Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy

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Background: We previously reported the results of a randomized placebo-controlled study of egg oral immunotherapy (eOIT) in which 27.5% of subjects achieved sustained unresponsiveness (SU) after 2 years. Here we report the results of treatment through 4 years and long-term follow-up.

Objective: We sought to evaluate the efficacy and safety of eOIT in participants treated up to 4 years.

Methods: Children with egg allergy (5-18 years old) received eOIT (n = 40) for up to 4 years or placebo (n = 15) for 1 year or less. The key outcome was the percentage of subjects achieving SU by year 4. Safety and immunologic assessments were performed, and long-term follow-up questionnaires (LFQs) were administered after study conclusion (LFQ-1) and 1 year later (LFQ-2).

Results: Of 40 eOIT-treated subjects, 20 (50.0%) of 40 demonstrated SU by year 4. For those subjects still dosing during years 3 and 4, mild symptoms were present in 12 (54.5%) of 22 subjects. At the time of the LFQ, more subjects receiving eOIT (LFQ-1, 23/34 [68%]; LFQ-2, 21/33 [64%]) were consuming unbaked and baked egg versus placebo (LFQ-1, 2/11 [18%], $P = .006$; LFQ-2, 3/12 [25%], $P = .04$). Of subjects achieving SU, 18 (90%) of 20 completed the LFQ, with 18 (100%) of 18 reporting consumption of all forms of egg. When compared with subjects not achieving SU, subjects achieving SU had higher IgG_4 values ($P = .001$) and lower egg skin prick test scores ($P = .0002$) over time and a lower median baseline ratio of egg-specific IgE to total IgE (1.1% vs 2.7%, $P = .04$).

Conclusions: SU after eOIT is enhanced with longer duration of therapy and increases the likelihood of tolerating unbaked egg in the diet. (J Allergy Clin Immunol 2016;137:1117-27.)

Key words: *Egg allergy, food allergy, oral immunotherapy, desensitization, sustained unresponsiveness, immune tolerance, IgE, follow-up*

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Abbreviations used
AUC: Area under the curve
eOIT: Egg oral immunotherapy
IQR: Interquartile range
kU_A: Kilounits of antibody
LFQ: Long-term follow-up questionnaire
OFC: Double-blind, placebo-controlled oral food challenge
OIT: Oral immunotherapy
OR: Odds ratio
SPT: Skin prick test
SU: Sustained unresponsiveness

Egg allergy is common in childhood, with a prevalence ranging from 0.5% to 2.5%.[1-4] Egg and egg-derived products are ubiquitous ingredients, and therefore avoiding accidental exposures leading to reactions is difficult.[5] Although the long-term prognosis of egg allergy is generally favorable, recent studies have suggested that resolution might occur more slowly than was previously appreciated, and a subset of patients with egg allergy have egg allergy that persists into adolescence.[6,7] Until and if tolerance develops spontaneously, patients are at risk for allergic reactions.

Several approaches to mitigating this risk have been examined in clinical trials. The best-studied approach is oral immunotherapy (OIT), a procedure that aims to decrease reactivity to allergen with gradual escalation of daily doses followed by a maintenance treatment period.[8] Our group previously reported that 10 months of treatment with egg oral immunotherapy (eOIT) was superior to placebo when comparing the successfully consumed dose during ongoing therapy (clinical desensitization) and that this benefit was enhanced with an additional year of therapy.[9] Sustained unresponsiveness (SU; defined as a lack of dose-limiting symptoms during a double-blind, placebo-controlled oral food challenge [OFC] to and subsequent open feeding of egg 4-6 weeks after stopping OIT) was achieved in 28% of the subjects receiving eOIT by month 24, with all reporting consumption of egg 1 year later. The results from this trial suggested that OIT might have a long-term disease-modifying effect, as noted for outcomes assessed during 2 years of therapy.

Evidence of such an outcome would be a major breakthrough in the development of a food allergy treatment. Currently, the stability of treatment effects after such trials are not well understood. Two recent studies have provided long-term follow-up data after milk and peanut OIT, and both demonstrated that regular oral intake of the allergenic food appears to be required to maintain the protective effect after OIT; however, continued intake was difficult for some patients to continue.[10,11] Another study comparing peanut OIT and sublingual immunotherapy demonstrated suppression of basophil effector cell function and dendritic cell–driven T_H2 cytokine responses after peanut OIT, with some reversibility of those responses noted when antigen was discontinued in those achieving SU.[12,13] These studies indicate that if allergen is avoided, clinical relapse can ensue, even among subjects previously considered to be treatment successes. This situation poses potential safety concerns if such subjects incorrectly believe themselves to be protected.[14] Additional long-term studies after OIT treatment are necessary to further examine the feasibility, safety, and durability of the treatment effect.

To investigate the effects of long-term OIT in patients with egg allergy, we continued the previously reported trial of eOIT for up to 4 years of treatment.[9] The proportion of subjects achieving SU in those 4 years was calculated. After the treatment phase of the study ended, an annual long-term follow-up questionnaire (LFQ) to assess egg consumption patterns was administered.

METHODS

Study design and end points assessed

The current study is an extension of a previously published multicenter, randomized, double-blind, placebo-controlled study of eOIT.[9] As previously reported, subjects were enrolled and treated with placebo or eOIT for 10 months. Placebo-treated subjects were discontinued from dosing after 10 months and were followed as treatment controls through year 2 and then surveyed for long-term follow-up. Subjects receiving eOIT continued dosing to year 4 and discontinued dosing after passing an OFC off therapy (ie, those achieving SU) after any yearly challenge point (years 2, 3, or 4). The key outcome of this study was the percentage of subjects with SU to egg after up to 4 years of eOIT. SU was defined as a lack of dose-limiting symptoms during a 10-g egg white powder (approximately 8 g of egg white protein) OFC and open feeding of a meal-sized portion of whole cooked egg 4 to 6 weeks after stopping eOIT while maintaining an egg-restricted diet. Secondary outcomes included safety during the additional years of treatment by using methods previously reported[9] and immunologic assessments. Egg consumption was evaluated after the last subject completed the treatment phase by having all available subjects complete an LFQ, which was repeated approximately 1 year later. Tolerance to baked egg consumption was not assessed during the study entry or at any point in the study.

Study population

Subjects were aged 5 to 18 years from 5 US sites, with inclusion/exclusion criteria previously reported.[9] The study was approved by each site's institutional review board, and written consent/assent was obtained. The study was conducted under a US Food and Drug Administration investigational new drug application and monitored by an independent data and safety monitoring board from the National Institute of Allergy and Infectious Diseases.

eOIT dosing and participant follow-up

Dried standard egg white powder (raw, uncooked egg) was purchased from a commercial manufacturer (Deb-El Food Products, Elizabeth, NJ) and manufactured for individual doses for eOIT dosing. The daily OIT dose was mixed in a vehicle, such as pudding or applesauce, for dosing. Limiting physical activity was recommended for all participants for the first 2 hours after OIT dosing. Subjects who attained SU at any challenge point were instructed to incorporate egg into their diets *ad libitum*; however, there were no specific recommendations made on the frequency, amount, or type of egg product.[9] Subjects who did not have SU at year 2 or year 3 were instructed to continue egg avoidance and to continue open-label dosing per protocol with 2000 mg/d eOIT for up to 4 years of treatment. Subjects who failed the SU OFC resumed eOIT maintenance dosing through dose escalations every 1 to 2 weeks beginning with 25% of their maintenance dose or their highest tolerated cumulative dose during the OFC, whichever was lowest. Subjects who withdrew from dosing for any reason other than achieving SU or were originally in the placebo treatment arm were instructed to continue dietary avoidance of egg. An exception included one site's institutional review board mandate to cross over placebo subjects to eOIT treatment after year 2 as part of a separate treatment protocol. Subjects who did not achieve SU after the 4-year study period were discontinued from dosing and instructed to continue dietary avoidance. For LFQ analysis, subjects were grouped into 4 categories based on their treatment and last known clinical outcome status: (1) eOIT-SU, (2) eOIT-desensitized, (3) eOIT-not desensitized, and (4) placebo.