A practical focus on egg oral immunotherapy

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ABSTRACT

Egg allergy usually develops in the first year of life, with an estimated prevalence of 2.6%–9%. Rates of resolution and timing vary, with approximately one-third of patients outgrowing their egg allergy by age 6 years. Persistent egg allergy has been associated with high egg white specific immunoglobulin E levels and sensitization to the egg allergen component Gal d 1, which is resistant to heat and digestion. These individuals seem to have a more severe and persistent phenotype of egg allergy. Recently, an active approach has emerged for patients with food allergy, including those with egg allergy, in the form of oral immunotherapy. Egg oral immunotherapy consists of the administration of gradually increasing doses of egg, with the aim to enable patients to consume small amounts of egg without having allergic reactions, which thus provides protection from accidental exposures to egg-containing foods. This article aims to discuss published evidence on egg oral immunotherapy, provide practical information on dosing protocols, and address special challenges associated with this intervention.

(J Food Allergy 4:132–135, 2022; doi: 10.2500/jfa.2022.4.220013)

A recent active approach, in the form of oral immunotherapy (OIT), has emerged for patients with egg allergy. Egg OIT consists of the administration of gradually increasing doses of egg with the aim to enable patients to consume small-to-medium amounts of egg without having allergic reactions,[1] which thus provides protection from accidental exposures to egg-containing foods. Egg OIT research has been conducted in the United States and in Europe, including pilot studies[2,3] and randomized clinical trials.[4–6] In addition, both daily ingestion of full servings of baked egg and egg ladder are approaches that have been described in the literature for management of certain phenotypes of egg allergy, but those approaches are beyond the scope of this article.[7]

EFFICACY AND SAFETY

In an early, pilot (proof of concept), open-label study of seven children with egg allergy and who were nonanaphylactic (7 months to 7 years old) Buchanan *et al.*[3] administered treatment in the form of 300 mg of egg white powder daily for 24 months. The intervention was successful in 57% of the participants, who were able to tolerate 10 g of egg powder (equivalent to 8 g of egg protein) in oral food challenge after therapy. A seminal multicenter randomized OIT study was conducted in the United States and included 55 children with immunoglobulin E (IgE) mediated egg allergy who received immunotherapy for a period of 10 months, with a maintenance dose of 2 g of egg white powder (equivalent to one-third of egg).[4]

The trial showed a 55% rate of successful desensitization in the active arm compared with 0% in the placebo arm, which supported the efficacy of this intervention,[4] with an additional year of egg OIT (total of 22 months of therapy), which increased the desensitization rate up to 75%.[4] Adverse events were reported to be highest during the first 10 months of treatment, and most were mild oropharyngeal associated with 25% of the doses in 78% of children who received egg OIT.[4] After the first 10 months, the rate of adverse events decreased to 8.3% of the OIT doses.[4] No severe adverse events as a result of the therapy were recorded. Approximately 15% of the children were unable to complete OIT, mostly due to recurrent and/or persistent allergic reactions (nonresponders).[4]

A high-dose OIT protocol was used in Spain in 32 children (5–18 years old) with persistent egg allergy.[8] The protocol involved a 5-day rush updosing phase, followed by 5 months of maintenance dosing every 48 hours. After 5 months of treatment, 93.8% of the participants were able to eat one egg (fried, scrambled, or omelet).[8] Adverse events were noted in 31% of the doses during the buildup phase, with 85.4% being classified as mild, 12.9% as moderate, and 1.7% as severe. Epinephrine was administered in two participants for

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A. Anagnostou has received honorariums from Aimmune Therapeutics, DBV Technologies, Alk and Food Allergy Research and Education

No external funding sources reported

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*This manuscript is part of the **Journal of Food Allergy** collection of published works referred to as the "Oral Immunotherapy Manual." The contents of this work reflects the opinion(s) of the author(s) and is not intended to replace published guidelines or the clinician's medical advice in the doctor-patient relationship*

anaphylaxis.[8] No episodes of anaphylaxis occurred during maintenance.

A separate U.S. trial examined 50 children ages 3–16 years, all reactive to unbaked egg, who received 2 years of treatment with either baked egg or egg OIT.[9] A comparison group of children who were reactive to baked egg were also included and received egg OIT. After 2 years of treatment, the OIT was discontinued for 8–10 weeks to evaluate sustained unresponsiveness.[9] It was reported that 11.1% of the children who consumed baked egg compared with 43.5% of the children who received egg OIT achieved sustained unresponsiveness to egg.[9] In the baked egg–reactive group, 17.9% achieved this outcome.[9] The investigators concluded that the participants who received egg OIT had a higher likelihood to achieve sustained unresponsiveness compared with those who consumed baked egg alone (without OIT).[9] Adverse events were described in 3.9% of the doses per participant, with most of these being oropharyngeal, followed by gastrointestinal and respiratory, and successfully treated with oral antihistamines.[9] No epinephrine-treated reactions were recorded.[9] Although sustained unresponsiveness has been explored by a variety of studies, it is important to note that egg is a common element of many diets and that it is likely that, after successful egg OIT, most patients may be exposed to variable amounts of egg protein at least once, if not several times a week.

Early egg OIT is an important consideration. Most individuals will outgrow egg allergy during childhood, but rates of resolution and timing vary, with approximately one-third outgrowing their egg allergy by age 6 years in a U.K. study[10]; in the United States, 4% were reported as outgrowing their egg allergy by age 4 years, 12% by age 6 years, 37% by age 10 years, and 68% by age 16 years.[11] Generally, persistent egg allergy has been associated with high egg white specific IgE levels and sensitization to the egg allergen component Gal d 1, which is resistant to heat and digestion.[12] These children seem to have a more severe and persistent phenotype of egg allergy. Although it may not be possible to predict if a 4-year-old will ever outgrow his or her egg allergy, it is reasonable to assume that, if the egg specific IgE level is high at 1 year and keeps increasing yearly by age four, the patient is unlikely to outgrow egg allergy within the next several years and may be considered a candidate for OIT. This is an important part of the discussion with some families.

After publication of multiple studies that evaluated egg OIT as an alternative management option for individuals with egg allergy, a systematic review was performed to investigate the efficacy and safety of this intervention.[13] A total of 10 randomized controlled trials were included (439 participants between ages 1 and 18 years overall).[13] The review showed that most children who received egg OIT were able to consume a partial serving of egg (1–7.5 g) compared with only 10% in those who avoided egg completely.[13] A full portion of egg was successfully consumed by almost 50% in the OIT group compared with 10% in children after an egg elimination diet.[13] The investigators concluded that OIT induces tolerance in almost 50% of subjects compared with only 1 in 10 subjects who followed egg avoidance.[13] However, it was noted that adverse events are likely to be more frequent in participants on OIT and that some children (~1 in 12 from the pooled data) may have severe allergic reactions and/or anaphylaxis that requires epinephrine administration.[13]

As shown, from the multiple trials described above, many OIT protocols allow for escalation to a target and a maintenance egg dose that permits incorporation into the diet, either as egg-containing products or as a whole egg. Generally, one large whole egg contains ~6 g of egg protein (the exact amount depends on the size of the egg). For comparison, a baked egg muffin contains approximately one-third of an egg (usually two eggs are used to prepare six baked egg muffins).

PUBLISHED DOSING SCHEDULES

A variety of egg OIT dosing schedules have been published by different research groups. Some of these are described in detail here. Staden *et al.*[6] report a 67-day specific oral tolerance induction schedule that uses hen's egg powder. The initial dose is 5 mg of powder (0.006 mg of egg protein), increasing gradually to 0.9 mg of egg protein by day 20, 148 mg of egg protein by day 40, and 2.8 g of egg protein by day 67. The powder is diluted in water, with increasing concentrations as the protein doses increase.

Buchanan *et al.*[3] used an initial rush phase that consisted of the following doses of powdered egg white (which contained 80% egg protein): 0.1, 0.2, 0.4, 0.8, 1.5, 3, 6, 12, 25, 50, 100, and 200 mg, every 30 minutes (200 mg of egg white powder are approximately equivalent to 160 mg of egg protein). The highest tolerated dose from the rush phase was given as the first dose in the buildup phase that followed. During the buildup phase, doses were increased by 25 mg every 2 weeks until reaching 150 mg and then increased by 50 mg at each visit until reaching the maintenance dose of 300 mg, which would be taken daily for the length of the study (24 months). This dose aimed to protect from accidental exposures to egg-containing products.

Burks *et al.*[4] initially performed a rush-day escalation that started at 0.1 mg to a maximum of 50 mg of egg white powder (~40 mg of egg protein), followed by every 2 weeks increases to 75, 100, 156, 195, 245, 306, 383, 479, 599, 749, 936, 1170, 1463, 1829, and 2000 mg of egg white powder (2 g of egg white powder is the approximate equivalent of 1.6 g of egg protein or one-third of an egg).

Pérez-Rangel *et al*.[8] offered a 5-day rush buildup phase, which started from 0.04 mg of egg white powder (0.03 mg of egg protein), followed by 0.08, 0.16, 0.32, and 0.64 mg of egg white powder at hourly intervals on day 1. Day 2 consisted of 0.4, 0.8, 1.6, 4, 20 mg of egg white powder at hourly intervals.[8] On day 3, five doses were administered: 20, 50, 100, 225, 450 mg of egg white powder, and, on day 4, a further three doses were given: 450, 900, 1800 mg of egg white powder.[8] On the final day, day 5, two doses were administered: 1800 and 3600 mg of egg white powder, the final equivalent to 2808 mg of egg protein or one whole egg.[8] Maintenance dosing started after completion of the updosing schedule in the form of one whole egg (fried, omelet, or scrambled) every 48 hours, for the length of the study (5 months).[8]

When comparing different trial escalation regimes, a few observations stand out. First, the rush buildup phase aims to increase the egg protein dose rapidly and, therefore, decrease the time to reach maintenance and the overall study duration. The disadvantage of such an approach is that the subjects may not tolerate such a fast increase in dosing and may have significant allergic reactions. Second, the target maintenance dose varies from tolerance to egg-containing products (estimated as containing 75–150 mg of egg protein) up to one whole egg. The advantage of a lower maintenance dose is that more patients are likely to tolerate it. The disadvantage is that patients are unlikely to tolerate ingestion to large amounts of egg protein, such as a whole egg. However, it is important to note that ingestion of a whole egg equivalent may not be necessary or practical for some patients, especially in the long term. Analysis of data from Japan suggests that continuous intake of low-dose OIT (1/32 of a volume of one egg) may improve egg allergy and even be as effective as the consumption of larger quantities,[14] although this has not been replicated in other studies.

DOSE PREPARATION AND MASKING

All OIT doses should be prepared in a clean area, free from contamination with any potential food allergens. For egg OIT, hen's egg powder (whole egg or egg white powder) is most frequently used in research studies (powder has been noted to sometimes be difficult to dissolve). Pasteurized liquid egg has also been used for egg OIT. Egg-free vehicles may be used for dose mixing and disguising taste. Apple juice, applesauce, yogurt, pudding, smoothies, or other age-appropriate food have all been used in research trials.

SPECIFIC CHALLENGES AND CONSIDERATIONS

Similar to other food allergies with a favorable natural history (likely resolution), the timing of egg OIT is a key consideration. It is important to allow time for natural egg allergy resolution and, if possible, to identify the phenotype for persistent egg allergy, which may be more in need of active intervention. Families will require time to understand the process, risks and benefits, and commitment for egg OIT. Their preferences and goals for treatment should be discussed, and all their related questions should be addressed before initiating this intervention to ensure the best patient outcome. Young children may also be involved in the decision-making process in an age-appropriate way.[15,16]

Long-term management of patients with egg allergy who were successfully desensitized will generally depend on both the immunotherapy response and the patients' treatment goals. Some individuals may prefer protection to egg-containing products and have no interest in regular consumption of larger amounts of egg. In this case, oral food challenges to assess for higher dose tolerance are unlikely to be useful. For other patients, who wish to incorporate large amounts of egg into the diet or free eating, follow-up oral challenges to assess the extent of desensitization and a discussion about which cumulative dose should be aimed for may be useful to patients and families. Shared decision-making will allow for the best plan to be made based on individual preferences.[17]

CLINICAL PEARLS

- OIT for egg allergy is effective but not without risk. The risk-benefit ratio should be clearly outlined and discussed in detail with patients and families so they can make the decision that best fits their expectations and preferences.
- Multiple protocols exist for egg OIT that use a variety of dosing schedules and buildup intervals. There is no standardized approach for egg OIT.

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