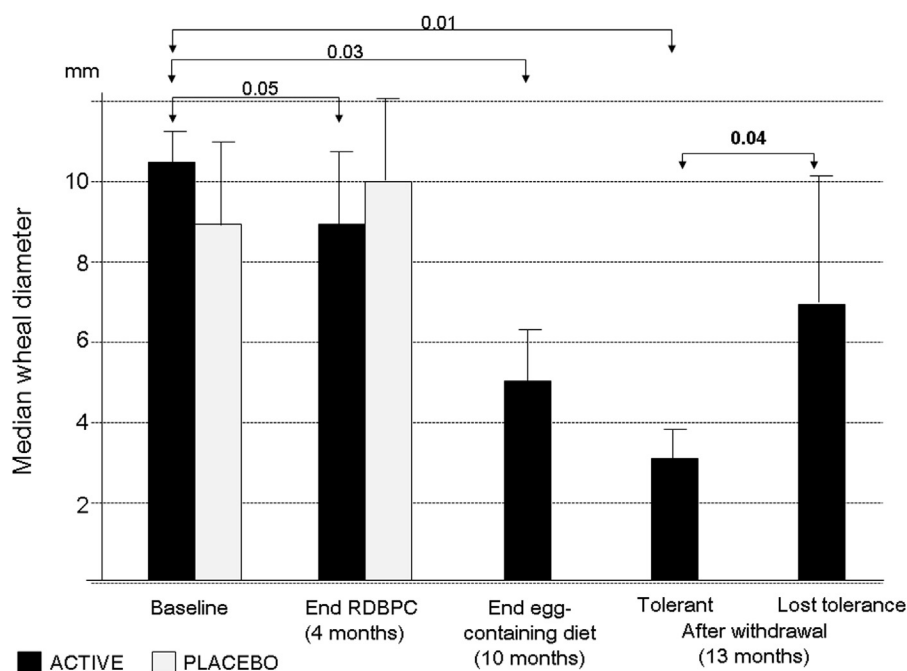


FIGURE 4. Wheal diameter (mm, mean $\pm$ SD) during the randomized, double blind placebo controlled phase, and during follow-up in patients who achieved desensitization. Only the significant intragroup and intergroup differences are shown above the bars. *RDBPC*, Randomized, double blind placebo controlled.

TABLE III. Summary of the safety data during desensitization and egg-containing diet period

Patients	Phase	Reaction	Dose of HE	Action taken	Outcome
1	Desensitization	Urticaria, throat pruritus, rhinitis, asthma, vomiting	3 mg	i.m. adrenaline and steroid, cetirizine, inhaled salbutamol; stop OIT	OIT failed; patient excluded
1	Desensitization	Erythema of face and hands	1.5 mg	No action	OIT completed
1	Desensitization	Abdominal pain; diarrhea	4 mg	No action	OIT completed
1	Egg-containing Diet	Urticaria, abdominal pain after exercise	One cooked egg	Egg ingestion stopped for 3 days; oral antihistamine	Tolerant after 3 months of egg withdrawal
1	Egg-containing Diet	Wheezing and cough during upper respiratory infection	One cooked egg	Egg ingestion stopped for 3 days; inhaled bronchodilator and steroid	Tolerant after 3 months of egg withdrawal

HE, Hen's egg; OIT, oral immunotherapy.

DISCUSSION

Over the past few decades the prevalence of allergic diseases substantially increased, especially in developed countries. Although the prevalence of asthma has remained stable, and the prevalence of eczema has appeared to decline, the number of patients with food allergy (and related anaphylaxis) continues to increase.^{18,19} Allergic reactions to food proteins range from immediate, potentially life-threatening reactions to chronic diseases that seriously impact the quality of life of patients and parents. Currently, there is no curative therapy available for IgE-mediated food allergy, and the only treatment option available is the total avoidance of the offending food(s). Therefore, a pressing need exists for an active treatment modality that can offer the patient with food allergy the possibility of ingesting the responsible food without adverse events. OIT has been repeatedly evaluated for its desensitizing effect against milk, egg, or peanuts,^{20,21} but the precise mechanism by which the procedure is successful is still

incompletely known. It is still unclear if the OIT-induced unresponsiveness is achieved by desensitization (transient state depending on the regular exposure to the allergen) or by tolerance, where the ability of consuming the food is retained even after a period of withdrawal from the diet. The present study was conducted to provide data that could help clarify some of the uncertainties related to the mode of action of OIT.

The clinical trial was performed in children with HE allergy, with a weekly up-dosing regimen requiring no complex hospitalization protocols. In addition, the whole procedure lasted approximately 4 months, for a total of 16 visits. The 16 subjects actively treated who achieved initial desensitization were placed on an egg-containing diet, followed by an egg-avoidance diet for 3 months. Then another DBPCFC was performed to assess if persistent tolerance had been maintained. At the end of this trial, 5 patients (31%) seemed to have achieved a sustained tolerance, but 11 (69%) had a relapse, confirmed by a positive DBPCFC. In

contrast, none of the placebo patients passed the challenge, and continued egg avoidance.

The potential of OIT to induce a long-lasting (possibly permanent) tolerance is still actively debated. Our results suggest that a minority of subjects achieve a clinical and immunological tolerance, whereas others, despite successful desensitization, lose the unresponsiveness status after a short withdrawal period. There are several limitations in this study that could affect interpretation. For example, we used a DEW preparation for the active treatment instead of a raw or cooked egg, and it is well known that there are different allergenic proteins in a whole egg. Nevertheless, DEW contains the majority of relevant allergens as repeatedly documented.⁹ In addition, DEW can be used for both DBPCFC and OIT.²²

A successful desensitization with OIT was previously reported for HE allergy, but few studies assessed the persistence of tolerance, as in the present study. In 2007, Staden et al. conducted a randomized clinical trial using OIT for cow's milk and HE.²³ Children with proven food allergy to milk or egg were randomly assigned to OIT (n = 25, 11 with HE allergy) or to an avoidance diet (controls, n = 20). The children of the active group were then assigned to a second elimination diet for 2 months before the DBPCFC to evaluate their tolerance. On rechallenge, 35% of subjects resulted tolerant, and some were "partial responders." In another study, 7 children with mild symptoms (urticaria) received OIT,²⁴ and 6 of them tolerated significantly more egg protein versus baseline. In an open study, OIT with egg was evaluated in 23 children >5 years of age.²⁵ Subjects underwent a 5-day OIT with fresh egg, and subsequently were placed on regular egg intake. A total of 20 (87%) subjects reached the goal dose of egg. In the first multicenter randomized, double blind placebo controlled study,⁹ children (5-11 years of age) who were suffering from HE allergy received OIT (40 children) or placebo (15 children). After 10 months, 55% of the children in the active group, and none in the placebo group, were desensitized, and after 24 months, 28% of the desensitized children were considered still unresponsive. In addition, in a randomized controlled open study with 20 children allergic to egg, 8 of 10 children achieved a reported daily intake of 25 mL (approximately 3 g egg proteins) over 6 months. In contrast, only 2 children of the control group became tolerant.²⁶ Recently, Vasquez Ortiz¹³ confirmed the efficacy of OIT performed with whole egg in 80% of children with HE allergy.

The immunological results of our study lend additional support for tolerance induction. Egg white-specific IgG4 significantly increased from baseline in the active group, whereas the changes in specific IgE were not significant. In desensitized patients, we also observed a decrease in specific IgE and wheal size, after the egg-containing diet. This is in agreement with the results of other studies with egg^{9,24} and other foods.^{6,8,27} At the end of egg-avoidance period, 31% of subjects had achieved tolerance and passed the DBPCFC. Nonetheless, we cannot exclude with certainty a spontaneously acquired tolerance in subjects with HE allergy. The clinical data confirm that OIT is an effective treatment for IgE-mediated food allergy. The protocol described was proven effective also in other trials with cow's milk,^{8,28} and its safety does not differ from OIT for other foods,^{20,29} with a well-tolerated up-dosing phase, comparable to other protocols described in the literature. The postdesensitization strategy represents a pivotal issue for patients, doctors, and families, because a persisting tolerance is the most desirable outcome. Given the results of this and other trials, which looked

for a curative treatment of food allergy, OIT represents a suitable option to be offered to patients in routine clinical practice.

REFERENCES

1. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol* 2007;120:1413-7.
2. Eggesbo M, Botten G, Halvorsen R, Magnus P. The prevalence of allergy to egg: a population-based study in young children. *Allergy* 2001;56:403-11.
3. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE mediated cow's milk allergy. *J Allergy Clin Immunol* 2007;120:1172-7.
4. Illi S, von Mutius E, Lau S, Niggemann B, Gruber C, Wahn U, et al. Perennial allergen sensitization early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;368:763-70.
5. Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, et al. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy* 2013;68:1353-61.
6. Skripak JM, Nash SD, Rolwey H, Brereton NH, Oh S, Hamilton RG, et al. A randomized double blind, placebo controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008;122:1154-60.
7. Narisety SD, Skripak JM, Steele P, Hamilton RG, Matsui EC, Burks AW, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2009;124:610-2.
8. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol* 2010;105:376-81.
9. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SM, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012;367:233-43.
10. Dello Iacono I, Tripodi S, Calvani M, Panetta V, Verga MC, Miceli Sopo S, et al. Specific oral tolerance induction with raw hen's egg in children with very severe egg allergy: a randomized controlled trial. *Pediatr Allergy Immunol* 2013;24:66-74.
11. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol* 2011;127:654-60.
12. Fleisher DM, Burks AW, Vickery BP, Scurlock AM, Woof RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double blind, placebo-controlled multicenter trial. *J Allergy Clin Immunol* 2013;131:119-27.
13. Vasquez-Ortiz M, Alvaro M, Piquer M, Dominguez O, Machinena A, Martín-Mateos MA, et al. Baseline specific IgE levels are useful to predict safety of oral immunotherapy in egg-allergic children. *Clin Exp Allergy* 2014;44:130-41.
14. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126:S1-S8.
15. Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics* 2003;111:1601-8.
16. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical Immunology. *Allergy* 2007;62:857-71.
17. Laemmli UK. Cleavage of structural proteins during the assembly of the head bacteriophage T4. *Nature* 1970;227:680-5.
18. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongranic J. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128:9-17.
19. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol* 2012;129:1187-97.
20. Pajno GB. Oral desensitization for milk allergy in children: state of the art. *Curr Opin Allergy Clin Immunol* 2011;11:560-4.
21. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. *J Allergy Clin Immunol* 2014;133:318-23.
22. Escudero C, Sanchez-Garcia S, Rodriguez del Rio P, Pastor-Vargas C, Garcia-Fernandez C, Perez-Ranger I, et al. Dehydrated egg white: an allergen source for improving efficacy and safety in the diagnosis and treatment for egg allergy. *Pediatr Allergy Immunol* 2013;24:263-9.
23. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reactions. *Allergy* 2007;62:1261-9.

24. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, et al. Egg oral immunotherapy in non anaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007;19:199-205.
25. Garcia Rodriguez R, Urrea JM, Feo Brito F, Galindo PA, Borja J, Gomez E, et al. Oral rush desensitization to egg: efficacy and safety. *Clin Exp Allergy* 2011;41:1289-96.
26. Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. *Pediatr Allergy Immunol* 2013;24:75-83.
27. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009;124:292-300.
28. Caminiti L, Passalacqua G, Barberi S, Vita D, Barberio G, De Luca R, et al. A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. *Allergy Asthma Proc* 2009;30:443-8.
29. Pajno GB, Cox L, Caminiti L, Ramistella V, Crisafulli G. Oral immunotherapy for treatment of immunoglobulin E-mediated food allergy: the transition to clinical practice. *Pediatr Allergy Immunol Pulmonol* 2014;27:42-50.

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