

Oral immunotherapy utilizes the pathways of oral tolerance, in which the ingestion of antigenic proteins promotes physiologic changes which suppress an allergic response to the ingested antigen

Ann Nutr Metab 2016;68(suppl 1):19–31

Oral Immunotherapy for Food Allergies

by Elizabeth Feuille and Anna Nowak-Węgrzyn

Key insights

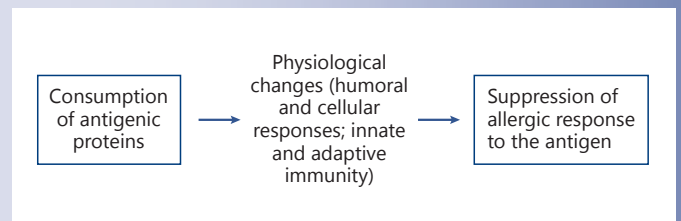
Oral immunotherapy (OIT) is a novel strategy for the treatment of food allergies. Clinical trials have shown that OIT can be effective at desensitizing subjects to a particular food allergen, such as peanut, milk, egg or wheat. The first clinical trial of peanut OIT indicated that OIT could be successfully used to induce desensitization in subjects with peanut allergy, with a favorable tolerability profile and low rates of anaphylaxis. The widespread use of OIT is currently limited by its safety and tolerability. Further studies are needed to determine whether the use of OIT can induce permanent tolerance to the food antigen.

Current knowledge

Food allergies are potentially life-threatening conditions that affect a growing number of individuals. In developed countries, up to 8% of children and 5% of adults are affected by food allergies. The standard of care currently relies on avoidance of the allergen and immediate treatment of reactions in the case of accidental exposure. This strategy is not only inadequate, but may result in nutritional deficiencies, financial burden, and has a social and psychological impact on the patient. Severe reactions and fatalities continue to occur upon accidental ingestion of small quantities of the food allergen.

Practical implications

In OIT, the offending food item is consumed either in natural or processed form in gradually increasing doses, with the goal of establishing permanent tolerance to ingestion. OIT protocols



OIT for the treatment of food allergies.

typically consist of an initial dose escalation day, followed by a buildup phase and a maintenance phase. Use of the anti-IgE monoclonal antibody omalizumab has been applied to enhance the safety and tolerability of OIT. The analysis of IgE levels and IgG4 binding to allergens may help in predicting patient outcomes and improving the safety of OIT. However, the optimal dosing regimen for initial escalation, buildup, and maintenance remains to be established, and it is still unclear what duration and frequency of OIT dosing are required to maintain desensitization.

Recommended reading

Burks AW, et al: Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012;367:233–243.

Oral Immunotherapy for Food Allergies

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Key Messages

- Oral immunotherapy is an investigational therapy for food allergy, which has demonstrated efficacy in desensitizing subjects to offending food proteins.
- As most subjects regain sensitivity within days to weeks of avoidance, it is as yet unclear whether oral immunotherapy has the potential to induce permanent tolerance.
- The safety and tolerability continue to limit the utility of oral immunotherapy in routine clinical practice.

Key Words

Oral Immunotherapy · Food allergy · Desensitization · Tolerance · Sustained unresponsiveness

Abstract

Oral immunotherapy (OIT) is a promising investigational therapy for food allergy. Clinical trials in peanut, milk, egg, and wheat allergy provide evidence that OIT can effectively desensitize a majority of individuals to a food allergen. While a portion of subjects demonstrate sustained unresponsiveness, the majority regain sensitivity with allergen avoidance. The safety and tolerability of OIT continue to limit its use in some patients. Virtually all studies report adverse reactions that are more frequent during dose escalation but may also

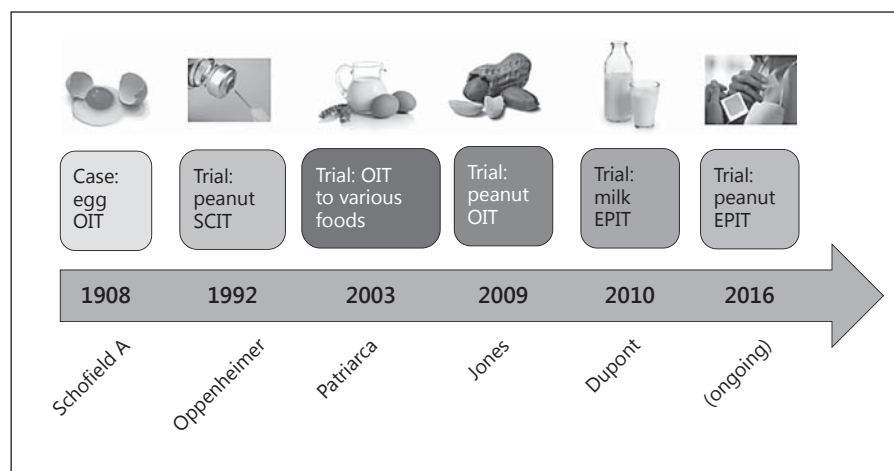
occur during maintenance therapy. Recent studies have identified adjunctive therapies (such as omalizumab) which may mitigate adverse effects. There is a paucity of data on the long-term safety and efficacy of OIT. Further study is required before OIT is ready for routine clinical practice. This review is intended to provide the reader with an up-to-date understanding of OIT, including its mechanisms, efficacy, safety profile, and potential utility in clinical practice.

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Introduction

With food allergies affecting up to 8% of children and 5% of adults in westernized countries, development of therapies for this potentially life-threatening condition has become a public health priority [1, 2]. The inadequacy of the standard of care, which calls for strict allergen avoidance and prompt treatment of reactions, is evidenced not only by the nutritional deficiencies, financial strain, and social and psychological consequences associated with food avoidances [3], but also by the severe reactions and fatalities that continue to occur with accidental ingestions of even tiny amounts of the offending food [4]. The need for disease-modifying therapies has spurred investigation into new management strategies using allergen-specific and allergen-nonspecific mechanisms. Among these, oral immunotherapy (OIT) has been most actively researched [5].

Fig. 1. Timeline of food allergen-specific immunotherapy. SCIT = Subcutaneous immunotherapy; EPIT = epicutaneous immunotherapy.



Historical Perspective

The concept of OIT for food allergy dates back to 1908, when Schofield successfully desensitized a boy with anaphylactic egg allergy. In response to the increasing prevalence of food allergies, interest in food-specific immunotherapies arose in the 1990s (fig. 1). Desensitization to foods via the subcutaneous route fell out of favor when a clinical trial with injection peanut immunotherapy reported unacceptably high rates of anaphylaxis [6]. In 2006, a successful desensitization to peanut using OIT was reported in 2 cases [7, 8]. The first clinical trial of peanut OIT, published in 2009, showed that OIT could be successfully used to induce desensitization in peanut-allergic patients with a favorable side-effect profile and low rates of anaphylaxis [9]. Sublingual immunotherapy (SLIT) for milk and peanut is less efficacious than OIT but has a favorable safety profile. Patch immunotherapy is undergoing clinical trials for milk and peanut allergy in children and adults.

OIT Protocol

In OIT, food is consumed either in natural or processed form in gradually increasing doses, with the goal of establishing permanent tolerance to ingestion. Protocols vary considerably but typically include an initial rapid dose escalation day, followed by a buildup phase, and then a maintenance phase, similar to inhalant subcutaneous immunotherapy (fig. 2). Specific to food OIT is the evaluation of the protection afforded by OIT [10–12].

Mechanisms of OIT

OIT utilizes the pathways of oral tolerance, in which the ingestion of antigenic proteins promotes physiologic changes which suppress an allergic response to the ingested antigen [9]. The mechanisms of OIT are not well understood. Early immunologic changes have been associated with decreased mast cell and basophil reactivity [13], increased food-specific serum and salivary IgG₄ and IgA, and initial increase followed by decrease in serum food-specific IgE [9, 11, 14]. These changes, at least initially, are contingent upon continued OIT; when dosing is held and sometimes even during maintenance phases, these changes can be reversed [15].

While inducible T-regulatory cells (Tregs) are thought to play a central role in oral tolerance to ingested antigens [16–18], evidence supporting the role of Tregs in OIT is controversial. In mouse models of food allergy, in conjunction with improved tolerance of the food, OIT resulted in an increase in CD4+CD25+FoxP3+ cells and IL-10- and TGF- β -producing Tregs in the lamina propria [19]. The increase in Tregs with OIT may be attributed to a replacement with polyclonal T cells, rather than to a ‘re-education’ of existing T cells [20].

Recent studies highlight alterations in both humoral and cellular responses as well as innate and adaptive immunity. Expansion and affinity maturation of allergen-specific memory B cells during OIT suggest a potential role of these cells in tolerance acquisition [21]. IgG antibodies induced during OIT can act through an inhibitory Fc γ RIIb to suppress IgE-mediated hypersensitivity [22]. Dendritic cells were found to secrete increased IL-10 and IFN- α and decreased IL-6 with OIT [23]. Similar findings were observed in a cohort of children undergoing egg OIT; in addition to

Table 1. Selected OIT trials

Food, endpoints	Study	Design	Study population	Protocol summary	Outcomes	AE; withdrawals	Additional significant findings
Peanut							
Peanut, DS	Jones, 2009	Open-label uncontrolled prospective	n = 29; median age 58 months, range 12–111 months	36 months of therapy; 27 subjects reached 1,800 mg maintenance dose for a median of 4.7 months	93% demonstrated DS to 3.9 g with OFC	AE with 3.7% of home doses; 2 required epinephrine	↓ sIgE and ↑ sIgG ₄ by 12–18 months; ↑ secretion of IL-10, IL-5, IFN-γ, TNF-α from PBCs in 6–12 months; ↑ Tregs until 12 months and decreased thereafter
Peanut, DS	Blumchen, 2010	Open-label uncontrolled prospective	n = 22, including high risk; median age 5.6 years, range 3–14	After a median of 7 months, 14 subjects achieved 500 mg maintenance dose	In 14 (64%) subjects who achieved maintenance, DS to a median of 1 g demonstrated with DBPCFC	AE with 2.6% of home doses; 0 required epinephrine; 4 discontinued therapy due to persistent AE	↑ sIgG ₄ with OIT ↓ specific IL-5, IL-4, and IL-2 production by PBMCs with OIT
Peanut, DS	Varshney, 2011	Randomized placebo-controlled	n = 28, with 19 in treatment group; 9 in placebo including high risk; median age 69 months	After 1 year of OIT, 16 subjects reached maintenance dose of 280 mg	84% demonstrated DS to 5 g with DBPCFC, compared to placebo arm tolerating a median of 280 mg	AE with 1.2% of home doses; 0 required epinephrine	Compared to placebo, ↓ SPT, IL-5, IL-13 ↑ sIgG ₄ ; initial increase in sIgE, no change by completion of OIT
Peanut, DS	Anagnostou, 2014	Randomized placebo-controlled crossover	n = 99, with 39 in OIT group for the first phase and 46 in OIT group in the second phase; age 7–16 years	26 weeks of therapy, with 84% in the first phase and 91% in the second phase achieving goal daily maintenance dose of 800 mg	62% in the first phase and 54% in the second phase demonstrated DS to 1,400 mg with DBPCFC	AE with at least 6.3% of home doses; 2 required epinephrine	↓ SPT ↑ sIgE; improved quality of life scores in treatment and placebo groups
Peanut, DS, SU, LT	Vickery, 2014	Open-label uncontrolled	n = 39; age 1–16 years	Up to 5 years, with 24 (62%) completing the protocol, to a maximum of 4 g daily maintenance dose	50% of 24 completing the protocol, or 31% by intention to treat, demonstrated SU 1 month after withdrawal of OIT with 5 g DBPCFC; median of 40 months after OIT, those with SU ingested a median of 555 mg/day, and reported no AE with this	Not reported; 15% of subjects withdrew from the study due to AE	SU was inversely related with SPT size and sIgE at baseline and end of study; sIgG ₄ level was not significantly associated with SU; strongest predictor of SU was sIgE:total IgE at baseline; and Ara h 2-sIgE at end of study
Peanut, DS, SU	Syed, 2014	Randomized controlled	n = 43, with 23 in OIT group and 20 controls; median age 10.4 years, range 4–45	24 months, with goal maintenance dose of 4 g	7 (30%) in OIT group and none in placebo group demonstrated SU 3 months off OIT with DBPCFC; of these 7, 3 demonstrated SU 6 months off OIT	Not available	Hypomethylation of FOXP3 CpG sites in Tregs and alterations in T-cell function were associated with SU; with prolonged avoidance from 3 to 6 months, those who regained sensitivity also demonstrated increase in methylation at these CpG sites
Peanut, DS, SU	Naresity, 2015	Randomized double-blind placebo-controlled	n = 21; age 7–13 years	Randomized to receive 12 months of active OIT (maintenance dose 2 g daily) with placebo SLIT or active SLIT (maintenance dose 3.7 mg daily) with placebo OIT	9 SLIT and 7 OIT completed the protocol; with DBPCFC, OIT groups had a greater increase in threshold dose (141- vs. 22-fold); SU was demonstrated 1 month without treatment in 3 on OIT and 1 on SLIT	33.3% in OIT and 5.2% in SLIT with AE during maintenance; 4 required epinephrine; 3 in OIT withdrew due to AE	Initial increase followed by decrease in sIgE, greater in OIT; ↑ sIgG ₄ in both, greater in OIT; subjects with SU had lower sIgE at baseline and greater decrease in IgE; SPT and IgG ₄ levels were not significantly associated with SU

Table 1 (continued)

Food, endpoints	Study	Design	Study population	Protocol summary	Outcomes	AE; withdrawals	Additional significant findings
Peanut, DS, SU	Tang, 2015	Randomized double-blind placebo-controlled	n = 62; mean age 6.1 years	Randomized to 18 months of peanut OIT (maintenance dose 2 g) with probiotic or placebo alone; 6 withdrew from study, leaving 29 in treatment group and 28 in placebo group	26 (90%) in treatment group demonstrated DS to 4 g peanut in DBPCFC compared with 2 in placebo; 23 (79%) in treatment group demonstrated SU 2–5 weeks off OIT	1 severe AE in 45% of OIT group and 32% of placebo; no significant difference in severe AE per subject between groups (p = 0.9)	The first RCT to both evaluate use of probiotic with OIT and assess its potential to affect achievement of possible SU
Egg and/or milk							
Egg, DS, SU	Buchanan, 2007	Uncontrolled prospective	n = 7; age 14–84 months	24-month protocol with 300 mg maintenance dose daily	All tolerated significantly more protein during DBPCFC, with 5 of 7 tolerating 8 g; 2 demonstrated SU 3 months after withdrawal of OIT	No symptoms with home doses.	One of the first studies to demonstrate safety and efficacy of egg OIT; ↑ sIgG ₄ with OIT; trend toward ↓ sIgE
Egg, DS, SU	Vickery, 2010	Uncontrolled prospective	n = 6, age 3–13 years	Mean of 33 months of OIT, using up dosing to individualized daily maintenance dosing with a mean of 2,400 mg	All achieved DS, and all demonstrated SU with 3.9 g DBPCFC 1 month after withdrawal of OIT	No AE with maintenance	↓ SPT ↓ sIgE and ↑ sIgG ₄ to egg and ovomucoid Trend toward increase in egg induced IL-10, TGF-β, and TH1:TH2 cytokine ratio
Egg, milk, DS, SU	Staden, 2007	Randomized controlled	n = 46, with 25 on OIT and 20 controls; age 6 months to 13 years	Randomized to egg or milk OIT or strict avoidance; median of 21 months of therapy with maintenance dose of 1.6 g egg and 3.5 g milk	16 (64%) of 25 on OIT tolerated DBPCFC to 4.6 g egg or 3.3 g milk and introduced allergenic food into the diet, compared with 7 (35%) of 20 controls; 9 (36%) showed SU at follow-up OFC 2 months after withdrawal of OIT	All OIT subjects had AE; maintenance AE not resolved from AE for entire study	Children who responded had lower sIgE levels than non-responders at the outset; authors noted certain augmentation factors lowering threshold for AE: infection, exercise, pollen allergy, and irregular intake
Egg, milk, DS	Morisset, 2007	Randomized controlled	n = 84 egg-allergic with 49 on OIT and 35 avoiding; n = 57, with 27 on OIT and 30 avoiding; age 1–8 years	6 months of OIT or avoidance	69% on egg OIT demonstrated DS with 7 g SBPCFC, compared to 51% of control; 89% on milk OIT demonstrated DS with 200 ml SBPCFC compared to 60% of controls	Not available	SPT and sIgE decreased with OIT and increased with avoidance; threshold for reactivity was often lower in avoidance group
Egg, DS, SU, LT	Burks, 2012	Randomized placebo-controlled	n = 55, with 40 on OIT and 15 on placebo; age 5–11 years	22 months of therapy, with maintenance daily dose of 2 g	75% on OIT demonstrated DS with 5 g DBPCFC compared to 0 on placebo; 28% on OIT demonstrated SU 6–8 weeks after withdrawal of OIT; 14 months off OIT, all with SU were consuming egg	After 10 months of therapy, 8.3% of OIT doses with AE; no serious AE	Smaller SPT and increases in sIgG ₄ were associated with SU
Egg, DS, SU	Caminiti, 2015	Randomized placebo-controlled	n = 31, with 17 on OIT and 14 on placebo; age 4–11 years	4 months of OIT to maximum daily dose of 4 g or placebo; those demonstrating DS at 4-month DBPCFC continued intake of 2–3 eggs per week for 6 months	16 of 17 completing 4 months of OIT demonstrated DS with 4 g DBPCFC; following 6 months of home egg ingestion, 5 (31%) in OIT group demonstrated SU 3 months after withdrawal of egg from diet, compared to 1 in placebo	On egg-containing diet, 1 with urticaria and abdominal pain, 1 with asthma exacerbation; no AE among controls	sIgG ₄ level at 14 weeks correlated with DS; sIgE and SPT did not differ between groups after 4 months of OIT or avoidance; after 3 months of egg avoidance to assess for SU, those achieving SU had higher sIgG ₄ , lower sIgE, and smaller SPT than those who regained sensitivity

Table 1 (continued)

Food, endpoints	Study	Design	Study population	Protocol summary	Outcomes	AE; withdrawals	Additional significant findings
Egg, DS, SU	Escudero, 2015	Randomized controlled	n = 61, with 30 on OIT and 31 avoiding egg; age 5–17 years	Randomized to 3 months of OIT or avoidance, followed by additional 1-month avoidance to assess SU	93% on OIT were desensitized; 11 (37%) on OIT demonstrated SU with DBPCFC compared to 1 in the control group	AE with 5.9% of all doses, and 4.7% of maintenance doses; 2 withdrawals due to persistent AE	Those achieving SU had lower egg and ovomucoid sIgE prior to avoidance period; sIgE to egg at the end of treatment predicted SU
Milk, DS, LT	Meglio, 2004; with follow-up 2008	Uncontrolled prospective	n = 21; age 5–10 years	6-month protocol, goal daily maintenance dose of 200 ml	15 (72%) demonstrated DS to maintenance dose; 3 achieving partial DS to lower doses; 4 years off OIT, 13 (65%) of 20 were tolerating cow milk fully	Not available; 3 withdrew due to persistent AE	Differences in sIgE to cow milk and casein with OIT were not significant
Milk, DS, SU, LT	Skripak, 2008; with follow-up by Narisety, 2009	Randomized double-blind placebo-controlled	n = 20, with 13 on OIT and 7 on placebo; age 6–17 years	Buildup to 500 mg followed by 3–5 months of maintenance; follow-up study with ongoing daily milk intake at home for a median of 17 weeks	Median threshold dose with DBPCFC was increased to 5,140 mg among 12 completing the protocol compared to 40 mg for placebo; after 17 weeks of daily milk intake, tolerance increased to a median of 7 g with open OFC	2 AE required epinephrine during maintenance; with ongoing daily milk intake, 6 AE required epinephrine and 1 developed EoE	With OIT, ↑ sIgG ₄ , particularly sIgG ₄ ; sIgE did not change significantly
Milk, DS	Longo, 2008	Randomized controlled trial	n = 60, with 30 on OIT and 30 avoiding; age 5–17 years, only included highly sensitive	1 year of OIT, with goal maintenance dose 150 ml	36% on OIT demonstrated DS (tolerating ≥150 ml daily); 54% tolerated partially; DBPCFC among controls remained positive	1 required epinephrine; 2 required ED visit; 3 subjects withdrew due to persistent AE	↓ sIgE with OIT
Milk, DS, SU	Keet, 2012	Open-label randomized controlled	n = 30; age 6–17 years	60 weeks of therapy, randomized to SLIT or alone (7 mg daily maintenance) or SLIT followed by OIT (1–2 g daily maintenance dose)	1 of 10 on SLIT; 6 of 10 on 1 g maintenance OIT, and 8 of 10 on 1 g maintenance OIT tolerated 8 g during open OFC; of these, 9 (60%, 3 on 1 g OIT, 5 on 2 g OIT, 1 on SLIT) demonstrated SU 6 weeks after withdrawal of OIT	Rates of any AE with SLIT and OIT similar, but severity was greater on OIT; 1 AE required epinephrine in OIT group	Only the OIT group demonstrated reduction in sIgE and spontaneous histamine release values
Wheat							
Wheat	Rodriguez del Rio, 2014	Noncontrolled prospective	n = 6	Updosing to daily maintenance dose of 100 g, which was continued for 6 months	5 of 6 completed the protocol and tolerated daily maintenance dose	1 reaction during maintenance, associated with exercise; 1 withdrew due to persistent AE	Initial rise in sIgE followed by decrease; ↑ sIgG ₄ and sIgG ₁
Wheat, DS, SU, LT	Sato, 2014	Prospective with historical control	n = 18 in OIT, n = 11 historical controls; mean age 9 years	After buildup to goal daily maintenance dose of 5.2 g, maintenance therapy was continued for a minimum of 3 months	16 completed the protocol and demonstrated SU with 5.2 g DBPCFC 2 weeks after OIT withdrawal; at the 2-year follow-up, 11 (61%) in the OIT group again tolerated 5.2 g with open OFC, compared to 1 (9%) historical control	AE with 6.8% of doses; AE with maintenance not stated; 1 withdrew due to persistent abdominal pain	In OIT group, sIgE decreased with therapy and had increased at 2 year follow up; controls had no significant change in sIgE at 2 year follow-up

DS = Desensitization; LT = long-term follow-up after study completion; AE = adverse event; ED = emergency department; SPT = skin prick testing; SU = sustained unresponsiveness.

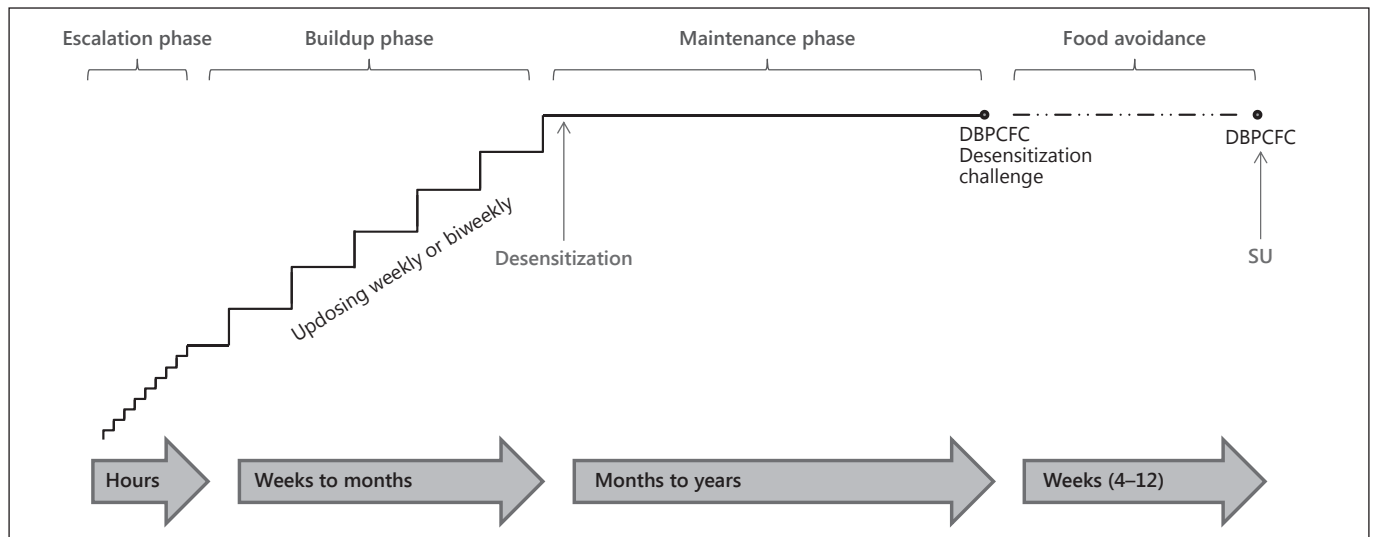


Fig. 2. Typical protocol of food OIT. Initial rapid escalation generally starts at a subthreshold dose (usually in quantity of micrograms) which is rapidly increased every 30 min over the course of several hours to identify the tolerated dose. The patient returns on a following day for a single administration of the highest tolerated dose during the initial rapid escalation day to confirm that this dose can be safely ingested every day at home. During the buildup phase, the daily dose is increased at typically weekly or biweekly increments until the target dose or highest tolerated dose (so-called maintenance dose) is reached, with modifications if there are reactions. At the end of the buildup phase, the patient has achieved desensitization, in which hyporesponsiveness is maintained with regular ingestion of the food and may be lost with even brief dosing interruptions. The dose achieved at the end of the

buildup phase is continued daily during a maintenance phase of months to years, after which a DBPCFC is performed to a regular serving of the food, referred to as a desensitization challenge as OIT has been continued until the day of the OFC. To assess the persistence of the desensitized state, daily dosing is then discontinued for a period of 4–12 weeks and reintroduced during DBPCFC. If the food is ingested without any adverse reaction, this state is defined as SU, as the desensitized state has been maintained for a prolonged period of time in the absence of regular food ingestion. To date, few studies have explored the duration of SU with OIT [10–12]. These data suggest that prolonged treatment is necessary to achieve SU, which is used as a surrogate for permanent oral tolerance; however, clinical trials of OIT have yet to demonstrate the true permanent oral tolerance attributed to OIT.

significant increases in IL-10 production, investigators found trends towards lower IL-5 and IL-13 production and higher tumor necrosis factor- α and interferon- γ levels [24].

Clinical Trials

Selected clinical trials are discussed below and additional details are provided in table 1.

Peanut

The first prospective open-label uncontrolled study reported successful desensitization in 93% of 29 participants treated with peanut OIT and a reassuring safety profile, and provided evidence of immunomodulation [9]. Another prospective cohort study, without a control group, demonstrated desensitization in 64% of the 22 subjects. Despite including high-risk patients who had had severe reactions to peanut and asthma, OIT was fair-

ly well tolerated, with just 4 patients withdrawing due to persistent adverse events [25].

In the first randomized placebo-controlled trial (RCT) of peanut OIT with double-blinding, after 1 year of OIT, 84% of 19 subjects in the treatment group reached the goal maintenance dose and demonstrated desensitization with double-blind placebo-controlled food challenge (DBPCFC). In this cohort, which included higher-risk subjects, just 1.2% of buildup doses required treatment. Injectable epinephrine was not required in the OIT group throughout the trial, though 3 of 19 subjects did withdraw due to adverse effects [26]. In another crossover RCT using peanut OIT, 62% of 39 patients in the first-phase treatment group and 54% of 46 patients in the second-phase treatment group demonstrated desensitization to 1,400 mg of peanut during DBPCFC, compared to 0 in the placebo group. Regarding safety, the authors did not report any serious adverse events [27].

The first study to evaluate the potential for OIT to induce sustained unresponsiveness (SU) reported that, of 24 subjects who completed 5 years of peanut OIT, 50% tolerated 5 g DBPCFC after suspending OIT for 1 month and successfully added peanut to the diet [10].

In another study, of 23 OIT subjects, 7 (30%) demonstrated SU with DBPCFC 3 months after OIT discontinuation [12]. T-cell function and methylation of FOXP3 CpG sites in antigen-induced Tregs differed significantly between those demonstrating SU and those who regained sensitivity. The 7 subjects with SU continued an additional 3 months without OIT; 3 demonstrated persistent SU, while the other 4 regained sensitivity as well as increased methylation of the FOXP3 CpG sites in antigen-induced Tregs [12].

There has been one study comparing OIT with SLIT for peanut allergy. In this double-blind study, 21 subjects were randomized to active SLIT with placebo OIT or active OIT with placebo SLIT. The 16 subjects (9 SLIT and 7 OIT) who continued treatment for 12 months underwent DBPCFC, during which all subjects had a greater than 10-fold increase in challenge threshold, compared to oral food challenge (OFC) at enrollment, with a significantly higher threshold dose in the OIT group. Four weeks after withdrawal of therapy, 3 of 7 subjects on OIT and 1 of 9 subjects on SLIT demonstrated SU. Adverse reactions were generally mild but accounted for early withdrawal in 3 OIT subjects [28].

In an effort to improve the likelihood of achieving SU with OIT, a probiotic was combined with OIT. This double-blind placebo-controlled trial randomized 62 peanut-allergic children to 18 months of treatment with peanut OIT given with the probiotic (*Lactobacillus rhamnosus*, LGG) or placebo alone. After completion of the protocol, the subjects avoided peanut for a 2- to 5-week period, after which 23 (82%) of 29 subjects in the active treatment group demonstrated SU, compared to 1 of 28 in the placebo group. While it may have been more informative to compare peanut OIT with and without a probiotic, the results of the study suggest that the addition of a probiotic may enhance immune tolerance in OIT. Interestingly, adverse events were not significantly different between the treatment and placebo groups [29].

Egg

The first studies on egg OIT conducted by Patriarca and colleagues [30, 31] reported successful desensitization in 5 of 5 egg-allergic subjects and in 11 of 15 egg-allergic subjects in 1998 and 2003, respectively. In an uncontrolled study, after 24 months of egg OIT, all 7 egg-

allergic subjects tolerated significantly more egg during DBPCFC. Following a subsequent 3-month period of strict avoidance, 2 subjects demonstrated SU. In this group of 7 egg-allergic patients, reactions during the protocol were limited to the escalation and buildup phase, and none required the use of injectable epinephrine [32].

In the first RCT of egg OIT, 45 children with allergy to egg or milk were randomized to OIT or strict avoidance. After a median of 21 months of therapy, 16 (64%) of 25 children on OIT demonstrated desensitization with DBPCFC and were able to introduce previously allergenic foods into their diet, compared to 7 of 20 (35%) controls [34]. A larger study by Morisset et al. [35], which included 84 egg-allergic children (aged 1–8 years) randomized to OIT or avoidance, showed similar rates of desensitization. After 6 months of therapy, 69% of 49 children in the egg OIT group demonstrated desensitization during single-blind placebo-controlled food challenge (SBPCFC) versus 51.4% of the 35 children in the avoidance group [35].

In an effort to improve the likelihood of inducing SU, a protocol with higher, individualized doses and longer duration was utilized. After a 1-month period of strict avoidance following OIT, all 6 patients demonstrated SU with DBPCFC [33].

A randomized placebo-controlled multicenter study provided a more rigorous assessment of SU and long-term outcomes with egg OIT. With DBPCFC after 22 months of OIT, 75% of 20 subjects on OIT were desensitized, compared to 0 in the placebo group. Following a 6- to 8-week period of egg avoidance, just 28% of those in the OIT group demonstrated SU. At 36 months, all children who had demonstrated SU were consuming egg. Smaller skin tests and higher egg-specific IgG₄ were associated with an increased likelihood of achieving SU [11].

Two recent studies explored SU after a much shorter OIT period. In the RCT employing just 4 months of egg OIT followed by 6 months of ingestion of 2–3 eggs per week, 5 (31%) of 17 patients treated with egg OIT demonstrated SU after 3 months of egg avoidance, compared to just 1 patient in the placebo group [36]. Similarly, after 3 months of egg OIT followed by 1 month of avoidance, DBPCFC demonstrated SU in 11 (37%) of the 30 children on OIT, compared to 1 amongst the 31 controls [37].

Milk

Similar to egg OIT, Patriarca et al. [31] were also among the first to conduct controlled trials on milk OIT [31]. A prospective study without a control group pub-

lished in 2004, reported desensitization in 15 (72%) of the 21 children completing the 6-month protocol, with 3 achieving partial desensitization. The remaining 3 could not complete the protocol due to persistent adverse effects at low doses of cow milk [38]. In a follow-up study 4 years later, the authors reported that 13 of 20 (65%) children were tolerating cow milk fully [39].

In 2007, another RCT reported similar rates of desensitization utilizing a median OIT duration of 21 months, with 16 (64%) of 25 milk-allergic children achieving desensitization in the treatment group, compared to 7 (35%) of 20 in the avoidance group [34]. In a comparatively large randomized study, Morisset et al. [35] reported the outcomes of their 6-month OIT protocol: 89% of the treatment group demonstrated successful desensitization, compared to 60% of the avoidance group.

Results of the first double-blind placebo-controlled study of milk OIT were published in 2008. Using a protocol which called for 3–4 months of maintenance following the buildup phase, the authors reported that the median threshold dose with DBPCFC was increased to 5,140 mg among the 12 patients who completed the protocol, which was significantly higher than the 40-mg threshold dose at baseline in the placebo group. Reactions occurred with a median of 35% of doses per participant [40]. With ongoing daily milk intake at home for a median of 17 weeks, a follow-up study showed increased tolerance to a median of 7 g with open OFC, with 33% of participants tolerating 16 g. The authors did report reactions with ongoing milk intake which were mostly mild; notably, injectable epinephrine was required on 6 occasions (0.2% of doses), and 1 subject developed symptoms of eosinophilic esophagitis (EoE) [41].

A RCT in a larger milk-allergic group aimed to specifically assess the efficacy of OIT among children with a history of severe reactions to milk. After 1 year of milk OIT, 11 (36%) children in the OIT group were desensitized, 16 (54%) were partially desensitized (5–150 ml), and 3 (10%) were unable to continue with therapy due to persistent abdominal or respiratory complaints. Among controls, DBPCFC after 1 year of avoidance were all positive [42].

Additional RCTs supported the efficacy and safety of milk OIT, reporting desensitization rates of approximately 90% [43, 44]. In one RCT of milk OIT, twice weekly dosing was as effective as maintenance therapy as daily dosing [45].

Milk OIT was compared to SLIT in an open-label RCT, showing improved desensitization but a worse safety pro-

file than SLIT. OIT was also more effective in inducing SU (8 of 20 subjects on OIT vs. 1 of 10 subjects on SLIT) [46].

Wheat

Wheat has been the subject of few OIT trials. In a small study, 5 of 6 children successfully completed buildup and 6-month maintenance. One subject experienced symptoms during maintenance: when exercising immediately after wheat ingestion, this subject developed urticaria, which improved with antihistamine and oral steroids [47].

Using a larger cohort with a historical control group, Sato et al. [48] reported that 16 of 18 subjects achieved the target maintenance dose of 5.2 g wheat protein and, following a 2-week period of avoidance, ingested this dose without symptoms during DBPCFC. At the 2-year follow-up, 11 (61%) subjects in the treatment group tolerated 5.2 g of wheat with open OFC, compared to 1 (9%) of 11 historical controls. Regarding safety, 6.8% of the 5,778 total treatment doses resulted in symptoms, with administration of epinephrine on one occasion [48].

Extensively Heated Milk and Egg Diet

In milk- and egg-allergic children with transient allergy, IgE antibodies bind to conformational epitopes that are destroyed with heating or processing [49–51]. Additionally, heated egg white protein forms insoluble complexes in baked products that further reduce its allergenicity [52]. Two clinical trials demonstrated that a significant portion (approx. 75%) of children reactive to unheated milk and egg will tolerate these allergens in their baked forms. This is not only advantageous for expanding the diet; compared to strict avoidance, regular ingestion of heated milk and egg shortens the time to tolerance acquisition to unheated forms [53, 54].

Regular ingestion of heated milk and egg shortens the time to tolerance acquisition to unheated forms

Baked milk diet was tested as immunotherapy for 15 highly milk-allergic patients (aged 4–12 years) who were previously unable to complete a milk OIT protocol due to severity and frequency of allergic reactions. In this uncontrolled open trial, a dose of baked milk smaller than the eliciting dose at entry OFC was gradually increased

to a maintenance dose of 1.3 g per day. OFCs were performed at 6 and 12 months of treatment. Eight patients could not continue with the protocol due to IgE-mediated reactions, with a number of participants having reactions to doses that they had previously tolerated for more than 1 month. Only 3 of the 14 patients who continued with the baked milk protocol reached maintenance dosing within 12 months. For the 6 participants who continued with the protocol, there was a significant increase in challenge threshold to unheated milk. The results of this study suggest that the use of baked milk as OIT may be useful for increased threshold reactivity; however, for patients who are highly sensitive to milk, it may be less realistic as a method of attaining clinical tolerance to milk [55].

With these data, experts have recommended that for children already tolerating baked products, it is safe to continue regular ingestion at home. For those who have been strictly avoiding milk, a physician-supervised food challenge to milk will be necessary to determine whether it is safe to introduce baked products into the diet [56].

OIT with Omalizumab

In recent years, the anti-IgE monoclonal antibody omalizumab has been explored to enhance the safety and tolerability of OIT. In a pilot phase I study of a milk OIT protocol, following 9 weeks of omalizumab pretreatment, 9 of 10 milk-allergic subjects (aged 7–17 years) reached the maximum dose of 1 g peanut protein during rapid dose escalation day. Nine of the 10 subjects were able to reach 2,000 mg milk protein over 5 weeks of buildup dosing with omalizumab. After another 8 weeks of maintenance dosing without omalizumab, these 9 subjects then tolerated 7,250 mg milk protein during DBPCFC. The mean frequency of reactions during the study was 1.6%. Epinephrine was required for 2 patients on the initial dose escalation day. There were 2 moderate reactions and 1 severe reaction (which required epinephrine) that notably occurred with maintenance home doses. This study suggests that pretreatment with omalizumab enhances the tolerability of rapid dose escalation in milk OIT; however, with discontinuation of omalizumab, clinically significant reactions may occur with home maintenance doses that were previously tolerated [57].

Another uncontrolled pilot study investigated the use of omalizumab in a peanut OIT protocol. The study specifically enrolled highly peanut-allergic children who are thus at a greater risk for adverse reactions with OIT. After

pretreatment with omalizumab for 12 weeks, all 13 subjects (aged 8–16 years) tolerated the initial dose escalation to 500 mg peanut flour. With another 8 weeks of therapy, 12 subjects reached the goal maintenance dosing of 4,000 mg peanut flour daily, and subsequently tolerated 8,000 mg peanut during DBPCFC, at which point omalizumab was discontinued. The maintenance dose was continued at home for another 6 months without omalizumab. One subject withdrew due to persistent symptoms with OIT doses. While reactions occurred with 2% of doses, and were mostly mild, there were 5 moderate reactions and 2 severe reactions (with epinephrine required on 5 occasions), which occurred with home maintenance dosing. Only 6 of the 13 subjects had only mild or no allergic reactions. These results suggest that omalizumab facilitates rapid oral desensitization even among subjects highly sensitive to a food allergen. However, adverse reactions may continue to occur during maintenance and with home dosing following discontinuation of omalizumab [58].

The only randomized controlled study on the use of omalizumab in milk OIT used omalizumab for the pretreatment, buildup, as well as maintenance phases. The investigators randomized 57 milk-allergic subjects (aged 7–32 years) 1:1 to receive omalizumab (for 4 months before treatment and continued dosing for 24 months of OIT) or placebo. Twenty-six in each group reached maintenance dosing (3.8 g daily) 6 months into OIT. Participants underwent 10 g DBPCFC after 24 months of OIT and again after a 4-month period of milk avoidance. Though rates of desensitization (89 and 71%) and SU (48 and 36%) were not significantly different between the omalizumab and placebo groups, omalizumab did improve the safety and tolerability of OIT. The portions of doses provoking symptoms (2.1 vs. 16.1%, $p = 0.005$) and requiring treatment (0.0 vs. 3.8%, $p = 0.0008$) were significantly reduced with omalizumab [59].

Multi-Food OIT

As approximately 30% of food-allergic children are reactive to more than one food, many would benefit from immunotherapy, which addresses more than one food allergy at a time. The safety and tolerability of multi-food OIT was investigated in a study comparing subjects (aged 4–46 years) on peanut OIT ($n = 15$) with those on multi-food OIT including peanut ($n = 25$). OIT with two foods was carried out in 24% of the participants, with three foods in 32%, with four foods in 20%, and with five foods in 24%. Dose escalation to the full maintenance dose of

4 g took a median of 4 months longer to attain with multi-food OIT (with 50% of participants on 4 g within 20 weeks) than with peanut OIT alone (with 50% on the full dose within 16 weeks). After 1 year of OIT, peanut-specific IgG₄ increased significantly for both groups, while peanut-specific IgE was not significantly changed in either. Rates (3.3% for single and 3.7% for multi-food) and severity of reactions (with 2 participants requiring epinephrine in each group) did not differ significantly between the two groups. These results suggest that desensitization and immunomodulation may be achieved with multi-food OIT, with a similar safety profile to single-food OIT [60]. Multi-food OIT, given its potential to be useful in the large portion of food-allergic individuals sensitized to multiple foods, certainly deserves further investigation.

The use of omalizumab was studied in a multi-food OIT protocol, which specifically enrolled children highly sensitive to the offending foods [61]. In an uncontrolled pilot study, 25 participants (median age, 7 years), all of whom failed DBPCFC to ≤ 100 mg of the offending allergens, received 8 weeks of pretreatment with omalizumab, followed by an initial dose escalation and buildup, achieving the goal maintenance dose of 4,000 mg protein per allergen in a median of 18 weeks. Omalizumab was discontinued 8 weeks into the maintenance phase. Mild reactions were reported in 5.3% of home doses, and one severe reaction (towards the beginning of the maintenance phase) was reported over the course of the study. Six months into OIT, reaction rates dropped by 70% [61]. Findings of these studies suggest that multi-food OIT may be a safe and effective approach to OIT that deserves further investigation.

Prediction of a Favorable Response to OIT

Smaller skin test sizes, lower specific IgE, and increased IgG₄ prior have been associated with an increased likelihood of achieving desensitization and SU. Smaller skin test size and lower allergen-specific IgE levels were associated with the successful completion of peanut OIT [10]. Smaller skin tests and higher egg-specific IgG₄ were associated with SU as well as with successful desensitization in egg OIT [11]. In a trial of milk OIT, the investigators found decreased IgE binding and increased IgG₄ binding to cow milk epitopes among children who achieved de-

sensitization. Those who discontinued OIT due to adverse effects had increased quantity and affinity of epitope-specific IgE antibodies and less overlap between IgE and IgG₄ binding to milk peptides [62]. These results suggest that analysis of IgE and IgG₄ binding to allergens and their specific epitopes may assist in predicting outcomes and improving the safety of OIT.

Safety Concerns with OIT

The safety and tolerability of OIT continue to limit its use in routine clinical practice. Most reactions are mild and limited to the oropharynx resolving without intervention or with antihistamine alone. However, virtually all trials are accompanied by one or a few severe reactions. Studies consistently report that reactions are most frequent during the initial dose escalation day and with buildup dosing, both of which are generally conducted under physician supervision. Maintenance doses administered at home are generally better tolerated; however, it remains that the occasional home dose (which has been previously tolerated without significant symptoms) is associated with a multisystem or severe reaction [63].

Certain augmentation factors can lower the threshold for reaction to OIT doses [34]. Five patterns associated with increased likelihood of adverse reactions during their

peanut OIT trial have been identified: concurrent illness or menses, poorly controlled asthma, administration on an empty stomach, and physical exertion following a dose [64]. With the aim to enhance safety of OIT, more recent studies have put in place protocols to address these augmentation factors, with reduction in home dosing when a subject has signs of infection, and exercise avoidance in the hours immediately following a dose [47, 57].

While severe reactions account for withdrawal from OIT for a small portion of patients, the majority of patients who discontinue OIT do so because of chronic symptoms, especially chronic abdominal pain. It is unclear what portion of the patients develops symptoms due to undiagnosed EoE. A meta-analysis reported that EoE may develop in up to 2.7% of subjects on OIT to milk, peanut, egg, or wheat; however, this number may be falsely elevated due to publication bias [65]. Further studies should clarify the true incidence and elucidate whether OIT may incite EoE or unveil a pre-existing disease.

The safety and tolerability of OIT continue to limit its use in routine clinical practice.

Long-Term Follow-Up

Studies evaluating long-term outcomes of OIT are limited and mostly address long-term outcomes following milk OIT. In one of the first studies, full tolerance was reported in only 31% of the 32 milk-allergic subjects who had undergone OIT in prior studies (discussed above) [40, 46]. A significant portion limited consumption due to symptoms or with exercise, illness, or anxiety [66]. In a large retrospective study, patients who were at least 6 months off OIT were contacted. Of the 195 responders, 180 were consuming milk regularly with approximately half experiencing mostly mild allergic reactions, and 13 (6.7%) reporting use of epinephrine. Factors associated with an increased reaction rate included more episodes of anaphylaxis prior to OIT and a lower starting dose. Promisingly, reaction rates decreased over time, from 0.28 per month for those 6–15 months off OIT, down to 0.15 per month in the group more than 30 months off OIT. Milk-specific basophil activation testing was significantly decreased in the group more than 24 months off OIT when compared to those less than 24 months off OIT [67]. Thus, both clinical and laboratory data suggest continued immunomodulation following completion of OIT, enhancing tolerance of the allergen. Without a control group, however, it is not clear whether OIT or the natural history of allergy is primarily responsible for immunologic changes.

A 7-year follow-up study included 28 children (aged 6–15 years) with cow milk allergy who were enrolled in a randomized double-blind placebo-controlled milk OIT protocol [44]. In the initial study, authors reported that 24 of the 28 children were consuming milk daily at 36 months from initiation of OIT. Of the 24 participants responding to a questionnaire 7 years after initiation of milk OIT, 8 (33%) had discontinued milk altogether, 2 consumed limited amounts, and 14 (58%) reported daily consumption of milk, with 3 among these reporting symptoms associated with milk ingestion [68]. The mixed results of these follow-up studies point to the necessity of further study to improve the safety and efficacy of OIT.

Quality of Life

Studies assessing quality of life with OIT are mixed. Some evidence suggests that OIT may improve quality of life scores, particularly with regard to social limitations, accidental exposures, and anxiety [27, 69]. However, quality of life may decline among subjects experiencing adverse reactions on OIT [70], suggesting that quality of life on OIT will improve with protocols that reduce the frequency and severity of OIT's adverse effects.

Recommendations for Clinical Practice

With both patients and providers eager for therapies for food allergy, some providers report currently offering OIT in their practice [71, 72]. However, considering the paucity of data on the long-term efficacy and safety, and an unfavorable risk-benefit ratio at present, it is the opinion of some experts that OIT is not ready for routine clinical practice [73–75]. As an exception to this, ingestion of heated milk and egg by milk- and egg-allergic children as OIT to hasten tolerance to the unheated allergen appears to be a safe and effective therapy, and may be incorporated into clinical practice as discussed above [75].

Ingestion of heated milk and egg by milk- and egg-allergic children as OIT to hasten tolerance to the unheated allergen appears to be a safe and effective therapy

Future Directions

In the coming years, establishment of standardized protocols for OIT will be essential if this is to be recommended for use outside of the research setting. The optimal dosing for initial escalation, buildup, and maintenance needs to be clarified. It is as yet unclear what duration and frequency of OIT dosing (or ingestion of the allergenic food) is required to maintain desensitization. While OIT has been effective in desensitizing many food-allergic individuals to an inciting food, further study is required to evaluate whether OIT can induce permanent tolerance. Furthermore, we are lacking criteria with which to evaluate and diagnose permanent tolerance. Strategies for improving safety will need to be standardized, including indications and dosing regimens for the use of omalizumab as well as protocols for dosing adjustment in the presence of augmentation factors. The use of probiotics to enhance the efficacy of OIT should also be further explored. In conclusion, while OIT shows significant promise in reducing sensitivity to food allergens, it remains an experimental therapy that continues to be the subject of active investigation.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the contents of the chapter.

The writing of this article was supported by Nestlé Nutrition Institute.

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