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Food specific oral immunotherapy: a potential treatment for food allergy

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Food allergy is a potentially life-threatening condition affecting up to 8% of children and up to 2% of adults in westernized countries. There are currently no approved treatments for food allergy apart from avoidance. The apparent increase in incidence of food allergies over the past few decades calls attention to the need for effective, disease-modifying therapies for food allergies. Oral immunotherapy (OIT) is a promising experimental treatment in which food allergic patients consume increasing quantities of food in attempt to increase their threshold for allergic reaction. Studies are ongoing to determine whether OIT is capable of safely inducing not only desensitization but also tolerance to the allergenic foods. This article focuses on recent relevant studies of OIT for the treatment of common food allergies.

KEYWORDS: desensitization • double blind placebo-controlled food challenge • food allergy • omalizumab • oral immunotherapy • probiotic • sustained unresponsiveness • tolerance

Food allergy is a potentially life-threatening condition that appears to have increased in incidence in westernized countries over the past 20 years. Based on patient surveys, food allergy is now estimated to affect up to 8% of children and up to 2% of adults in the US, though these numbers may be overestimated due to several factors [1–4]. In a study addressing food allergy prevalence among infants, one study found that >10% of Australian infants aged 12 months had challenge-proven IgE-mediated food allergy to common allergenic foods such as peanut, egg and sesame [5]. Estimated prevalence of cow's milk allergy varies, with one group estimating a prevalence of 2.2% in a Danish cohort of children while another estimating a combined prevalence of allergy and intolerance to cow's milk of 1.1% in Norwegian children [6,7]. The prevalence of egg allergy has been estimated at 1.6% of Norwegian children aged 2.5 years [8]. Strict avoidance of milk and egg is difficult and requires extreme vigilance on the part of the caregiver in order to avoid accidental ingestion. Nutritional deficiencies and impaired growth are significant concerns in children on avoidance diets [9,10]. A 2015 UK study of fatalities due to anaphylaxis revealed that 21% of fatal cases of food-related anaphylaxis in children under

16 years were caused by cow's milk ingestion [11]. While approximately 85% of cow's milk- and egg-allergic children are expected to achieve natural tolerance to these foods by adulthood, only 15–20% of peanut or tree nut allergic individuals 'out grow' their allergies [12]. Peanut is a common food allergen in children in westernized countries with a prevalence of up to 1.8% of children in the UK and up to 1% of children in the US [13,14]. Peanut is implicated in over half of all fatal food allergy-related deaths in the US, and the amount of peanut required to elicit allergic symptoms is often quite small [15,16]. Accidental exposures are common and estimated to affect 12.5% of children with peanut allergy annually; adolescents appear to be at even higher risk due to risk-taking behaviors [11,17]. A large proportion of food-allergic patients who experience fatal reactions are teenagers and young adults, and in one case series of 32 fatal reactions, 69% were between the ages of 13 and 21 years [18,19]. The negative impact of food allergy on quality of life has been well documented [20]. Families of food-allergic children report lower general health perception, increased emotional impact on parents and disruption of normal family activities owing to the burden of vigilance and fear of accidental

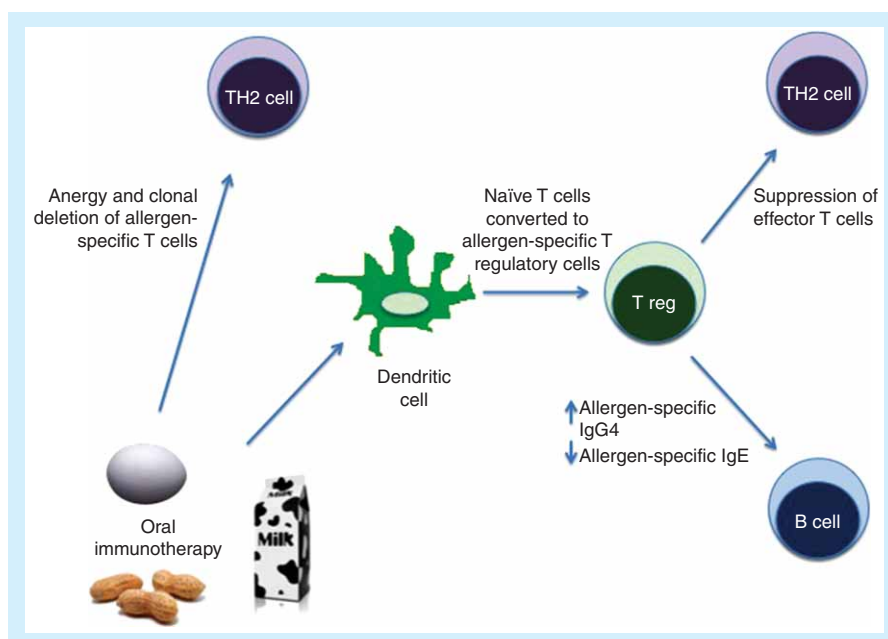


Figure 1. Proposed mechanisms of oral immunotherapy. Oral immunotherapy may contribute to clonal anergy and deletion of allergen-specific Th2 effector cells as well as induction of tolerogenic dendritic cells that convert naïve T cells to antigen-specific T-regulatory cells. These Tregs can then suppress antigen-specific Th2 effector cells as well as B cells, decreasing production of antigen-specific IgE and increasing production of neutralizing IgG4.

ingestion [21]. Currently, there is no known cure or disease-modifying treatment for food allergy.

Mechanisms of oral tolerance

The gastrointestinal tract is the body's largest immunologic organ and is exposed to an enormous array of antigens from food proteins to microbial structures from commensal gut flora [22]. Despite this constant exposure to non-self proteins, immune responses against these proteins are relatively rare, suggesting that tolerance is the default response [23]. Oral tolerance is thought to be the result of active suppression of antigen-specific immune responses. Food allergy may result from a defect in this process [22,24].

The mucosal-associated lymphoid tissue (MALT) is a collection of connective tissue filled with lymphocytes, antigen-presenting cells and other immune cells that are separated from the intestinal lumen by a single layer of epithelium [25]. Upon ingestion, gastric acidity and digestive enzymes alter food proteins and, in some cases, cause changes in the three-dimensional shape of the proteins, resulting in loss of conformational antigenic determinants, or epitopes [25,26]. Antigens that escape processing are presented to the MALT either by uptake by epithelial cells, specialized microfold or M cells or specialized mucosal dendritic cells [22,25]. The pivotal step for induction of oral tolerance is believed to be the presentation of antigen to T cells in the mesenteric lymph nodes, which under normal circumstances promotes activation of inducible T-regulatory

cells that suppress immune responses through production of IL-10 and TGF- β [23].

Proper functioning of this mechanism of oral tolerance depends on a complex interplay of factors that includes physical properties of the antigen, antigen dose, timing of administration, genetic susceptibility of the host, integrity of the intestinal epithelium and factors in the microenvironment including stimulation of the innate immune system by commensal microbes in the gut [22,25,27].

Food allergy is believed to be the result of either failure to establish tolerance upon initial exposure or a breakdown of established tolerance to the antigen. Instead of the default T-cell-mediated suppression of immune responses, patients develop a T helper (Th)2-pre-dominant immune response characterized by production of IL-4, IL-5 and IL-13, leading to B-cell activation and production of antigen-specific IgE [28]. Upon re-exposure to the antigen, IgE on the surface of mast cells and basophils is cross-linked, triggering degranulation of

the cells, release of mediators and generation of the symptoms typically associated with immediate allergic reactions.

The mechanism by which oral immunotherapy (OIT) induces desensitization (and possibly tolerance) is still under investigation (FIGURE 1). Some studies have shown that OIT alters the binding pattern of antigen to antigen-specific IgE, either by reduction in the amount of specific IgE, reduction in the diversity of epitope recognition, altered affinity of IgE for antigen or the generation of neutralizing antigen-specific IgG [29]. Studies of OIT have demonstrated decreased allergen-induced skin prick test (SPT) and basophil activation in the first few months of immunotherapy [30,31]. However, these effects may be transient or lost with discontinuation of immunotherapy, though this does not necessarily correlate with clinical outcomes [30]. After 6–12 months of OIT, there appears to be a shift away from Th2 cytokine production toward a pro-inflammatory profile characterized by increased production of IL-1 β and TNF- α [31]. Immune suppression by T-regulatory cells and clonal anergy are thought to occur later in the course of OIT. Syed *et al.* demonstrated increased function of antigen-specific CD4⁺CD25⁺FoxP3⁺ T-regulatory cells following OIT supporting the theory of active suppression of immune responses to food allergens [32]. Oral antigen-induced deletion of food-specific T cells in Peyer's patches has been demonstrated in mouse models [33].

Definition of OIT

While allergen-specific immunotherapy has long been used successfully in the treatment of aeroallergen-associated allergic

rhinitis, its role in treatment of food allergy is still emerging. In the early 1990s, clinical trials were performed using subcutaneously injected peanut protein in the treatment of peanut allergy [34,35]. While this approach was associated with some improvement in symptom scores during double-blind, placebo-controlled food challenge (DBPCFC) and reduced peanut-induced SPT, the treatment was associated with an unacceptably high rate of systemic allergic reactions [34,35]. Subcutaneous immunotherapy for food allergy was abandoned in favor of safer alternative strategies.

OIT involves consuming the allergenic food in gradually increasing doses. While OIT protocols vary depending on the study, in general they involve an initial escalation phase, followed by a build-up phase and maintenance phase [36]. The initial escalation phase is conducted in a controlled setting and involves rapid up-dosing, which is often achieved in a single day [36]. The dose is escalated incrementally typically over several weeks until a maintenance dose is reached. The dose chosen for maintenance therapy often depends on the study and sometimes on the clinical course of the patient, particularly symptoms experienced during build-up [37]. Length of maintenance therapy varies by study, with some patients continuing maintenance dosing indefinitely to maintain a desensitized state. In order to assess for development of tolerance, some studies instruct participants to stop their maintenance dosing for a period of time followed by an oral challenge.

Effectiveness of OIT

When reviewing the primary outcomes of OIT studies and interpreting their results, it is imperative to distinguish between desensitization and tolerance. Desensitization involves increasing the threshold or amount of food needed to trigger an allergic reaction and requires continued consumption of the allergenic protein to prevent the development of allergic immune responses [37]. A patient is considered tolerant if they can consume the food without symptoms despite prolonged avoidance of the food [12]. The controversy in the field is to define how long a patient needs to be off of OIT before they can be declared tolerant; thus many authors use the term 'sustained unresponsiveness' rather than tolerance [38]. While there is abundant evidence that the majority of patients treated with OIT can be successfully desensitized to particular foods, it remains unknown if OIT is capable of promoting a state of permanent clinical tolerance [29–33,39].

Summary of clinical trials

Cow's milk, hen's egg, peanut, tree nut, wheat, soy, fish, and shellfish are the foods most often associated with food allergy in the US [2]. Trials of OIT for milk, egg, and peanut allergy have been promising, and the results of key studies are summarized in (TABLE 1).

Milk trials

Staden *et al.* conducted a trial of 47 children with cow's milk or hen's egg allergy randomized to food-specific OIT or an

avoidance diet [40]. After a median of 21 months, the patients underwent DBPCFC. Those in the active treatment group were then placed on an avoidance diet for 2 months followed by another food challenge to determine if tolerance was sustained. In the active treatment group, 9 of 25 children consumed cow's milk or egg at follow-up challenge without symptoms, demonstrating that they had become tolerant. Three of 25 remained desensitized with continuation of the daily maintenance dose, and 4 of 25 remained partially desensitized using a smaller maintenance dose. In the avoidance group, 7 of 20 were tolerant to the food at follow-up challenge. Allergen-specific IgE decreased significantly in the active treatment group among responders and partial responders as well as in the subjects in the avoidance group that achieved natural tolerance.

Another important study included 60 children with a history of severe cow's milk allergy characterized by severe cow's milk-induced systemic allergic reactions and very elevated cow's milk-specific IgE levels who were randomized to receive either gradually increasing amounts of cow's milk daily or a milk-free diet [41]. Most patients had cow's milk-specific IgE levels greater than 100 kUA/l. After 1 year, 11 of 30 patients in the active treatment group were able to consume 150 ml or more of cow's milk daily, and 16 could tolerate smaller amounts of milk. Of the 30 children in the milk-free diet group, all 30 reacted to milk during DBPCFC at 1 year. Cow's milk-specific IgE was significantly decreased in 15 of 30 subjects in the active treatment group at 6 and 12 months compared to baseline. Adverse reactions occurred in all subjects on active treatment, and four patients required intramuscular epinephrine during the initial escalation period. Ten percent of subjects on active treatment were not able to complete the study due to recurrent allergy-related respiratory and abdominal symptoms. The frequency of adverse reactions and rate of successful desensitization to cow's milk in this study were very likely influenced by the selection of patients with low thresholds of reactivity and high cow's milk-specific IgE levels [42].

Zapatero *et al.* successfully desensitized 16 of 18 cow's milk allergic patients over a median 14-week period, and all 16 continued to consume cow's milk in their diet following completion of the study [42]. Eleven of 16 patients completing the protocol experienced symptoms with dosing, and while most symptoms were mild, three subjects had more severe symptoms and required epinephrine.

Skrupak *et al.* conducted the first randomized, double-blind, placebo-controlled study of milk OIT in 2008 [43]. Twenty pediatric patients were randomized to receive milk OIT or placebo. Entry DBPCFC demonstrated a median threshold dose of 40 mg of milk protein to produce an allergic reaction in both treatment and placebo groups. After the build-up phase, patients in the active treatment group were continued on a daily maintenance dose of 500 mg of cow's milk for 3–4 months. After OIT, the treatment group achieved a median threshold of 5140 mg of milk protein compared to the placebo group in which all patients reacted with 40 mg of milk protein.

Table 1. Studies of oral immunotherapy for food allergy.

Study (year)	N	Study design	Results	Immunologic changes	Safety	Comments	Ref.
Milk							
Longo <i>et al.</i> (2008)	60	RCT	Active treatment: - 36% fully desensitized - 54% partly desensitized - 10% failed Milk avoidance: - 0% desensitized	Decreased egg IgE	10% of active treatment patients unable to complete protocol due to persistent respiratory and abdominal symptoms		[41]
Skripak <i>et al.</i> (2008)	20	RCT	Active treatment: - Significant increase in median milk threshold dose to produce reaction Placebo: no change	No change in milk IgE No change in milk SPT Increased milk IgG4	At least one adverse effect in all patients in active treatment; most were mild, 90% required no treatment	First randomized, placebo-controlled trial of milk OIT	[43]
Narisety <i>et al.</i> (2009)	15	Open label	93% tolerated twofold or greater increase in daily maintenance dose of milk OIT	Decreased milk IgE Decreased milk SPT Increased milk IgG4	Local reactions with 17% of doses; multisystem reactions with 5.8% doses	Patients who completed milk OIT in study by Skripak <i>et al.</i> enrolled to study safety and efficacy of continued milk intake	[44]
Egg							
Buchanan <i>et al.</i> (2007)	7	Open label	57% desensitized 28% sustained unresponsiveness	No change in egg IgE Increased egg IgG	One patient experienced mild transient hypotension		[48]
Burks <i>et al.</i> (2012)	55	RCT	Treatment group: - 75% desensitized - 28% sustained unresponsiveness Placebo group: - 0% desensitized	Decreased egg SPT Decreased egg-induced BHR Increased egg IgG4	25% of OIT doses 3.9% of placebo doses	Large randomized, placebo-controlled trial of egg OIT	[53]
Peanut							
Jones <i>et al.</i> (2009)	39	Open label	29 completed protocol 93% tolerated 3900 mg peanut	Decreased peanut SPT Decreased peanut-induced BHR Decreased peanut IgE Increased peanut IgG4 Increased peanut-specific FoxP3 ⁺ T cell (at 12 months)	92% had symptoms during initial escalation day. Symptoms occurred with 46% of build-up doses. Symptoms with 3.7% of home doses		[31]
Blumchen <i>et al.</i> (2010)	23	Open label	14 reached maintenance dose of 500 mg peanut; Tolerated median 1000 mg peanut during DBPCFC	Increased peanut IgG4; Decreased peanut-specific IL-2,4,5 production by PMBCs	Four discontinued study due to adverse events		[55]

Table 1. Studies of oral immunotherapy for food allergy (cont.).

Study (year)	N	Study design	Results	Immunologic changes	Safety	Comments	Ref.
<i>Peanut (cont.)</i>							
Varshney <i>et al.</i> (2011)	28	RCT	<i>Active treatment:</i> - 16 of 19 passed 5000 mg challenge (20 peanuts). <i>Placebo:</i> - Ingested median dose of 280 mg (one peanut)	Decreased peanut SPT size Decreased IL-5 Decreased IL-13 Increased peanut IgG4 No change in peanut IgE Increased ratio FoxP3hi: FoxP3int CD4⁺CD25⁺ Tregs	47% had symptoms during initial escalation day, including two subjects who required epinephrine. Three subjects in OIT group withdrew due to allergic side effects	First double-blind, placebo-controlled study of peanut OIT	[3]
Anagnostou <i>et al.</i> (2014)	99	RCT, crossover	<i>Active treatment:</i> - 62% desensitized - 2.5-fold increase in peanut threshold <i>Placebo:</i> - 0% desensitized	Decreased peanut SPT Increased peanut IgE Improved quality-of-life scores	Oral pruritis with 6.3% of doses. Skin symptoms with 0.16% of doses. Wheezing with 0.41% of doses. One patient required epinephrine (two occasions)	One of few studies that did not exclude patients with history of severe life-threatening reaction to peanut or severe asthma	[56]

No significant difference was seen between the two groups with respect to cow's milk-induced SPT or milk-specific IgE. There was a significant increase in milk-specific IgG4 in the active treatment group only. While all active treatment patients experienced at least one adverse effect, most experienced only oral pruritus and/or gastrointestinal symptoms, and 90% of acute reactions required no treatment. Participants who successfully completed this phase of the study were continued on maintenance home dosing of cow's milk protein and followed to determine safety and effectiveness of cow's milk consumption after OIT. Narisety *et al.* published these findings in 2009 [44]. Fifteen patients, all of who tolerated 2540 mg or more of milk protein during their post-OIT food challenge were eligible, and follow-up ranged from 3 to 17 months. Fourteen of 15 subjects were able to escalate their daily dose by at least twofold (median 7000 mg), with six subjects reaching a maximum dose of 16,000 mg without symptoms. Patients had significant decrease in milk-induced SPT and milk-specific IgE as well as increased milk-specific IgG4 during the follow-up period. Even as milk protein daily dose increased, the number of reactions tended to decrease over time. Adverse events tended to be gastrointestinal in nature.

In another randomized double-blind controlled trial of cow's milk OIT, 28 patients were randomized to receive milk OIT or placebo [45]. After completing the protocol, subjects in the placebo group then were treated with open-label OIT. Twelve months after completion of the double-blind phase and 6 months after completion of open-label OIT, the subjects were contacted to determine if they were ingesting cow's milk. The authors found that 13 of the 18 subjects who completed active treatment during the double-blind phase were consuming 200 ml (or 6400 mg) of cow's milk protein daily, and all 10 subjects who originally received placebo followed by open-label OIT were tolerating cow's milk protein daily. Cow's milk-induced symptoms, primarily oral pruritus, occurred in 13 of 23 (57%) of subjects during the 6- to 12-month period following completion of the study. At 3–3.5 years post-OIT, 22 of 28 (78.5%) patients continued to consume cow's milk protein on a regular basis, and only 4 of 22 (18%) continued to experience symptoms with cow's milk ingestion.

Keet *et al.* conducted a study comparing the effectiveness and safety of OIT and sublingual immunotherapy (SLIT) for cow's milk allergic patients [46]. Thirty cow's milk-allergic patients were randomized either to SLIT with dose escalation to 7 mg of cow's milk protein or to an initial SLIT escalation followed by OIT escalating to either 1000 mg or 2000 mg of protein. OIT was continued for 60 weeks with 8000 mg milk challenges at 12 and 60 weeks. At the 60-week challenge, 1 of 10 patients receiving SLIT tolerated the milk dose, while 6 of 10 patients receiving 1000 mg of OIT and 8 of 10 receiving 2000 mg of OIT tolerated the dose. Those subjects who passed the 60-week challenge were then told to avoid cow's milk and were re-challenged 1 and 6 weeks later. Two of 15 subjects became clinically reactive to cow's milk at 1 week and another four subjects were reactive at 6 weeks. All groups displayed a

significant decrease in milk-induced SPT and increase in milk-specific IgG4. Only the group receiving OIT had a significant decrease in milk-specific IgE. While overall reaction rates were similar between the groups, systemic reactions occurred more often in the OIT group compared to the SLIT group.

Keet *et al.* collected follow-up data on 32 subjects previously enrolled in this and one other clinical trial of OIT for treatment of cow's milk allergy [47]. The median time since the end of dose escalation was 4.5 and 3.2 years, respectively. Participants were asked about frequency of cow's milk consumption and presence or absence of symptoms upon consumption. Frequent, predictable symptoms involving more than oropharyngeal symptoms were reported in 28% of the patients. A significant proportion (22%) reported limiting cow's milk in their diet because of symptoms. Factors associated with worse long-term outcomes included those with higher baseline cow's milk-specific IgE, a history of gastrointestinal or lower respiratory symptoms with OIT, end-of-study food challenge threshold dose of <4000 mg, lower daily dose of cow's milk OIT and larger cow's milk-induced SPT at follow up.

Egg trials

In 2007, Buchanan *et al.* conducted a proof-of-concept study of seven egg-allergic subjects treated with 24 months of egg OIT with the goal of desensitization to egg [48]. The protocol involved a modified rush phase followed by build-up and eventually maintenance therapy with 300 mg of egg protein daily. After 24 months of therapy, all patients underwent DBPCFC with 8000 mg of egg protein. Four of the seven subjects passed 8000 mg egg challenge, though all seven tolerated more egg protein than at the beginning of the study. Those who passed the challenge were placed on an egg-restricted diet and re-challenged 3–4 months later. Two of the four patients passed DBPCFC, demonstrating achievement of oral tolerance to egg. Egg-specific IgG increased significantly from baseline to 24 months, while no statistically significant change was seen in egg-specific IgE levels. The ability to successfully desensitize pediatric subjects to hen's egg was demonstrated in several other important studies, with some implementing a rush protocol achieving desensitization in a matter of days [49–52].

In 2012, Burks *et al.* published the first randomized, double-blind, placebo-controlled study of egg OIT in 55 egg allergic children [53]. Children were randomized to receive egg white powder OIT or placebo and underwent DBPCFC at 10 months and 22 months. After 10 months of treatment, 22 of 40 (55%) in the active treatment group passed a food challenge, and 30 of 40 (75%) passed the food challenge at 22 months. No patients in the placebo group passed the food challenge at 10 or 22 months. Those active treatment patients that passed the 22-month challenge then avoided egg for a period of 4–6 weeks followed by another food challenge. At 24 months, 11 of 40 (28%) passed the food challenge, indicating sustained unresponsiveness and incorporated egg *ad libitum* into their diet. At 30 and 36 months, all of these children continued to tolerate egg with no reported adverse events. Higher

egg-specific IgG4 levels at 10 months were predictive of desensitization at 22 months and sustained unresponsiveness at 24 months. Egg-induced SPT at 22 months correlated inversely with likelihood of desensitization at 22 months and sustained unresponsiveness at 24 months. When compared to the placebo group, patients receiving egg OIT had reduced egg-induced SPT, reduced egg-induced basophil activation, and increased egg-specific IgG4 with no significant change in egg-specific IgE levels. Adverse events occurred in 25% of doses of OIT administered and in 3.9% of doses of placebo, mostly oropharyngeal discomfort. Symptoms decreased to 8.3% of doses of OIT after 10 months of therapy. No serious adverse events occurred.

Recently Caminiti *et al.* conducted a study of egg-allergic children treated with egg OIT or placebo for 4 months [54]. Of the 17 subjects enrolled in the OIT group, 16 achieved desensitization and added egg to their diet. After 6 months, they assumed an egg-avoidance diet for a period of 3 months followed by DBPCFC with egg. In the OIT group, five patients (31%) remained tolerant to egg after the 3-month avoidance period, while only one patient in the placebo group was tolerant to egg during the final oral challenge.

Peanut trials

As previously mentioned, peanut allergy is one of the most common food allergies in children in westernized countries and is responsible for many of the fatal allergic reactions to foods that occur each year. In 2009, Jones *et al.* published an open-label, multicenter, uncontrolled trial of peanut OIT in which clinical desensitization (defined as tolerance of 3900 mg of peanut protein during oral food challenge) was achieved in 27 of 29 peanut-allergic patients who received greater than 8 months of peanut OIT [31]. Patients had significant reduction in the size of peanut-induced SPT and reduced basophil reactivity to peanut by 6 months of therapy. Peanut-specific IgE levels initially rose then fell significantly below baseline by 18 months. Peanut-specific IgG4 rose significantly by 3 months and remained elevated throughout the study. Peanut-specific CD4⁺CD25⁺FoxP3⁺ T-regulatory cells were increased early on, then decreased again after 12 months of therapy. Following peanut OIT, IL-10 levels were significantly increased while Th2 cytokines were decreased. The group hypothesized that OIT facilitates a transition from desensitization to tolerance, and FoxP3⁺ T-regulatory cells potentially mediate this process by inducing suppression of Th2 responses to peanut.

In 2010, Blumchen *et al.* published the results of a study involving 23 children with peanut allergy confirmed by DBPCFC who received peanut OIT [55]. Of these 23, 14 patients reached a maintenance dose of 500 mg of peanut protein after a median of 7 months. Eight weeks after reaching the maintenance dose, OIT was discontinued for a period of 2 weeks followed by an oral challenge. During the post-OIT food challenge, patients tolerated a median of 1000 mg of peanut protein compared to 190 mg peanut protein prior to OIT. Peanut-specific IgG4 was significantly increased. Peripheral

blood mononuclear cells (PBMCs) stimulated with peanut showed a significant reduction in production of Th2 cytokines after OIT.

Varshney *et al.* published in 2011 the first randomized, double-blind, placebo-controlled, multicenter trial of OIT as a treatment for peanut allergy [3]. Patients received OIT followed by an oral food challenge at 1 year. Of 16 patients in the active treatment group who reached maintenance therapy, all tolerated the maximum dose of 5000 mg peanut during DBPCFC at 1 year compared to a maximum dose of 280 mg peanut in the placebo group ($n = 9$). Patients in the OIT group showed significant reduction in peanut-induced SPT, increase in peanut-specific IgG4 and reduced production of IL-5 and IL-13 by PBMCs treated with peanut protein.

Anagnostou *et al.* recently published findings from a randomized controlled crossover study comparing effectiveness of peanut OIT in achieving desensitization to peanut compared to a control group in children aged 7–16 years with peanut allergy [56]. Of 39 participants receiving peanut OIT, 24 (62%) passed a DBPCFC to 1400 mg of peanut protein at 6 months compared to 0 of 46 in the control group. Of those on peanut OIT, 84% could tolerate a maintenance dose of 800 mg of peanut protein daily (equivalent to about five peanuts). Control participants were then placed on active treatment followed by DBPCFC, with 54% passing a 1400 mg peanut challenge and 91% tolerating 800 mg of peanut protein daily. Side effects were generally mild and frequently involved gastrointestinal complaints and oral pruritus. However, wheezing occurred during treatment in 22% of subjects. One patient required epinephrine during the study for a severe allergic reaction.

A 2012 Cochrane Review of OIT for peanut allergy concluded that peanut OIT is capable of inducing desensitization and increasing the threshold dose of peanut required to trigger an allergic reaction [13]. Immunologic changes including statistically significant increases in peanut-specific IgG4 were seen, suggesting an immune modulatory role of OIT but with insufficient data available to draw conclusions about its ability to induce tolerance. The authors emphasized the frequent rates of adverse events, including some severe events, associated with OIT, underscoring the need for further study prior to implementation in clinical practice.

These important studies have proven the effectiveness of peanut OIT in desensitization to peanut, but until recently none have demonstrated evidence of a disease-modifying effect of OIT. In 2014, Vickery *et al.* published the results of a multicenter, open-label study of 24 peanut allergic children who were treated with peanut OIT maintenance therapy of 4000 mg daily followed by a 5000 mg peanut DBPCFC [38]. Patients who passed the oral challenge then avoided peanut for 4 weeks followed by a second DBPCFC. Those that passed both food challenges went on to consume a full serving of peanut butter (8000–10,000 mg of peanut) the next day. Twelve patients (50%) completed the DBPCFC and open feeding with no symptoms 4 weeks after stopping OIT. These patients were considered to have achieved sustained unresponsiveness to

peanut and incorporated the food into their regular diet. Those patients that did not exhibit sustained unresponsiveness tolerated a median dose of 3750 mg of peanut protein, a significantly larger amount than the dose tolerated prior to treatment. Sustained unresponders had smaller peanut-induced SPT at baseline, reduction in SPT during and after discontinuation of OIT, as well as lower peanut-specific IgE compared to those who failed DBPCFC. Peanut-specific IgG4 increased in all patients but was not associated with clinical outcome. Predictors of sustained unresponsiveness at baseline included lower ratio of peanut-specific IgE to total IgE.

Multiple foods

Begin *et al.* conducted a Phase I single-center study of OIT in patients with multiple food allergies to determine the safety of multi-food OIT compared to single food OIT [57]. Forty patients ranging in age from 4 to 46 years were recruited and underwent DBPCFC to peanut followed by challenges to other allergenic foods including tree nuts, sesame, dairy or egg. Of the 40 subjects, 25 were reactive to peanut plus at least one other food during challenge. The remaining 15 were reactive only to peanut. Patients were started on OIT containing peanut and, in the poly-sensitized patients, up to four additional foods. Frequency of adverse reactions was similar between the peanut OIT group and the multiple food OIT group. However, dose escalation occurred more rapidly in the peanut OIT group than in the multiple food OIT group.

Safety

Adverse reactions during OIT are common and occur in upward of 25% of doses, though symptoms are generally mild [12]. As previously discussed, OIT protocols typically consist of an initial escalation day followed by a build-up phase and home dosing phase. A study examining the safety of the various phases in peanut OIT found that the greatest risk of allergic symptoms occurred during the initial escalation day, with 26 of 28 (93%) patients experiencing at least one symptom [36]. Of all symptoms experienced, respiratory and abdominal symptoms were the most frequent. Four of 28 patients (15%) received epinephrine for symptoms of allergic reaction during the initial escalation day. Risk of reaction with home dosing was low at 3.5%, though two patients in their study required epinephrine after a home dose. A recent meta-analysis of randomized, controlled trials of cow's milk OIT demonstrated a significant number of adverse reactions in the studies reviewed, though symptoms were mild in most cases. The authors found that the percentage of study patients requiring epinephrine treatment ranged from 6.7 to 30.8% depending on the study [58].

OIT studies in general have a significant dropout rate, as high as 20% in some studies, owing mostly to GI symptoms that often start in the first few days of dosing and do not resolve [59].

Efforts are underway to improve safety and feasibility of OIT. In a recent letter to the editor, Bird *et al.* reported

successful desensitization to peanut in a small cohort ($n = 9$) of peanut-allergic children using a lower daily maintenance dose of 2000 mg of peanut flour, compared to previously published studies that used maintenance dosing of up to 4000 mg per day [60]. This group also modified their entry protocol eliminating the initial dose escalation day. Overall, their cohort was able to achieve maintenance dosing more quickly and with no increase in the frequency of reactions when compared to published protocols with higher daily maintenance dosing.

There is also interest among food allergy researchers in identifying patients who are at higher risk of adverse reactions during OIT. Vazquez-Ortiz *et al.* conducted a safety study of egg OIT in 50 children [61]. After completing a median of 18 months of egg OIT, the authors examined the frequency and severity of allergic symptoms experienced during therapy and stratified patients into different safety phenotypes: those who experienced infrequent and mild reactions that improved over time, those that had more frequent and severe reactions that did not improve with time and those who had very frequent reactions resulting in study discontinuation. The authors found that the presence of asthma, higher egg-specific IgE and lower threshold dose of egg during DBPCFC were associated with the early discontinuation phenotype. Ovomucoid-specific IgE of greater than 8.85 kU/l was an excellent predictor of frequent reactions and/or early study discontinuation. Similarly a study of cow's milk OIT revealed that frequency of allergic reactions during the build-up phase correlated with the measured number of IgE-binding peptides [62]. In other words, 'high-risk' patients recognized significantly more casein peptides at baseline and at all other time points. In addition, the authors identified a profile of IgE-binding peptides that correlated with safety and efficacy of OIT, potentially allowing for selection of patients likely to derive the most benefit with the lowest risk of adverse effects from OIT. High levels of cow's milk-specific IgA, IgE, IgG1 and IgG4 at baseline have been associated with discontinuation of OIT due to frequent allergic reactions [63]. Presence or absence of asthma appears to impact OIT outcomes in multiple studies, with asthmatic patients being more likely to discontinue OIT due to adverse reactions [61,64,65]. Vazquez-Ortiz reported three cases of life-threatening anaphylaxis to OIT, all in asthmatic teenagers with suboptimal control [66]. One patient experienced anaphylaxis while on maintenance phase OIT for cow's milk, while the other two patients developed anaphylaxis during build-up phase for cow's milk or egg OIT. In addition, the authors noted that these patients had a history of poor compliance with their OIT. These reports highlight the importance of optimal asthma control and good compliance with OIT to avoid life-threatening allergic reactions.

Little is known about long-term safety of OIT. Varshney *et al.* noted five patterns associated with reactivity to previously tolerated doses in peanut OIT, including concurrent illness or fever, timing of OIT dosing in relation to food ingestion, exercise in close proximity to OIT dosing, the presence of uncontrolled asthma and menses [65].

Several case reports have been published reporting development of eosinophilic esophagitis (EoE) after OIT. A recent meta-analysis of these reports revealed that EoE occurred in as many as 2.7% of patients undergoing OIT to milk, peanut, egg or wheat [67]. However, using funnel plot analysis, the authors found a significant degree of publication bias and indicated that the actual prevalence of EoE following OIT is much lower. In one case report, three pediatric patients developed EoE while undergoing cow's milk OIT [68]. All three patients achieved histologic remission with a milk-free diet, indicating that their EoE was triggered by the same food they were receiving as OIT. Whether or not OIT induces EoE is unclear, and the mechanism by which this occurs is not understood. A recent study suggests a role for IgG4 in EoE disease [69]. Clayton *et al.* conducted a randomized, double-blind, placebo-controlled trial of adults with EoE treated with omalizumab or placebo. Their results showed no changes in symptoms or histologic evidence of EoE in patients treated with omalizumab compared to placebo, calling into question the role of IgE in EoE development. They found a 45-fold increase in IgG4 content in esophageal biopsies of EoE patients compared to controls. In addition, EoE patients had a 1.9-fold increase in serum IgG4 compared to healthy controls, and significantly higher levels of food-specific IgG4 to the four most common trigger foods in EoE: wheat, milk, egg and nuts. Most of the OIT studies described report an increase in food-specific IgG4 levels during OIT. However, more studies are needed in this area to define the role of OIT, if any, in the development of EoE.

Advances in treatment

Heating: baked milk & egg studies

During extensive heating, cow's milk and hen's egg appear to undergo loss of some conformational epitopes responsible for allergic reactions. Heating has been shown to have significant effects on proteins such as ovalbumin found in hen's eggs or beta-lactoglobulin found in cow's milk. Ovomucoid found in hen's eggs and casein found in cow's milk tend to be more heat-stable [70].

Most patients with cow's milk or egg allergy can tolerate baked forms of these foods. This has been demonstrated in multiple studies and is widely recognized in clinical practice [71–75]. Introduction of baked forms of milk and egg allows for a less restrictive diet and may improve nutrition and quality of life. Some authors have hypothesized that introduction of baked egg and/or milk in patients with egg or milk allergy who tolerate them may be a safe form of immunotherapy that hastens the development of tolerance of unmodified forms of the foods [74–76]. The counterargument is that perhaps those children who tolerate baked forms of milk/egg have a more mild, transient phenotype of allergy, and these children would achieve natural tolerance to milk/egg regardless of consumption of baked forms of the foods [77,78]. Jarvinen *et al.* found that children with persistent egg allergy showed higher levels of egg-specific IgE to particular sequential epitopes, or sequences of

amino acids, of ovomucoid compared to children who outgrew their egg allergy [77]. Children with persistent egg allergy were found to have IgE specific to one to four major IgE-binding sequential epitopes in egg protein. In comparison, none of the egg-allergic children who subsequently became tolerant had IgE against these epitopes. Currently, there are no accurate predictors of tolerance to baked milk/egg known, so it is important that these foods be introduced safely in a controlled setting in milk/egg allergic patients. Use of baked forms of foods as immunotherapy is an interesting area of study, but further evaluation of these hypotheses is needed.

Anti-IgE therapy

Humanized anti-IgE antibody therapy has been proposed as a potentially effective therapy for food allergy. Anti-IgE antibody acts by binding the Fc region of the IgE molecule that mediates binding to the high-affinity Fcε receptor, thus preventing IgE from binding to the surface of mast cells and basophils. In 2003, Leung *et al.* published a study of primarily adult patients with IgE-mediated peanut allergy who received anti-IgE therapy every 4 weeks for four doses or placebo with baseline and end-of-study DBPCFC [79]. Patients who received 450 mg of anti-IgE antibody showed significant increase in the threshold dose of peanut protein required to produce allergic symptoms (178 mg at baseline to 2805 mg after anti-IgE therapy). A Phase II randomized, double blind, placebo-controlled study was conducted to determine if omalizumab reduces the risk of peanut-induced allergic reactions in children and adults with IgE-mediated peanut allergy [80]. Results of this small study of 14 patients were similar to previously published data, with omalizumab-treated patients tolerating an increased dose of peanut protein compared to baseline. Savage *et al.* found that peanut-allergic patients who received omalizumab for 6 months displayed either total suppression of basophil histamine release (BHR) to peanut or required 10-fold more peanut allergen to induce basophil histamine release (BHR) [81].

Trials of humanized monoclonal antibody against IgE have been studied in combination with OIT to determine if anti-IgE therapy improves safety and effectiveness of OIT. In 2011, Nadeau reported a Phase I pilot study of 11 patients treated with omalizumab for 9 weeks followed by cow's milk OIT [82]. Patients underwent a rapid dose escalation protocol followed by gradually increasing daily doses up to a maximum dose of 2000 mg milk protein. Omalizumab was discontinued at week 16 with continued daily dosing of cow's milk protein. At 24 weeks, all nine patients who reached the 2000 mg daily dose of cow's milk passed a 7250 mg cow's milk oral challenge and incorporated cow's milk into their diets. Omalizumab appeared to facilitate rapid dose escalation in most patients undergoing cow's milk OIT. While most adverse effects were mild and required no treatment, the rate of epinephrine use was not different from that seen in previously published OIT studies without use of omalizumab.

Schneider *et al.* conducted a similar study of omalizumab treatment during peanut OIT in 2013 [83]. This study enrolled patients who were felt to be at high risk of significant allergic reaction during peanut OIT because of high levels of peanut-specific IgE. Thirteen peanut-allergic patients were treated for 12 weeks with omalizumab followed by peanut desensitization. Twelve subjects reached a daily maintenance dose of 4000 mg of peanut in a median of 8 weeks. Omalizumab was then stopped, and 12 weeks later patients underwent DBPCFC with 8000 mg of peanut. All 12 patients passed the challenge. Despite being high risk, these patients achieved desensitization more rapidly and tolerated a higher cumulative dose of peanut than studies without omalizumab therapy. Omalizumab has also been used with reported success in a Phase I trial to facilitate rush desensitization in multiple food OIT [84].

Probiotics

There has been intense interest of late in the role of probiotics in food allergy, particularly its potential role as an adjuvant therapy to induce tolerance via signaling through innate immune receptors such as Toll-like receptors. Tang *et al.* conducted a study of 62 peanut-allergic children who were randomized to receive probiotic plus peanut OIT or placebo [85]. Sustained unresponsiveness to peanut after 2–5 weeks of peanut avoidance was achieved in 82% of patients on active treatment and only 3.6% of patients receiving placebo. Patients on active treatment had reduced peanut-induced SPT, decreased peanut-specific IgE and increased peanut-specific IgG4. Further studies are needed to compare OIT plus probiotics to OIT alone to determine the significance of probiotic therapy in achieving sustained unresponsiveness.

Effects on quality of life

There are few controlled studies of the effects of OIT on quality of life. One uncontrolled study of egg allergic children found no difference in parent-perceived health-related quality of life (HRQL) scores from pre- to post-OIT [86]. However, child-reported HRQL scores were significantly improved after OIT. An uncontrolled study of peanut OIT revealed significant improvement in child- and parent-perceived food allergy quality of life questionnaires (FAQLQ) in children 5–12 years of age in all domains including dietary restriction, emotional impact, food-related anxiety, risk of accidental exposure and social limitations [87]. Similar improvements were seen in adolescent quality-of-life scores in all domains except emotional impact of food allergy. A pilot study of cow's milk OIT in patients 3–12 years using the FAQLQ parent form revealed significant improvements in all domains including food anxiety, emotional impact, and social and dietary limitations, particularly in patients over 4 years of age [88]. In addition to lack of a control group, many studies excluded patients who discontinued OIT because of frequent adverse reactions, so their results could represent an overestimation of the benefit of OIT on quality of life [86]. Controlled studies are needed to determine the effect of OIT on quality of life.

Expert commentary & five-year view

Food allergy affects a substantial number of children and adults, particularly in westernized countries. Despite the significant impact of food allergy on patients and health care systems, there are currently no approved therapies for food allergy apart from strict avoidance. Now more than ever, there is a great unmet need for effective disease-modifying therapies for food allergy. Multiple studies have demonstrated the effectiveness of OIT in achieving desensitization to allergenic foods, though whether or not OIT is able to induce lasting tolerance remains to be seen. Further mechanistic studies are needed to improve our understanding of the origin of food allergies and to better define the immunologic changes induced by OIT. Adverse events are common during OIT. There are ongoing studies looking for methods of making OIT safer and better tolerated, including modified OIT protocols, use of allergen non-specific therapies like anti-IgE therapy and identification of biomarkers that predict which patients will have more adverse reactions and thus early discontinuation of OIT. Incorporation of novel therapies such as modified food allergens, probiotics and other immunomodulatory

therapies in conjunction with OIT will optimistically make the next 5 years a period of significant advancement in the treatment of food allergy. Larger, well-designed randomized, double-blind, placebo-controlled trials are needed to determine the effectiveness and acute and long-term safety of OIT before it can be implemented in general clinical practice.

Financial & competing interests disclosure

W Burks has consulting agreements with the following commercial entities: Allertein, Dynavax Technologies Corp, GLG Research, Mastcell Pharmaceuticals, Inc., Perrigo Company, Regeneron Pharmaceuticals, Inc., Persphere, Inc., ActoGeniX, SRA International, Genetech, Valeant Pharmaceuticals, and Sanofi US Services. W. Burks serves on the boards of FARE and the World Allergy Organization and has research sponsored by Hycor Biomedical and the Allergen Research Corp. W Burks also holds a faculty appointment at The University of North Carolina at Chapel Hill. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Key issues

- There are currently no approved treatments for food allergy.
- A number of studies of oral immunotherapy (OIT) for the treatment of milk, egg and peanut allergies have demonstrated the ability to induce desensitization.
- There is limited data on the ability of OIT to induce long-term tolerance to foods and warrants further study.
- Studies show varying results in terms of changes in immunologic parameters during OIT. Changes in food-specific SPT and IgE, Th2-cytokines production and food-specific T-regulatory cell numbers vary, but a rise in food-specific IgG4 is seen consistently across studies.
- Adverse effects are common and highlight the importance of escalating doses of OIT in a controlled setting where patients can be treated immediately for life-threatening allergic reactions.
- Alteration of allergenic milk or egg proteins through extensive heating may accelerate the process of achieving natural tolerance to milk or egg. Tolerance of heated forms of milk or egg may define a separate, milder phenotype of milk or egg allergy.
- Anti-IgE therapies may be effective for increasing safety and effectiveness of OIT.
- Long-term safety of OIT is not known. Approximately 10–20% of subjects will experience GI side effects, and cofactors such as viral infections and exercise may increase the likelihood of accidental allergic reactions to OIT dosing
- For these reasons, OIT is not recommended for use in clinic practice as of yet. Further studies are needed to determine the effectiveness and improve safety of OIT as a treatment for food allergy.

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