

Efficacy and safety of high-dose rush oral immunotherapy in persistent egg allergic children

A randomized clinical trial

Inmaculada Pérez-Rangel, MD^{*}; Pablo Rodríguez del Río, MD, PhD^{*,†}; Carmelo Escudero, MD^{*,‡}; Silvia Sánchez-García, MD, PhD^{*,†}; José Javier Sánchez-Hernández, MD, PhD[‡]; María Dolores Ibáñez, MD, PhD^{*,†}

^{*} Allergy Department, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

[†] Health Research Institute Princesa, Madrid, Spain

[‡] Unidad de Investigación en Salud Pública, Monterrey, Mexico

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ABSTRACT

Background: Egg oral immunotherapy is effective but time consuming.

Objective: To assess the efficacy and safety of egg rush oral immunotherapy (ROIT) with a targeted dose equivalent to a raw egg white.

Methods: Thirty-three persistent egg allergic children confirmed by double-blind, placebo-controlled food challenge (DBPCFC) were randomized to receive egg ROIT immediately after randomization (ROIT1 group), or to continue an egg avoidance diet for 5 months after randomization (control group [CG]). A 5-day build-up phase starting with the highest single tolerated dose at baseline DBPCFC was scheduled and several doses administered daily until achieving a dose of approximately 2,808 mg of egg white protein. In the maintenance phase, patients ate an undercooked egg every 48 hours for 5 months. The CG participants who failed the DBPCFC at 5 months began active treatment. Children from the ROIT1 group plus children from the CG who failed a second DBPCFC at 5 months and then received egg ROIT were randomized to the ROIT2 group. Adverse events (AEs) and immune marker evolution were recorded.

Results: A total of 17 (89%) of 19 children in the ROIT1 group and no CG patients were desensitized at 5 months ($P < .001$). A total of 31 (97%) of the 32 children in the ROIT2 group completed the build-up phase in a median of 3 days (range, 1–14 days), and 30 (94%) of 32 maintained desensitization at 5 months. From baseline to 5 months of treatment, skin prick test, specific IgE, and specific IgE/IgG4 ratio to egg fractions significantly decreased, whereas specific IgG4 increased. During the build-up phase, AEs occurred in 69% of patients (50% had ≤ 2 AEs) and 31% of doses (2% severe, 55% gastrointestinal). Lower threshold dose in the DBPCFC and higher egg white and ovalbumin specific IgE levels at baseline revealed an association with a higher rate of AEs.

Conclusion: The proposed 5-day egg ROIT desensitized 94% of the allergic patients, with most AEs being mild or moderate.

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Introduction

Egg allergy is the second most frequent food allergy in the pediatric population worldwide.^{1,2} Fortunately, egg allergy typically resolves during childhood. It has been described that

approximately half of a cohort of 213 infants aged 3 to 15 months with egg allergy resolved at a median age of 72 months.³ However, a study of a referral population found persistent egg allergy in 42% of children in late adolescence,⁴ thereby suggesting that the number of adults with egg allergy may increase with time.⁵

Strict avoidance of egg proteins is the standard of care, although this approach is made difficult by the extensive use of egg in many foodstuffs, which significantly impairs patients' quality of life.⁶ Inadvertent egg contact is frequent and can trigger life-threatening reactions.^{7,8} Therefore, development of effective active therapies is vital.

In recent years, several studies have focused on oral immunotherapy (OIT)^{9–24} that involves regular oral administration of

Reprints: María Dolores Ibáñez, MD, PhD, Allergy Department, Hospital Infantil Universitario Niño Jesús, Avda/Menéndez Pelayo, No. 65, 28009 Madrid, Spain; E-mail: mibanezs@salud.madrid.org.

Drs Pérez-Rangel and Ibáñez contributed equally to this work.

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progressively increasing amounts of allergen until a predetermined amount is reached. Most published protocols imply prolonged dose-increasing phases of 2 to 3 months or more.^{10,16,20,22,23} Moreover, the aim of some such protocols is to achieve a low maintenance dose^{10,11,13,16} rather than attaining a normal diet. Currently, there are only 2 rush protocols of 12¹⁴ and 5¹⁵ days that aim to reach a targeted dose of one cooked egg.^{14,15}

We performed a prospective randomized clinical trial to evaluate the efficacy and safety of a new protocol for high-dose rush OIT (ROIT) to desensitize children with persistent IgE-mediated egg allergy. We also evaluated immunologic changes detected during the treatment and possible risk factors of adverse events (AEs).

Methods

Study Design and Participants

A controlled, randomized, parallel-group intervention study was performed in a single center. The study protocol was approved by the institution's independent ethics committee (internal code R-0019/12). Written informed consent was given by the parents or guardians, and assent was obtained from children older than 11 years.

Egg allergic children who followed an avoidance diet, including extensively heated egg, were invited to participate and were consecutively recruited between April and May 2012 at the Department of Allergy, Hospital Infantil Universitario Niño Jesús, Madrid, Spain. Follow-up was completed in July 2013. The inclusion criteria were children between 5 and 18 years of age; egg allergy diagnosis based on the presence of IgE-mediated symptoms, positive skin prick test (SPT) result (≥ 3 mm) and/or specific IgE (sIgE) levels of 0.7 kU/L or higher for whole egg, egg white (EW), ovalbumin (Gal d 2), and/or ovomucoid (Gal d 1); and positive baseline double-blind, placebo-controlled food challenge (DBPCFC) to EW. Participants were excluded if they had a history of anaphylactic shock after egg consumption in the previous year, severe or not controlled bronchial asthma, non-IgE-mediated adverse reactions to egg, eosinophilic esophagitis, immunologic diseases or malignant diseases, any baseline disease contraindicating the use of epinephrine, or allergy to any component of the placebo.

Participants were assigned to groups using a computer-generated randomization table. The study groups were as follows: intervention group 1 (ROIT1), children receiving egg ROIT immediately after randomization; control group (CG), children continuing an egg avoidance diet for 5 months after randomization; and intervention group 2 (ROIT2), children from ROIT1 plus children from CG who failed a second DBPCFC at 5 months and then received egg ROIT.

Double-blind, Placebo-Controlled Food Challenge

The allergen source used for active challenge and egg ROIT was dehydrated EW (OVO-DES NM, Nutrición Médica SL, Madrid, Spain) with entirely preserved allergenicity.²⁵ According to the manufacturer, 3,600 mg of product is equivalent to one medium-sized EW, and its protein content is 78% (approximately 2,808 mg). A DBPCFC²⁶ with both active and placebo was performed during the same week, administering 8 doses of dehydrated EW masked in 50 mL of cocoa soy smoothie or placebo (cocoa soy smoothie). Egg white doses of 4, 20, 50, 100, 225, 450, 900, and 1,800 mg (cumulative dose of approximately 2,808 mg of protein) were administered at 20-minute intervals until objective IgE-mediated manifestations occurred or subjective but mild-moderate symptoms consisting of mild-moderate abdominal pain persisting for 40 minutes or severe abdominal pain regardless of duration (positive DBPCFC result). Patients who successfully consumed the maximum dose of EW (negative DBPCFC result) were considered to have

Table 1

Egg ROIT Protocol Build-up Phase

Dehydrated EW, ^a mg	Day of ROIT	No. of doses	ROIT starting dose of dehydrated EW, mg ^a	Approximate EW protein, mg
4	1	1	0.04	0.03
		2	0.08	0.06
		3	0.16	0.125
		4	0.32	0.25
		5	0.64	0.50
		6	0.4	0.31
		7	0.8	0.62
		8	1.6	1.25
20		9	4	3.12
		10	20	15.6
50	3	11	20	15.6
		12	50	39
100		13	100	78
		14	225	175.5
225		15	450	351
		16	450	351
450	4	17	900	702
		18	1800	1404
900		19	1800	1404
		20	3600	2808

Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; EW, egg white; ROIT, rush oral immunotherapy.

^aThe allergen source used for DBPCFC and ROIT was dehydrated EW (OVODES NM, Nutrición Médica SL, Madrid, Spain). The ROIT starting dose was based on the eliciting dose threshold, so the build-up phase started with the highest single egg dose tolerated in the baseline DBPCFC. When the test result was positive with 4 mg, the starting dose was 0.04 mg. Doses were administered in the hospital at intervals of 60 minutes.

passed the challenge. Every patient was kept under surveillance for at least 2 hours after the last dose was administered or 2 hours after symptoms had totally subsided.

Egg ROIT Protocol

A consecutive 5-day build-up phase was designed, starting at the highest tolerated single dose in the baseline egg DBPCFC (Table 1). The regimen was conducted on an outpatient basis. After 1 hour of observation without symptoms, the subsequent dose was administered. In case of an AE, the previously tolerated dose was administered as the first dose on the following day. During the weekend, patients continued with the in-home daily intake of the last dose tolerated. The build-up phase target dose was 3,600 mg of dehydrated EW (approximately 2,808 mg of EW protein). A cumulative dose of 5,400 mg of dehydrated EW (approximately 4,212 mg protein) was administered on the last day. The maintenance phase consisted of eating 1 undercooked egg (undercooked fried egg, scrambled egg, or omelet) every 48 hours. In addition, the patients could freely take any other egg-containing foodstuffs.

Adverse Events

Patients received daily 10 mg of cetirizine as pretreatment during the build-up phase and the first half-week of the maintenance phase. AEs, treatment, and aggravating factors (infections, stress, exercise, or intake of nonsteroidal anti-inflammatory drugs) were recorded. AEs were classified according to severity as mild (oropharyngeal symptoms, skin, digestive, and/or rhinitis manifestations), moderate (mild AEs plus mild respiratory distress), or severe (severe respiratory distress and/or symptoms of hypotension).²⁷ The criteria used for anaphylaxis followed the European Academy of Allergy and Clinical Immunology guidelines.²⁸ The causes for discontinuation and failure of treatment were (1) more than 1 severe reaction, (2) more than 3 moderate reactions, (3) decision by the patient or parents or guardians, and (4) low adherence to treatment.

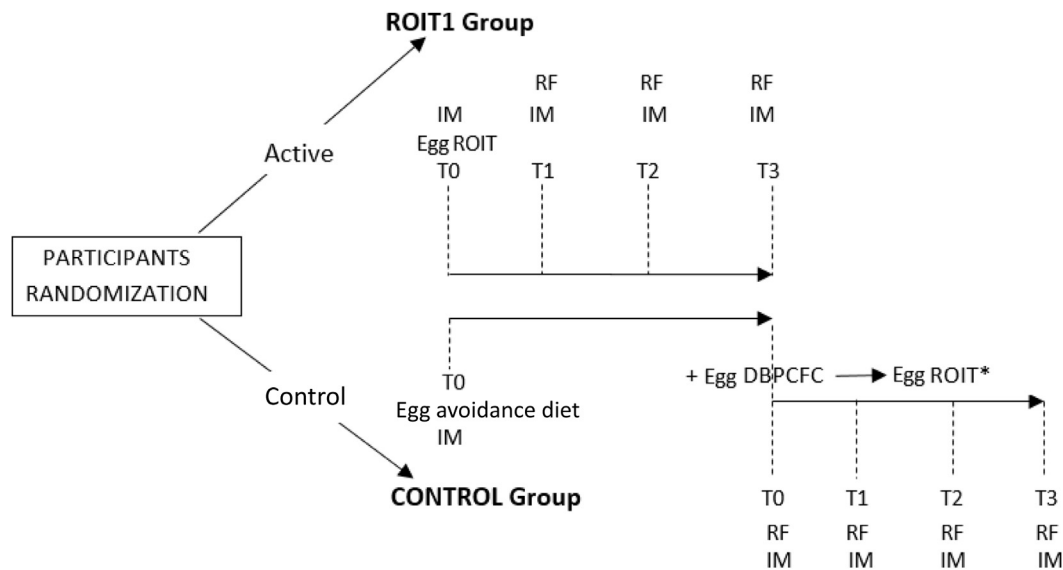


Figure 1. Study flowchart according to groups and interventions at different times. Asterisk indicates beginning of the egg ROIT protocol in the control group (T3 of the control group matches T0 of the egg ROIT group in patients from the control group who failed the second DBPCFC that was exclusively performed in this group). DBPCFC, double-blind, placebo-controlled food challenge; IM, immune markers; RF, registry forms (record of adverse reaction); ROIT, rush oral immunotherapy. ROIT1, egg ROIT at baseline; T0, baseline (beginning of egg ROIT protocol in ROIT1 group and egg avoidance diet in the control group); T1, 15 days from the end of the build-up phase; T2, 1 month from T1; T3, 5 months from baseline; +, positive.

Follow-up

Registry forms were provided for the parents or guardians. Families were instructed on procedures for administering doses of egg and recognizing and treating AEs.²⁸ Subjective parameters, such as taste for egg and fear of eating undercooked egg, were also recorded.

Immune Markers

We performed SPTs to whole egg, EW, ovalbumin, and ovomucoid. We measured blood cell count; total IgE; sIgE to whole egg, EW, ovalbumin, and ovomucoid; serum specific IgG4 (sIgG4) to EW, ovalbumin, and ovomucoid; and sIgE/IgG4 ratio to EW, ovalbumin, and ovomucoid at baseline and throughout the treatment. SPTs were performed and evaluated according to the standard procedure for prick testing²⁹ with commercial extracts of whole egg (5 mg/mL), EW (1 mg/mL), ovalbumin (1 mg/mL), and ovomucoid (1 mg/mL) (Leti, Madrid, Spain). Levels of total IgE, whole egg sIgE, EW sIgE, ovomucoid sIgE, and ovalbumin sIgE were analyzed in addition to EW sIgG4, ovalbumin sIgG4, and ovomucoid sIgG4 using the ImmunoCAP System (Thermo Fisher Scientific, Waltham, Massachusetts).

Schedule of Interventions

The different time points were as follows: time 0 (T0): baseline; time 1 (T1): 15 days from end of the build-up phase for ROIT; time 2 (T2): 1 month from T1; and time 3 (T3): 5 months from baseline. Only patients in the control group underwent a second DBPCFC. CG participants who failed the second DBPCFC at T3 were enrolled into ROIT and followed up for 5 months. Procedures relating to DBPCFC, registry forms, and immune markers were performed according to the groups and times indicated in Figure 1.

Outcomes

The primary study outcome was the efficacy to induce desensitization to egg after 5 months of treatment. Desensitization was defined as the patient's ability to eat 1 undercooked egg (fried, scrambled, or omelet) without or mild AEs.³⁰ The secondary objectives were (1) to evaluate the safety; (2) to assess potential individual,

single predictors for development of more than 2 AEs; and (3) to detect immunologic changes linked to the clinical parameters.

Statistical Analysis

The sample size calculation was made as detailed in the eMaterial. All clinical outcomes were assessed by intention-to-treat analysis. Descriptive data were analyzed using means (SDs) and ranges for normally distributed variables, and medians and ranges for not normally distributed variables. The Fisher exact test was performed to determine whether the proportions of patients achieving desensitization were different between the ROIT1 and CG groups. To assess immune marker differences between CG and ROIT1 at T0 and T3 and intragroup differences in ROIT2 at T1, T2, and T3 compared with T0, the *t* test was used for quantitative variables, and the χ^2 test was applied for qualitative variables. We used the double-tailed statistical test with a significance level of 5% and a power of 80%. A 2-tailed *P* < .05 was considered significant. Multivariate regression analysis was used to analyze the variables related to the number of days for the build-up phase. Univariate and, subsequently, multivariate logistic regression analysis was used to assess independent risk factors for more than 2 AEs. The diagnostic performance of SPT, sIgE, IgG4, and sIgE/sIgG4 ratio at baseline to predict the risk of more than 2 AEs was studied by receiver operating characteristic curve analysis. After identifying the cut-off, positive and negative predictive values were calculated to determine the likelihood of developing more than 2 AEs. Statistica, version 7.1 (StatSoft Inc, Tulsa, Oklahoma), and STATA, version 12 (StataCorp, College Station, Texas) were used.

Results

Study Participants

Thirty-three patients were included (eTable 1) and randomized (Fig 2): 19 to ROIT1 and 14 to CG. Patients were distributed homogeneously between ROIT1 and CG at baseline (Table 2), except for respiratory symptoms (cough, wheezing, and/or dyspnea), which was more frequently observed in the CG during DBPCFC (*P* = .04). The median single dose of dehydrated EW eliciting

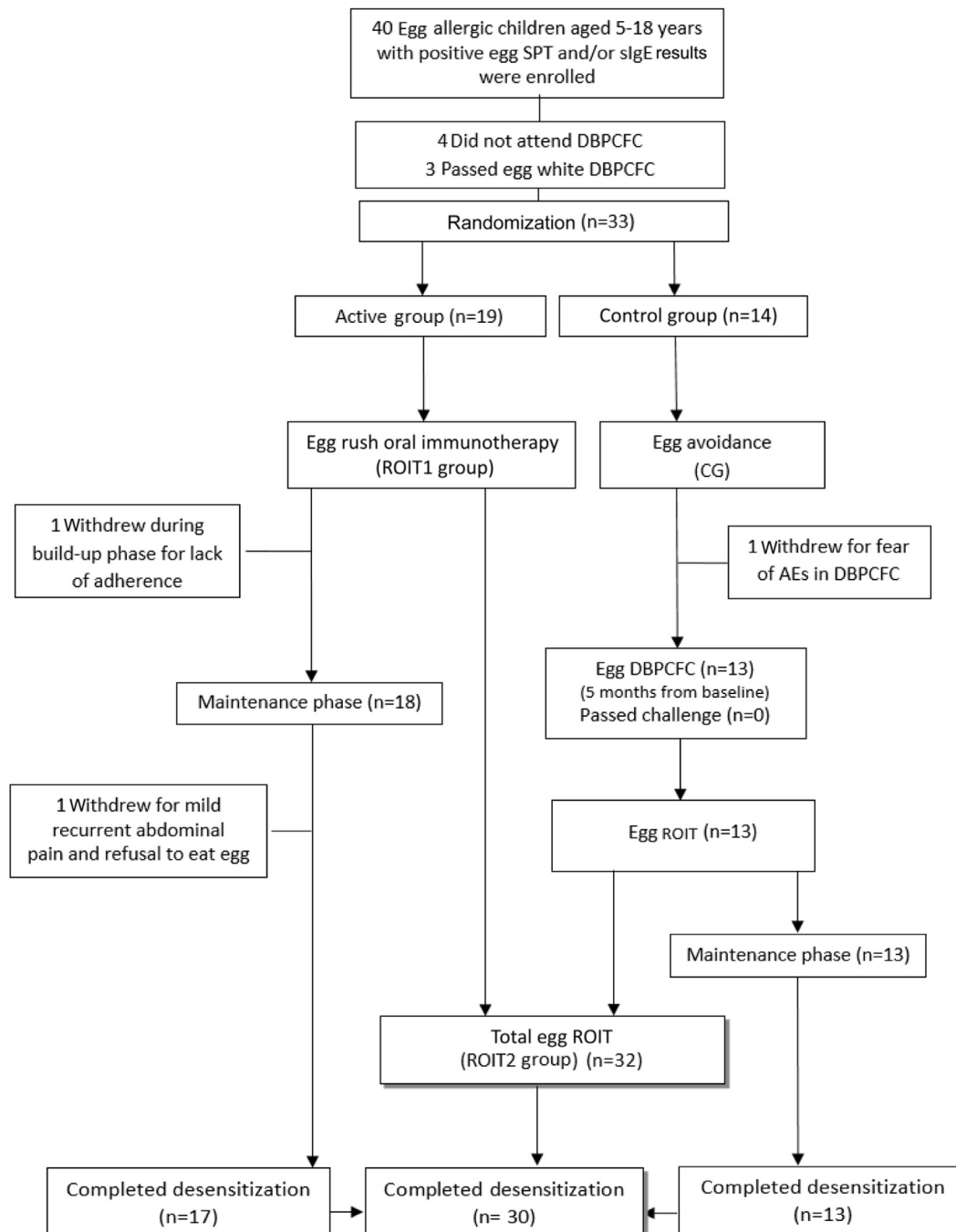


Figure 2. Study flowchart and distribution of patients in the different groups. AEs, adverse events; DBPCFC, double-blind, placebo-controlled food challenge; ROIT, rush oral immunotherapy; SPT, skin prick test.

symptoms at baseline DBPCFC was 225 mg (range, 20–3,600 mg). Both ROIT1 and CG patients had 2 peak response levels at 225 mg and 1,800 mg (30.3% and 21.2% of patients, respectively).

Outcomes

Efficacy

Seventeen (89.5%) of 19 patients in the ROIT1 group completed build-up phase and maintenance phase. One patient did not adhere to the protocol at the end of the build-up phase, and another patient failed because of mild recurrent abdominal pain and refusal to eat egg after 1 month in the maintenance phase (EW sIgE levels of

25.4 and 112 kU/L, respectively). Thirteen of 14 patients (92.9%) in the CG remained on an egg avoidance diet for 5 months. One individual in this group dropped out before undergoing the second DBPCFC for fear of AEs. None of the 13 patients in the CG passed the egg DBPCFC at 5 months (T3) (Fig 2). The egg ROIT protocol obtained an efficacy of 89.5% in ROIT1 compared with 0% in the CG (95% confidence interval, 59%–97%; $P < .001$). All 13 CG patients who failed the DBPCFC underwent egg ROIT.

A total of 32 patients underwent the egg ROIT protocol (ROIT2). Thirty-one children (96.9%) completed the build-up phase and 30 completed the maintenance phase, with a 93.8% rate of treatment success at 5 months (Fig 2).

Table 2
Baseline Clinical Characteristics and Baseline DBPCFC Results According to Study Group

Variable	Total (N = 33)	CG (n = 14)	ROIT1 (n = 19)
Male, No. (%)	18 (54.6)	7 (50)	11 (57.9)
Age, mean (SD), y	10.4 (2.6)	9.7 (2.3)	10.9 (2.7)
Age at first egg reaction, mean (SD) mo	12.9 (13.6)	15.5 (20.4)	11 (4.6)
Asthma, %	57.6	27.3	30.3
Allergy to other foods, %	69.7	85.7	57.9
Previous anaphylaxis, %	42.4	57.1	31.6
Symptoms at baseline DBPCFC, %			
• Cutaneous	20.9	17.8	23.6
• Angioedema	4.2	6.7	2.0
• Dermatitis	2.1	0	3.9
• Urticaria	14.6	11.1	17.7
• Oropharyngeal	30.21	31.11	29.4
• Digestive	29.17	26.67	31.4
• Conjunctivitis	1.04	0	2.0
• Respiratory	18.8	24.5	13.7
• Rhinitis	14.6	15.6	13.7
• Asthma	4.2	8.9 ^a	0
• Anaphylaxis	0	0	0
Threshold dose at DBPCFC, median (range), mg	225 (20–3,600)	225 (20–1,800)	225 (50–3,600)
SPT to egg protein fractions, median (range), mm			
• Whole gg	7 (4–12)	7 (5–10)	7 (4–12)
• EW	7 (4–12)	7 (4–12)	7 (5–10)
• Ovalbumin	6 (3–15)	6.5 (3–15)	6 (3–11)
• Ovomucoid	8 (0–16)	9.5 (0–16)	7 (4–11)
Serum specific IgE, median (range), kU/L			
• Whole egg	6.0 (0.32–3065)	7.0 (0.67–832)	5.9 (0.32–3065)
• EW	5.6 (0.28–1735)	5.9 (0.64–780)	5.4 (0.28–1735)
• Ovalbumin	2.7 (0.15–1075)	2.7 (0.35–474)	3.6 (0.15–1075)
• Ovomucoid	4.8 (0.26–515)	5.6 (0.27–222)	4.1 (0.26–515)
Serum specific IgG ₄ (mg/mL), median (range)			
• EW	0.4 (0–2.96)	0.4 (0–2.06)	0.2 (0.02–2.96)
• Ovalbumin	0.3 (0–2.39)	0.4 (0–1.51)	0.2 (0.02–2.39)
• Ovomucoid	0.1 (0.01–1.99)	0.2 (0.01–1.22)	0.1 (0.01–1.99)

Abbreviations: CG, control group; DBPCFC, double-blind, placebo-controlled food challenge; EW, egg white; SD, standard deviation; SPT, skin prick test; ROIT, rush oral immunotherapy (ROIT1 indicates the group who underwent ROIT at baseline).

^aThere were no significant differences between CG and ROIT1, except for asthma in DBPCFC, which was more frequently observed in the CG ($P < .05$).

Duration of build-up phase of egg ROIT

The median duration of the build-up phase in ROIT2 was 3 days (range, 1–14 days). Twenty-six of the 32 patients (81.3%) completed the build-up phase in 5 days or less, 2 patients required 6 days, 1 patient required 10 days, and 3 patients (baseline EW sIgE levels of 112, 1,735, and 1,023 kU/L) finished in 12, 12, and 14 days, respectively. Higher baseline ovomucoid sIgE levels were associated with increased duration of the build-up phase ($P = .01$). An association was observed between the duration of the build-up phase and the appearance of more than 2 AEs (mean [SD], 2.43 [0.81] for ≤ 2 AEs vs 6.31 [3.51] days for > 2 AEs) ($P < .001$).

The median initial dose of the build-up phase was 225 mg (range, 4–1,800 mg). Thirty-two children received a total of 372 doses during the build-up phase, with a mean (SD) of 11.6 (9.39) doses per patient (range, 2–42 doses). The most frequent number of doses needed to complete the build-up phase was 4 (9 patients). Three patients (9.4%) required more than 30 doses (31, 36, and 42 doses).

Immunologic changes

At 5 months, ROIT1 values from SPT to all egg protein fractions were significantly lower ($P < .05$) than in the CG, and sIgG₄ levels to EW, ovalbumin, and ovomucoid were higher ($P < .05$) (data not shown). However, no significant differences were found between the 2 groups in sIgE levels to whole egg, EW, ovalbumin, or ovomucoid, total IgE level, and blood eosinophil count (data not shown). In the ROIT1 group but not in the CG, SPT results decreased significantly (Fig 3A) and IgG₄ levels increased (Fig 3B) compared with baseline.

In the ROIT2 group, the median baseline EW sIgE level was 6.01 kU/L (range, 0.28–1,735 kU/L). However, 6 patients (18.8%) had levels higher than 20 (67% were desensitized), and 2 (6.3%) presented levels greater than 1,000 kU/L (both were desensitized) (Table 3). SPT results, sIgE levels, and sIgE/IgG₄ ratios to egg and fractions (except sIgE to EW at all time points and to egg and ovomucoid in T1 and T2) decreased, and sIgG₄ levels increased significantly at all time points compared with baseline. Decreasing SPT results to whole egg and EW occurred at an earlier stage than sIgE (Fig 4A and C). SPT results decreased significantly but remained steady between T1 and T2 and tended to increase in T3 (Fig 4A). Specific IgG₄ levels increased but exhibited a tendency to decrease from T1 to T3, although without reaching the baseline level detected at T0 (Fig 4B). Specific sIgE/sIgG₄ ratio decreased, remaining steady between T1 and T3 (Fig 4D). Peripheral eosinophilia and total IgE did not change throughout the protocol (data not shown).

Safety of egg ROIT

Safety was assessed in the ROIT2 group. Only 4 patients (12.5%), with baseline EW sIgE levels of 0.28, 1.7, 1.8, and 3.0 kU/L, had no reaction in either the build-up phase or maintenance phase.

Twenty-two of 32 patients (68.8%) in the build-up phase had 1 or more AE. The median number of reactions per child was 2.5 (range, 0–17); 16 children (50%) had 2 or fewer and 3 (9.4%) developed more than 10 events (baseline EW sIgE levels of 112, 1,023, and 1,735 kU/L). AEs occurred in 116 (31%) of the administered doses. Of 155 symptoms recorded, 54.8% were gastrointestinal, 19.4% oropharyngeal symptoms, 11% cutaneous, 7.7% rhinitis, 5.8% bronchospasm, and 1.3% (2 episodes) anaphylaxis. Ninety-nine

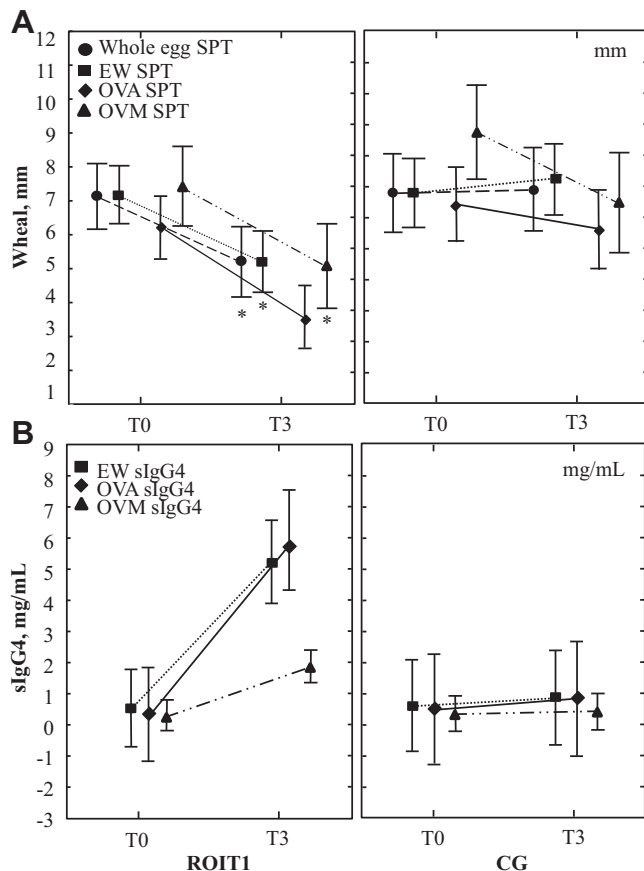


Figure 3. Mean levels of immune markers at baseline (T0) and at 5 months (T3) according to active (rush oral immunotherapy 1 [ROIT1]) and control groups (CG). A, Skin prick test (SPT) results to egg protein fractions ($P = .05-.001$). B, Serum specific IgG4 levels to egg protein fractions ($P = .05-.001$). Error bars indicate 95% confidence intervals. EW, egg white; OVA, ovalbumin; OVM, ovomucoid; slgG4, specific IgG4; T0, baseline; T3, 5 months from baseline.

AEs (85.4%) were mild, 15 (12.9%) moderate, and 2 (1.7%) severe. Most AEs occurred with the doses of 900 mg (29%) and 1,800 mg (22%). Medication used was oral antihistamine (46.9%), oral

corticosteroid (12.5%), inhaled short-acting β_2 -bronchodilator (9.4%), oxygen (6.3%), and intramuscular adrenaline in 2 (6.3%) patients.

In the maintenance phase, 5 patients (16.1%) had no AEs, and 22 (71%) experienced fewer than 10 events. Most AEs were mild and local (oropharyngeal symptoms, 75%; mild abdominal pain, 21.5%). No differences were observed in the frequency or severity of AEs between time points. The mean number of AEs per day per patient was as follows: 0.03 between the end of build-up phase to T1, 0.01 between T1 and T2, and 0.01 between T2 and T3. Aggravating factors were respiratory tract infections or digestive reactions in 10 AEs (4.2%) and stress and physical exercise in 1 AE each (0.4%).

At 5 months, 13% of children still feared undercooked egg intake, and 48.4% disliked the taste. However, 96.8% of patients had good treatment adherence.

Identification of risk factors to predict AEs

Because half of the patients in the ROIT2 group had more than 2 AEs in the build-up phase, this number was selected for the analysis of risk factors. No association was found in age, sex, age at first egg reaction, underlying asthma, or symptoms developed during the DBPCFC and the appearance of more than 2 AEs. Lower thresholds in the DBPCFC were associated with greater probability of AEs ($P = .04$).

Whole egg, EW, and ovalbumin slgE levels, followed by EW and ovalbumin slgE/slG4 ratio, at baseline had the best diagnostic performance for prediction of more than 2 AEs in the build-up phase. The best cut-off to predict more than 2 AEs was 18 kU/L or higher to whole egg and EW slgE, 15 kU/L or higher to ovalbumin slgE, and 11 kU/L or higher to EW and ovalbumin slgE/slG4 ratio (Table 4).

Discussion

The present randomized clinical trial reveals early desensitization in an egg ROIT protocol with a targeted dose equivalent to one raw egg white, displaying a relatively safe profile. All patients but 2 (89%) could eat egg at 5 months compared with 0% in the CG. After the enrollment of controls into the active treatment group, 94% were treated successfully with a build-up phase that lasted a median of 3 days and a 5-month of maintenance phase.

As opposed to other publications^{12,16,20,21} in which challenge was not performed, in the present study every patient underwent a DBPCFC before inclusion. This approach allowed the inclusion of only

Table 3

Median Levels of Immune Markers in the Rush Oral Immunotherapy 2 Group According to Different Times Throughout the Treatment

Immune Mark	T0 (n = 33)	T1 (n = 32)	T2 (n = 30)	T3 (n = 30)
SPT to egg protein fractions, median (range), mm				
Whole egg	7 (3–12)	4 ^a (2–12)	4 ^a (2–9)	6 ^a (1–9)
EW	7 (5–13)	5 ^a (2–9)	5 ^a (2–10)	5 ^a (2–9)
Ovalbumin	6 (2–11)	4 ^a (2–6)	4 ^a (2–8)	4 ^a (2–5)
Ovomucoid	8 (0–11)	5 ^a (0–10)	5 ^a (2–8)	5 ^a (1–11)
Serum specific IgE, median (range), kU/L				
Whole egg	6.5 (0.32–3065)	6.1 (0.33–2765)	5.1 (0.21–3360)	4.4 ^b (0.22–3080)
EW	6.0 (0.28–1735)	5.7 (0.34–2140)	4.9 (0.2–1990)	3.8 (0.2–2110)
Ovalbumin	2.5 (0.15–1075)	1.6 ^a (0.07–1326)	1.6 ^a (0.06–1020)	1.4 ^a (0.05–1170)
Ovomucoid	4.1 (0.18–515)	4.4 (0.22–596)	3.6 (0.16–640)	3.0 ^b (0.21–505)
Serum specific IgG4, median (range), mg/mL				
EW	0.6 (0.01–2.96)	5.8 ^a (0.08–30)	5.9 ^a (0.05–30)	3.9 ^a (0.11–25.8)
Ovalbumin	0.4 (0.01–3.08)	4.6 ^a (0.03–30)	5.3 ^a (0.02–30)	3.8 ^a (0.12–23.6)
Ovomucoid	0.3 (0.01–1.99)	2.5 ^a (0.05–30)	2.0 ^a (0.05–25)	1.5 ^a (0.05–14.6)
Serum specific IgE/IgG4 ratio, median (range)				
EW	25.9 (0.53–3154.5)	1.3 ^a (0.07–309.3)	0.9 ^a (0.11–331.1)	1.1 ^a (0.09–314.5)
Ovalbumin	15.1 (0.38–2150)	0.6 ^a (0.03–161)	0.4 ^a (0.02–215.5)	0.5 ^a (0.03–174.4)
Ovomucoid	28.3 (0.22–1839.3)	2.4 ^a (0.01–463.5)	0.1 ^a (0–13.1)	1.7 ^a (0.05–455)

Abbreviations: EW, egg white; SPT, skin prick test; T0, baseline; T1, 15 days from the end of the build-up phase; T2, 1 month from T1; T3, 5 months from baseline.

^a $P < .001$.

^b $P < .05$.

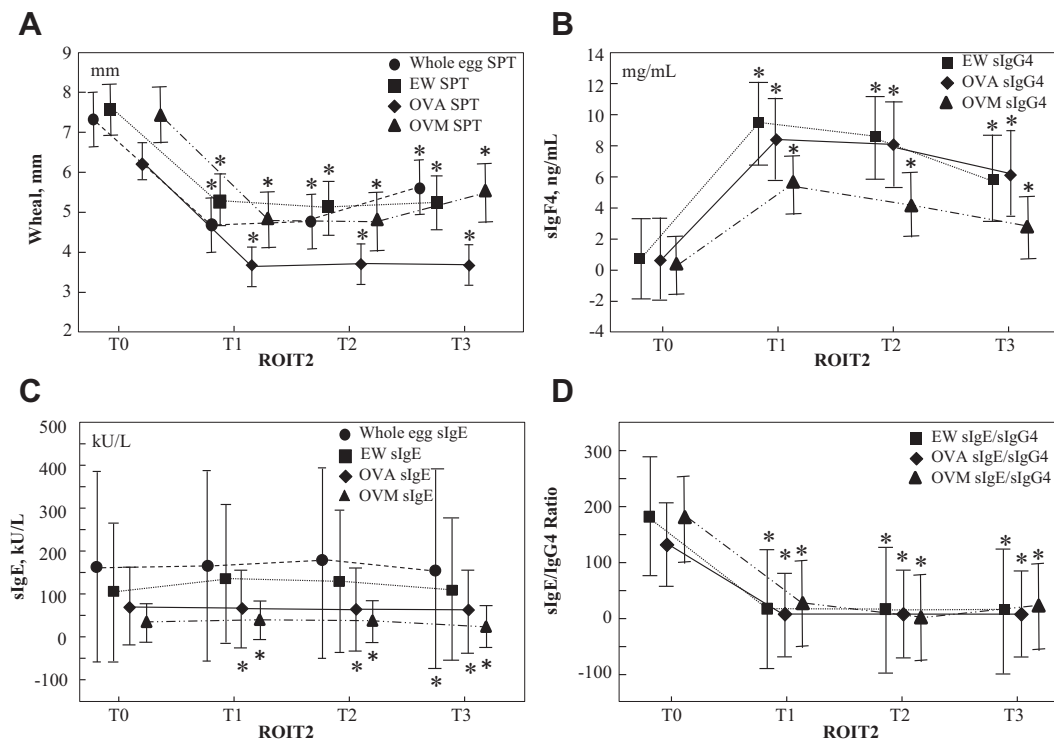


Figure 4. Mean levels of immune markers in the rush oral immunotherapy 2 (ROIT2) group according to different times throughout the treatment. A, Skin prick test (SPT) results to egg protein fractions ($P < .001$). B, Serum specific IgG4 (slgG4) levels to egg protein fractions ($P < .001$); C, Serum specific IgE (slgE) to protein fractions ($P < .001$); D, serum slgE/slG4 ratio to egg protein fractions ($P < .001$). Error bars indicate 95% confidence intervals. EW, egg white; OVA, ovalbumin; OVM, ovomucoid; slgG4, specific IgG4; T0, baseline; T1, 15 days from the end of the build-up phase; T2, 1 month from T1; T3, 5 months from baseline.

patients currently allergic to egg. Thanks to this approach, we avoided the inclusion of 8% of patients with egg tolerance in the protocol.

Use of the threshold dose at the baseline DBPCFC avoided the administration of the lowest doses in all patients. Only 2 previous nonrandomized, noncontrolled studies^{14,19} have begun treatment following a similar method. Nevertheless, in the study by Ruiz-García et al,¹⁹ only 4 patients underwent a baseline egg oral challenge, and in the protocol followed by Itoh et al,¹⁴ the initial dose was set at approximately one-tenth of the threshold dose at DBPCFC for each patient (6 children), rather than in the last single tolerated dose. To date, most published egg OIT protocols have been designed for a build-up phase of approximately 60 days.³⁰ Only García-Rodríguez et al¹⁵ used a 5-day protocol in 21 patients, using a less allergenic target dose that consisted of a cooked egg (ie, boiled egg, omelet) plus only 8 mL of raw EW.

Studies have found that OIT is able to induce desensitization to egg, with effectiveness ranging from 0%³¹ to 100%¹⁴ and a median success rate of more than 80%.³⁰ Under the current protocol, after 5 months of therapy, none of the children in the CG were able to eat a regular serving of egg, compared with 89% of those receiving ROIT. After increasing the total number of treated patients to 32 egg allergic

children, the proportion of desensitized individuals increased to 94%; this figure is similar to the percentage achieved using the 32-day protocol previously published by our group (93%).²⁴ In the only systematic review of studies on egg OIT,³² with 4 randomized controlled studies using an extract with preserved allergenic capacity,^{16,20,21,31} 39% of the active treatment patients were able to tolerate a full serving of egg (1 egg) compared with 11.9% of control patients. With our protocol, 94% ingested 1 egg after 5 months.

The better outcomes seen in the present study may be related to differences in baseline egg slgE levels. In our active group, the median baseline EW slgE level was lower (6.0 kU/L) than those reported in the studies by Dello Iacono et al (23.3 kU/L),³¹ Vickery et al (12.5 kU/L),¹³ and Burks et al (10.3 kU/L).¹⁶ However, in our study, all but 2 patients with EW slgE levels greater than 20 kU/L were desensitized. Notably, 2 patients with baseline EW slgE levels of 1,023 and 1,735 kU/L were desensitized, although with more doses, more AEs, and a longer build-up phase than the mean. In addition, patients ingested a higher egg dose (approximately 2,808 mg of protein) with the present protocol than in other studies (300 mg¹¹ and 1,600 mg¹⁶), despite being a shorter protocol, thereby highlighting its efficacy.³³ Caminiti et al,²³ with a high

Table 4
Optimal Cut-offs for Serum slgE and Serum slgE/IgG4 Ratio at Baseline and Their Discriminative Potential to Determine the Development of More Than 2 Adverse Events

	Cut-offs, kU/L	AUC (95% CI)	P Value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR
Whole egg slgE	18	0.88 (0.71–0.96)	<.001	81.3	87.5	81.2	100	6.5
EW slgE	18	0.89 (0.75–0.98)	<.001	81.3	87.5	81.2	100	6.5
Ovalbumin slgE	15	0.88 (0.71–0.96)	<.001	87.5	81.3	80.1	100	4.7
EW slgE/slG4	11	0.84 (0.67–0.94)	.001	100	62.5	87.5	62.5	2.7
Ovalbumin slgE/slG4	11	0.82 (0.67–0.94)	.002	100	62.5	81.3	75.0	2.7

Abbreviations: AUC, area under the curve; CI, confidence interval; EW, egg white; LR, likelihood ratio; NPV, negative predictive value; OVA, ovalbumin; PPV, positive predictive value; slgE, specific IgE; slgG4, specific IgG4.

target dose (3,200 mg), also achieved a high rate of success (94%), although with a longer build-up phase (112 days).

There has been debate surrounding the effect of using either raw or cooked egg on treatment efficacy. Some studies using cooked egg found a decrease in efficacy during the maintenance phase. In the study by Itoh et al,¹⁴ all 6 patients enrolled achieved the intermediate goal of 1 g of powdered raw egg followed by 1 heated egg as the main outcome of the protocol, doing so in a build-up phase of approximately 12 days (range, 9–18 days). However, only 50% of patients tolerated 1 g of dehydrated EW after 9 months of the maintenance phase. Fuentes-Aparicio et al²¹ reported that only 20 (54%) of 37 patients who tolerated a raw EW at the end of the build-up phase passed the OFC with raw EW 6 months later. In both studies, patients' build-up phase was performed with raw egg, although the maintenance phase included cooked egg, which may have been the cause of the loss of desensitization. In the current study, egg was given in an undercooked state (nearly raw) during the maintenance phase. Although nonstandardized, it was preferred to preserve its allergenicity, improve adherence, and mimic a real-life egg consumption.

In sum, several critical factors may explain the high efficacy obtained with our protocol: the lower sIgE to egg proteins compared with that of other protocols, the high target doses in the build-up and maintenance phases, raw or undercooked egg with preserved allergenic material used to perform not only build-up phase but also the maintenance phase, and use of a rush schedule in build-up phase.

The immunologic mechanisms underlying the clinical changes observed during egg OIT are not entirely elucidated. Increases in sIgG4 antibody levels, with or without decreases in sIgE antibody levels, have been associated with loss of clinical reactivity to milk and egg.^{16,33–35} In the current study, the decrease of the wheal size on SPT, suggesting a suppression of mast cells, and an increase in sIgG4 antibody levels were noted only in children receiving OIT. The intragroup analysis of the final egg ROIT2 group revealed a significant decrease of wheal size for the SPT to all egg fractions and sIgE/sIgG4 ratios. The decrease of ovalbumin sIgE was also very significant, although this was lower for ovomucoid and whole egg sIgE and of little relevance for EW sIgE. The decrease in SPT results and sIgE/sIgG4 ratios occurred earlier and were more significant than the changes in sIgE levels.

AEs occurred in 31% of doses administered during the build-up phase, which is comparable to the 36% reported by Burks et al.¹⁶ In all studies of egg OIT except one,²³ the percentage of patients with at least 1 AE during build-up phase is high (50%–100%).³⁰ In our study, 68.7% of patients experienced at least 1 AE in the build-up phase, with a median of 2.5 episodes per patient; this finding is similar to other published studies.^{17,24} In the 2 published rush protocols, with a build-up phase of 12 and 11 days, 100% and 78% of patients developed AEs, respectively.^{14,15} Although in published protocols serious reactions were rare or nonexistent,^{13,14,16,24} treatment discontinuation was sometimes required.^{16,22,24,31} In our study, it was not necessary to discontinue the treatment during the build-up phase for this reason because of the mild intensity of most events. As in our study, the most frequent AEs reported in egg OIT are gastrointestinal (55%).^{11,14,17,21,22,24} One patient in our study dropped out because of persistent mild abdominal pain and refusal to eat egg. We attempted to rule out eosinophilic esophagitis,³⁶ but parents refused to perform endoscopy. All symptoms subsided after withdrawal of egg.

Several attempts have been made to find clinical and/or biological markers to identify patients who are more prone to develop AEs during egg OIT. Clinical risk factors, such as underlying asthma and lower threshold at DBPCFC, have been associated with anaphylaxis or early discontinuation of egg OIT.²² In our study, lower threshold at baseline DBPCFC was associated with higher risk

of AEs during the build-up phase. Immunologic markers correlated with a higher risk of more than 2 AEs were high baseline egg and EW sIgE (both ≥ 18 kU/L), ovalbumin sIgE (≥ 15 kU/L) levels, and EW and ovalbumin sIgE/sIgG4 ratios (both > 11 kU/L). Published cutoffs for sIgE predicting a higher risk of AEs in egg OIT are lower (> 8.85 kU/L for EW and ovomucoid sIgE and > 6.49 kU/L for ovalbumin)²² than those reported in this article, although the risk criteria analyzed are significantly different. Like other authors, we identified infections^{10,20,23} to be the most common aggravating factor for AEs occurring during the maintenance phase.

Although usually overlooked, the taste of egg itself might be a relevant factor that influences the adherence to the treatment.²⁴ However, we did not record a lack of adherence attributable to this factor in the 48% of patients who disliked it.

It could be argued the lack of a placebo group decreases the reliability of the data reported; however, the use of baseline DBPCFCs in the entire population and exit DBPCFCs in the CG minimizes this weakness. In addition, the success ratio in patients with low and high sIgE levels to EW (> 20 kU/L) was higher than that found in a recent systematic review.³² Therefore, the different profiles of patients treated allow the use of this treatment in patients with both profiles (low or high IgE sensitization), bearing in mind the different expectations of success. Another factor that could explain the increased efficacy of our protocol compared with that of other authors might be the fact that the baseline DBPCFC threshold was high in 8 patients; this should be taken into consideration before extrapolating these data into another population.

In conclusion, we found that the build-up phase for egg OIT may be shortened by establishing the starting dose based on the eliciting threshold and a 5-day rush build-up phase. This approach was safe and effective in 94% of the population studied, which is greater than longer protocols. The protocol provides protection and diet normalization in a short time. Threshold dose at baseline egg DBPCFC, egg sIgE levels, and egg sIgE/IgG4 ratio could be used as potential predictors of adverse events. This study not only provides additional support for the existing scattered data on the efficacy of ROIT, but also provides evidence of the extension of its efficacy throughout the maintenance with uncooked egg.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.11.023>

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Supplementary Data

eMaterial. Sample Size

The necessary sample size was predetermined to estimate the proportions of patients after egg rush oral immunotherapy (ROIT) and without it; an α of 95% and a statistical power ($1 - b$) of 90%; an

expected proportion of 86% in the ROIT1 group based on the study by García Rodríguez et al¹⁵ and 20% in the control group, although it was expected to find a very low proportion in this group. Assuming of 20% of participants were lost to follow-up in each group, the minimum required sample size was 12 patients in each group. Finally, a few more patients were included because of the opportunity to do so and to ensure achieving our final goal.

eTable 1
Study Participant Characteristics

Patient No. ^a	Sex/ age, y	Age of first AE, mo	Diagnosis of respiratory symptoms ^c	Allergy to other foods	Previous anaphylaxis with egg	Symptoms in DBPCFC	Threshold doses, mg	Whole egg SPT result, mm	EW SPT result, mm	Ovalbumin SPT result, mm	Ovomucoid SPT Result, mm	Whole Egg sIgE, kU/L	EW sIgE, kU/L	Ovalbumin sIgE, kU/L	Ovomucoid sIgE, kU/L	EW sIgG4, mg/mL	Ovalbumin sIgG4, mg/mL	Ovomucoid sIgG4, mg/mL
1	M/16	10	Yes	Milk Fish Fruits Shellfish	No	Digestive ^d OPS Rhinitis	50	11	8	5	7	7.78	6.09	4.75	0.85	0.14	0.12	0.03
2	M/15	12	Yes	No	Yes	Digestive OPS Urticaria Rhinitis	225	9	8	9	10	10.8	10.5	5.53	11.5	0.02	0.02	0.01
3	F/12	12	No	Fruits Nuts	No	Digestive OPS	450	10	7	5	6	5.45	4.78	1.54	1.6	0.17	0.22	0.03
4	F/12	5	Yes	Milk	No	Digestive OPS Dermatitis	1800	5	7	7	5	1.83	1.74	0.63	1.92	0.07	0.08	0.03
5	M/10	5	No	Milk	Yes	Urticaria OPS Urticaria Rhinitis	225	6	8	10	6	6.81	6.02	4.1	6.09	0.04	0.03	0.01
6 ^b	F/10	6	No	No	No	Digestive OPS	100	9	8	10	5	32.8	25.4	6.9	4.76	0.63	0.42	0.26
7	F/10	9	Yes	Fish Shellfish	Yes	Digestive OPS Rhinitis	100	12	10	7	6	3065	1735	1075	515	0.55	0.5	0.28
8 ^b	F/9	9	Yes	Milk	Yes	Digestive Rhinitis	225	7	6	6	7	104	112	50.5	46.1	2.96	2.39	1.99
9	M/12	10	Yes	No	No	Digestive OPS Urticaria	450	10	9	12	11	5.48	5.43	3.61	6.57	0.21	0.14	0.13
10	F/8	9	Yes	No	No	Digestive OPS	225	7	5	3	6	10.9	9.83	8.73	3.78	0.83	0.76	0.97
11	M/8	11	No	Milk Fish Shellfish Nuts	No	Digestive Urticaria	1800	5	6	5	4	1.96	1.82	1.85	0.66	0.04	0.03	0.01
12	M/8	12	No	No	No	Digestive OPS	100	6	6	6	5	4.85	4.75	2.19	5.59	0.07	0.04	0.06
13	M/7	8	No	Shellfish Nuts	No	Digestive OPS Urticaria Rhinitis	225	5	7	7	6	3.34	3.12	1.23	3.78	0.06	0.07	0.02
14	M/8	18	No	No	No	Digestive OPS Urticaria Rhinitis	450	5	7	5	5	15.2	13.9	9.16	13.3	1.12	0.87	0.73
15	F/12	24	No	No	No	Urticaria	3600	4	8	4	3	0.68	0.61	0.43	0.46	1.15	1.12	0.13
16	M/13	14	Yes	Fruits Nuts	Yes	Angioedema Conjunctivitis	1800	5	6	5	4	0.32	0.28	0.15	0.26	0.09	0.07	0.01
17	F/10	8	Yes	Shellfish	No	Digestive OPS Urticaria	225	7	7	8	9	14.3	13.1	7.23	13.4	0.56	0.48	0.25
18	M/13	16	No	No	No	Digestive OPS Urticaria	1800	8	6	5	8	3.13	3.02	1.53	4.1	0.57	0.42	0.82

(continued on next page)

eTable 1 (continued)

Patient No. ^a	Sex/age, y	Age of first AE, mo	Diagnosis of respiratory symptoms ^c	Allergy to other foods	Previous anaphylaxis with egg	Symptoms in DBPCFC	Threshold doses, mg	Whole egg SPT result, mm	EW SPT result, mm	Ovalbumin SPT result, mm	Ovomucoid SPT Result, mm	Whole Egg sIgE, kU/L	EW sIgE, kU/L	Ovalbumin sIgE, kU/L	Ovomucoid sIgE, kU/L	EW sIgG4, mg/mL	Ovalbumin sIgG4, mg/mL	Ovomucoid sIgG4, mg/mL
19	M/15	12	Yes	Fish	Yes	Digestive OPS	1800	5	8	6	5	5.95	4.72	0.76	0.92	2.37	1.79	0.66
20	M/12	6	Yes	Nuts	Yes	Digestive OPS	225	8	7	4	5	7.1	6.02	2.48	4.14	0.48	0.28	0.6
21	M/11	8	Yes	No	Yes	Urticaria Rhinitis Respiratory	100	10	9	6	5	3.56	3.1	2.31	1.72	0.34	0.26	0.3
22	M/10	8	Yes	Fruits	Yes	Angioedema Digestive OPS	225	7	7	5	5	6.49	6.01	2.55	7.7	2.22	3.08	0.68
23	F/10	6	Yes	Nuts	No	Urticaria Rhinitis	1800	8	5	7	6	2.52	2.21	1.83	1.76	1.41	1.08	0.37
24	M/11	8	Yes	Milk	Yes	Respiratory Digestive OPS	1800	12	10	12	8	13.7	7.52	1.78	6.45	1.15	1.13	0.78
25	M/8	6	No	Fish	No	Urticaria Digestive OPS	450	6	7	6	4	2.33	2.11	0.98	2.56	0.68	0.72	0.28
26	F/13	9	No	Shellfish	Yes	Urticaria Rhinitis	225	7	13	8	9	8.11	7.89	3.49	10.5	0.12	0.1	0.08
27	M/6	9	No	Nuts	Yes	Digestive OPS	20	5	7	7	5	56.6	48.7	25.8	37.9	0.28	0.18	0.3
28 ^b	F/7	6	Yes	Cereals	No	Rhinitis Digestive OPS	50	8	11	11	7	664	580	526	184	0.85	0.78	0.47
29	F/11	84	No	Milk	No	Respiratory Digestive OPS	450	5	5	4	7	1.89	1.67	2	0.18	1.06	0.67	0.83
30	F/7	13	Yes	Shellfish	No	Digestive OPS	50	11	10	13	10	59.3	45.3	24.3	8.51	1.18	1.27	0.28
31	F/8	25	Yes	Legumes	Yes	OPS	900	3	5	6	2	0.97	0.91	0.63	0.65	0.29	0.22	0.27
32	M/13	15	Yes	Milk	Yes	Angioedema Rhinitis Respiratory	225	5	8	5	7	0.55	0.55	0.31	0.59	0.01	0.01	0.01
33	F/9	14	No	Fruits	No	Angioedema Rhinitis Digestive OPS	50	8	6	11	7	1312	1023	816	402	2.29	2.08	0.89

Abbreviations: AE, adverse event; DBPCFC, double-blind, placebo-controlled food challenge; EW, egg white; OPS, oropharyngeal symptoms; sIgE, serum specific IgE; SPT, skin prick test.

^a1–19, Patients belonging to rush oral immunotherapy 1 group; 20–33, patients belonging to the control group.

^bPatients who did not finish the protocol.

^cRespiratory symptoms include cough, wheezing, and/or dyspnea.

^dDigestive symptoms include moderate-severe persistent abdominal pain, nausea or vomiting, and/or diarrhea.