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

A randomized clinical trial

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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.

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

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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 12[14] and 5[15] 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 DBPCFC[26] 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 passed the challenge. Every patient was kept under surveillance for at least 2 hours after the last dose was administrated or 2 hours after symptoms had totally subsided.

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
	2	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
100		12	50	39
225		13	100	78
450		14	225	175.5
		15	450	351
900	4	16	450	351
1800		17	900	702
		18	1800	1404
	5	19	1800	1404
		20	3600	2808

Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; EW, egg white; ROIT, rush oral immunotherapy.
[a]The 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 administrated in the hospital at intervals of 60 minutes.

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.