



Egg oral immunotherapy

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Purpose of review

Egg allergy is one of the most common food allergies of childhood and no interventional therapy is currently approved by the Food and Drug Administration. Much recent research has focused on the safety, efficacy, and mechanism of oral immunotherapy (OIT) as a disease-modifying treatment.

Recent findings

Small pilot studies with varying protocol designs have shown egg OIT to be relatively well tolerated, and efficacy is suggested but not formally demonstrated. At this time, no placebo-controlled randomized trial has been published confirming desensitization and no published study has convincingly demonstrated the development of OIT-induced tolerance to egg.

Summary

Egg OIT is a promising modality for providing temporary protection from reactions caused by accidental egg exposure. However, the overall strength of the evidence in favor of egg OIT is limited by small sample sizes and the lack of controls, both of which are important considerations given the spontaneous resolution expected in egg allergy. More high-quality studies are necessary before egg OIT can be recommended as a viable treatment option.

Keywords

desensitization, egg allergy, oral immunotherapy, tolerance

INTRODUCTION

Allergy to hen's egg is very common in childhood, with an estimated cumulative prevalence of 2.6% by age 2.5 years [1]. The prevalence of egg allergy has been shown to be significantly higher in children with atopic dermatitis [2], and in young children, egg sensitization is a known risk factor for later progression to allergic respiratory disease [3]. Allergic reactions to egg may vary in severity from an atopic dermatitis trigger to mild urticaria to systemic anaphylaxis, and the latter represents an important precaution when administering certain vaccines, especially influenza [4[■]]. Most egg allergens are susceptible to heat and gastric digestion, and it has been hypothesized that these characteristics account for the observation that many egg-allergic children outgrow it in early life [5]. Tolerance to extensively heated (e.g. baked) egg is common and appears to be an intermittent step in this process, supporting the idea that much of childhood egg allergy is due to IgE recognizing conformational epitopes [6]. However, a recent study [7] reported persistence of egg allergy into the second decade. These patients tend to be distinguished by more severe clinical reactions and a robust IgE response, especially to the linear epitopes of the major allergen ovomucoid, which is a stable glycoprotein

that is resistant to heat and digestion [8]. These data suggest that multiple egg allergy phenotypes exist, and that they may be identified by specific IgE-epitope repertoires, a distinction which may have important therapeutic implications. Although many children will spontaneously outgrow their egg allergy by early school age, clearly a significant proportion, who represent the group at highest risk of anaphylaxis, will not. Oral immunotherapy (OIT) is the most extensively studied approach toward a treatment for food allergy, and there has been significant focus on using OIT for egg allergy. However, the evidence base at this stage is not robust enough [9[■]] to change clinical practice from the current standard of care, a strict diet eliminating exposure to the allergen [10[■]]. The purpose of this article is to review recent advances made in the study of OIT for egg allergy.

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KEY POINTS

- Oral immunotherapy is an investigational treatment for egg allergy.
- Early pilot trials suggest efficacy, but definitive conclusions are prevented by study design flaws including small sample sizes, soft outcome measurements, lack of controls, and absence of randomization.
- Large, high-quality studies with well defined endpoints are needed and the first is already underway.
- In the absence of stronger evidence of safety and efficacy, egg OIT cannot be currently recommended for routine clinical practice.

CONVENTIONAL PILOT STUDIES

Studies of the treatment of food-allergic patients with a form of OIT were published at least as early as 1930 [11] and continued throughout the 20th century. These early attempts at oral therapy were based on the concept of gradually increasing allergen administration in the treatment of allergic rhinoconjunctivitis, popularized by subcutaneous injection immunotherapy. They utilized primarily crude extracts of fresh food and did not include mechanistic studies. In the 2000s, several investigators, primarily although not exclusively working in Europe, published small pilot studies that established the feasibility of egg OIT [12–15]. This included a trial that used interferon- γ as an adjuvant [16]. In one of the first controlled studies of OIT, Patriarca *et al.* [13] showed safety and proof-of-concept, documenting gradual clinical, and immunologic changes in most treated patients but not untreated standard-care controls. In this study of 59 adults and children with milk, egg, fish, and other food allergies, the control group consisted of 16 patients who refused to participate in active treatment; such a control group may have important reasons for not participating in active treatment, and thus may not be as generalizable as those randomly assigned allergen avoidance. Fifteen egg-allergic patients were treated with a liquid extract of raw whole egg, and doses were gradually escalated to the equivalent of one full egg per day over the course of approximately 5 months, at which time they were instructed to eat one whole egg at least twice per week as a maintenance therapy. Desensitization was considered successful by virtue of regular egg ingestion without evident clinical symptoms. Double-blind, placebo-controlled food challenges (DBPCFC) were performed at baseline to confirm the diagnosis, but there was no food

challenge conducted after treatment to formally assess eliciting dose thresholds. Eleven of 15 (73%) completed the protocol and were considered successful. The ages of these patients and their egg-specific immunologic data were not reported in this study. Across the active treatment group as a whole, allergen-specific IgE declined and was accompanied by a rise in allergen-specific immunoglobulin G (IgG)4, similarly to other immunotherapy studies. Among the control group, there were no changes in skin prick tests or in-vitro tests and after 18 months, the DBPCFCs remained positive in all controls. Fifty-one percentage of treated patients developed allergic side effects that responded well to standard antihistamines or cromolyn.

In one of the first US studies of egg OIT, Buchanan *et al.* [17] enrolled seven children aged 14 months to 7 years in an open-label clinical trial in a large referral center. After 24 months of maintenance treatment, in which all patients were treated with 300 mg of daily egg white powder mixed into a vehicle food, four of seven (57%) patients passed an oral food challenge without any symptoms while on treatment and were considered desensitized. However, thereafter egg OIT was stopped for 3 months to assess whether the desensitization effect would persist, and two of four (50%) regained clinical sensitivity during a follow-up food challenge, suggesting that the state of desensitization was transient. No changes in egg IgE levels were observed, but egg IgG levels increased. Subsequent patients in the same center were enrolled in a modified protocol, reported by Vickery *et al.* [18[†]]. In this follow-up study, the maintenance dose of egg OIT was individualized based on the patient's egg white IgE level, and serial dose escalations were incorporated in an attempt to decrease the IgE level below 2 kU_A/l to increase efficacy. The result of using such an approach was that patients were treated with higher daily dosages (median 2400 mg) and for much longer (median 33 months) than in the study of Buchanan *et al.* As a result, six of six (100%) patients, including three patients whose egg white IgE remained more than 4 kU_A/l despite dose escalation, passed a DBPCFC 1 month after stopping OIT were considered tolerant and were advised to consume egg products *ad libitum*. Skin prick tests and specific IgE levels to egg white decreased, and there were no changes in egg-specific cytokines or CD4⁺ CD25⁺ T cell numbers. Although both of these studies from the same center demonstrated that some OIT-treated patients will develop tolerance, as evidenced by passage of a DBPCFC after discontinuing OIT, it is not possible to conclude that the OIT caused the tolerance to occur.

None of these studies incorporated randomization techniques or a placebo control, which are key limitations in the study of a disease for which spontaneous improvement is the expected course. As a result, these studies can be regarded as proof-of-concept (e.g. OIT can be safely and feasibly performed and has immunomodulatory properties), but they do not provide definitive evidence of the efficacy of egg OIT. These studies suggest that short trials with relatively low-maintenance doses may only provide evidence of transient desensitization, whereas true tolerance, if it does occur with OIT, may require longer treatment with higher dose therapy. This concept is consistent with the similar results of two trials of milk OIT, in which partial efficacy in desensitization was demonstrated after a short randomized placebo-controlled trial [19], followed by consolidation of the effect during a longer, higher dose open-label extension [20].

'RUSH' PILOT STUDIES

Other investigators have also reported desensitization with more rapid up dosing protocols, for example, 'rush' immunotherapy. In the first known study of rush OIT for egg allergy, Itoh *et al.* [21] enrolled six Japanese children aged 7–12, all of whom had grade 4 or 5 anaphylaxis to egg in the preceding year. These children were admitted to the hospital and given a baseline DBPCFC, during which the median dose eliciting symptoms was 0.152 g of egg protein. All six patients could tolerate 60 g of egg protein (approximately one whole medium egg) after an inpatient rush protocol that required a median 12 days to complete. Side effects were common, but most responded to conventional allergy therapies and no patients required epinephrine. Thereafter, patients were asked to consume at least one cooked (i.e. scrambled) egg at least twice a week. Interestingly, after 1 year, and evidently despite consuming heated egg regularly, only three of six patients (50%) passed a food challenge to 1 g of powdered egg protein, whereas the remaining three had allergic symptoms during the challenge. Compliance with the maintenance diet was not reported. In keeping with other studies, egg-specific IgE levels declined, whereas egg-specific IgG4 levels increased. At 1 year after rush OIT, there were no changes from baseline in values for skin prick tests, egg-specific basophil histamine release assays, or T cell cytokines after incubation with egg allergen.

Recently, Garcia Rodriguez *et al.* [22[†]] reported a larger uncontrolled study of rush egg OIT in 23 Spanish children aged between 5 and 17 years. In contrast to the Itoh study, this rush protocol was conducted in an outpatient research facility,

enrolled patients with a milder phenotype, and utilized a 5-day protocol, although slower alternatives were permitted in patients having reactions to the rush protocol. Patients stayed in the research unit for 7 h per day and underwent multiple up dosings of a liquid raw egg extract, beginning with the equivalent of 0.13 mg egg white powder and culminating in a 2 g equivalent of a heated egg product (i.e. an omelette). Patients did not undergo follow-up food challenges but were considered desensitized if they could eat a whole cooked egg and 8 ml of raw egg white extract after the rush procedure. Fourteen patients were able to complete the protocol in 5 days. When compared with the eight patients that required longer than 5 days to complete the protocol, those patients adhering to the original protocol had statistically significantly smaller egg skin test size (8.6 versus 11.2 mm) and lower egg white-specific IgE levels (4.35 versus 18.6 kU_A/l). One patient was withdrawn after multiple reactions during desensitization. Overall, 78% of the patients had reactions during rush OIT, most of which were mucosal or gastrointestinal; 35 reactions were judged to be mild and 20 were moderate, and no severe reactions were reported. Interestingly, seven of twenty (35%) of those patients able to complete the rush protocol within 10 days had a reaction to the omelette on the final day of the desensitization procedure. Patients completing desensitization were advised to eat one whole cooked egg per day for 3 months, and then one egg every other day for 3 additional months, and finally one egg at 72 h intervals. With a follow-up period ranging between 6 and 14 months, three patients have had three total reactions that were possibly attributable to egg exposure. Egg white-specific skin prick test wheal diameter and specific IgE levels were significantly reduced at 6 months after desensitization and IgG levels were increased. Given the high rates of allergic side effects during the rush procedures, the frequency with which treated patients had subsequent reactions, the labor-intensive nature of this approach, and the relative ease of food allergen avoidance (as compared with stinging insect avoidance), rush protocols appear to offer no clear advantage over standard OIT.

RANDOMIZED CLINICAL TRIALS

Further evidence of the transience of desensitization after short-term therapy was previously shown in one of the earliest randomized controlled trials of OIT for food allergy. In this study, 45 German children were randomized by Staden *et al.* [23] to receive egg (maintenance dose 1.6 g/day) or milk (3.5 g/day) OIT or usual care (e.g. strict avoidance

diet). They assessed the persistence of any treatment effect, operationally defined as clinical tolerance, by performing oral food challenges 2 months after stopping OIT. After a median of 21 months of therapy, the rate of permanent tolerance was 36% in the OIT group, and 35% in the avoidance group, suggesting that the OIT-treated patients that developed tolerance had independently outgrown their allergy, which is the expected natural history of egg and milk allergy. However, an additional 28% of the treated group also experienced clinical improvement, which returned to baseline once treatment was stopped and thus was considered to be desensitized, an important potential benefit of OIT. Interestingly, among those patients who become fully tolerant, the egg-specific IgE declined over time regardless of whether they received OIT or outgrew their allergy.

In the largest and most definitive trial of egg OIT to date, 55 children aged 5–18 years were enrolled in a randomized and double-blinded clinical trial at five US centers in the Consortium of Food Allergy Research [24]. Although this study is currently ongoing, interim results were reported at the 2010 annual meeting of the American Academy of Allergy, Asthma and Immunology [25]. After 10 months of maintenance treatment with a maximum dose of 2 g of egg white powder per day, 21/40 (52.5%) of patients receiving egg OIT passed an oral food challenge and were considered desensitized, compared with zero of fifteen (0%) on placebo OIT; 30/40 (75%) had achieved desensitization after an additional year of therapy. This is the first large multicenter study designed and powered to formally test the safety and efficacy of OIT for egg allergy by using a placebo control, and using clinical tolerance of egg OIT as the primary endpoint. As such, the clinical and mechanistic results are eagerly awaited in 2012 and beyond.

CONCLUSION

Egg allergy is a common clinical problem, and although the natural history favors spontaneous resolution, this may not occur until midadolescence or later. Pilot studies have shown OIT to be a promising approach to the development of an initial disease-modifying treatment for egg allergy. To date, between 50 and 90% of patients have been reported to achieve desensitization, although desensitization has often been used as a clinically defined outcome (i.e. the ability to eat an egg product). Rarely has desensitization been quantitatively measured with a dose threshold elicited during a blinded food challenge performed after a course of OIT. A further caveat to the promise of these pilot

trials is the fact that many of these studies enrolled young children and did not include a control group, both of which confound the interpretation of OIT's efficacy in the treatment of a disorder that is frequently outgrown. Longer treatment and/or higher doses may be necessary in some patients to produce lasting clinical tolerance, although no published study has rigorously investigated this concept. OIT appears to be generally well tolerated, but side effects are common and prevent 10–20% of patients from continuing with therapy. In addition, eosinophilic esophagitis, a very important and potentially severe adverse effect of oral food allergen administration, was recently reported in a patient receiving egg OIT [26[■]]. In order to validate the observations inferred from pilot studies, and to better understand the safety profile of egg OIT, large well controlled studies are necessary before egg OIT may be advanced as a viable treatment option for routine clinical practice [10[■]]. A large, multicenter, randomized clinical trial with a rigorous scientific design is currently ongoing in the United States and will provide key findings to help the field move forward. Two recent meta-analyses [9[■],27[■]] focusing on the diagnosis and treatment of food allergy concluded that there is a great need for high-quality evidence from randomized controlled trials, and as such the results of these studies are greatly anticipated.

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Conflicts of interest

No funding support present conflicts of interest relevant to this article.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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Although just a case report, this citation deserves special attention because it highlights the possible association of egg OIT with eosinophilic esophagitis (EoE), as has been seen in other forms of OIT. Whether oral food allergen administration to atopic individuals causes EoE to develop, or whether it occurs independently, much more study is needed to examine this potentially concerning association.

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