

# Oral Immunotherapy for the Treatment of Food Allergy

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**ABSTRACT:** Food allergies have increased significantly over recent decades and are the most common cause of admissions for anaphylaxis in childhood, particularly in children under 5 years of age. Current management of food allergy is limited to strict food allergen avoidance together with education on the recognition and emergency management of allergic reactions, and in some cases provision of self-injectable adrenaline. Although this supportive management approach is generally effective, it is burdensome for patients and families, and in turn leads to reduced quality of life. Patients with food allergy would benefit greatly from a definitive treatment that could achieve long-term tolerance. Recent studies demonstrate that oral immunotherapy (OIT) can induce desensitization and modulate allergen-specific immune responses. However, it remains uncertain whether long-term tolerance can be achieved with current OIT regimens. Increased allergen dose, duration of OIT and/or inclusion of an immune modifying adjuvant may enhance the tolerogenic potential of OIT. Allergic reactions during OIT are common, although severe reactions are infrequent. Oral immunotherapy holds promise as a novel approach to the definitive treatment of food allergy.

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**KEY WORDS:** food allergy, allergen, oral immunotherapy

Over the past few decades, the prevalence of allergic diseases has increased substantially especially in developed countries. While the prevalence of asthma has stabilized, and the rise in prevalence of eczema and allergic rhinitis appears to be slowing, the prevalence of food allergy and anaphylaxis continues to rise [1,2]. A recent cross-sectional survey of households with children in the United States for the period June 2009 to February 2010 reported a food allergy prevalence of 8.0%, with the commonest being to peanut (25.2%), followed by milk (21.1%) and shellfish (17.2%) [1]. In Australia, a large population-based study (HealthNuts) reported the prevalence of challenge-proven immunoglobulin E-mediated food allergy among 12 month old infants to be > 10% [5].

Among the common food allergens, peanut and tree nut are particularly important since allergies to these foods gen-

erally persist into adulthood and reactions are often severe. Furthermore, they are the commonest cause of fatality due to food anaphylaxis, accounting for 81%, 38% and 43% of deaths in the U.S., Britain and Australia respectively [4-6]. A treatment that could modify the natural history of food allergy by inducing long-term tolerance would be of great benefit to those individuals who fail to outgrow their food allergy.

## MECHANISMS OF FOOD ALLERGY

The mechanisms by which ingested food proteins are identified as allergens leading to the development of food allergy remain poorly understood (reviewed in [7]). Antigen-presenting cells, especially intestinal epithelial cells and dendritic cells, and regulatory T cells play a central role in the induction and maintenance of oral tolerance. Oral tolerance may develop with repeated low dose exposure to antigen mediated by activation of Treg cells. It can also be induced by a single high dose antigen exposure involving lymphocyte anergy or deletion by Fas-mediated apoptosis [7]. Aberration in the normal induction of oral tolerance results in the generation of allergen-specific Th2 immune responses and elevation of food allergen-specific IgE levels. Studies suggest that imbalance of Th2/Th1 responses in food allergy is caused by dysregulation of Treg cell activity [8]. Oral tolerance induction may be bypassed by several pathways. Reduced ultraviolet exposure and vitamin D levels, alteration in intestinal physiologic barrier function, diet and the way in which antigen is prepared or presented in food (e.g., boiled vs. roasted peanut, baked vs. other forms of egg or milk), the route of antigen exposure, and the timing of food introduction (reviewed in [7,9]) have all been suggested to play a role in determining whether responses are directed towards tolerance or allergy.

## CURRENT MANAGEMENT OF FOOD ALLERGY

There is currently no effective long-term treatment to change the natural history of food allergy. Management is only supportive, comprising avoidance of the food concerned, early recognition of allergic reaction symptoms, and initiation of appropriate emergency treatment. Avoidance of food allergens

Treg = regulatory T  
IgE = immunoglobulin E

is difficult to achieve, particularly with commercially prepared foods. Furthermore, 40%–100% of deaths from food anaphylaxis involved ingestion of foods catered or prepared away from home [4–6]. Several self-injectable adrenaline devices are available for the emergency treatment of anaphylaxis. However, the use of these devices is not intuitive and requires specific training [10]. Moreover, half the food anaphylaxis deaths in the UK series involved failure to carry or use an EpiPen<sup>®</sup> correctly [4]. Adrenaline, however, may not always be sufficient to prevent fatality, since early and repeated administration of adrenalin failed to prevent death in 12–14% of anaphylaxis fatalities [4,5]. These significant limitations of current food allergy management highlight the need for alternative treatment options to induce long-term tolerance.

### ALLERGEN-SPECIFIC IMMUNOTHERAPY AS A TREATMENT FOR ALLERGIC DISEASE

Allergen-specific immunotherapy is effective for the induction of tolerance and has been used for the long-term treatment of insect venom anaphylaxis, asthma and allergic rhinitis. Subcutaneous immunotherapy has been shown to modulate the immune response to allergen by inducing allergen-specific CD4<sup>+</sup>CD25<sup>+</sup> Treg cells that restore the balance of allergen-specific Th1/Th2 effector cells, leading to reduced Th2 cytokine expression (interleukin 4 and 5), and in most studies increased Th1 cytokine responses (interferon-gamma). These changes in turn lead to reduced allergen-specific IgE and increased allergen-specific IgG4 (reviewed in [11]). Other immunological effects of SCIT include increased apoptosis of allergen-specific Th2 cells, reduced tissue mast cell numbers and reduced serum levels of tumor necrosis factor-alpha and IL-1 $\beta$  [11]. Sublingual immunotherapy has also been shown to be effective in reducing clinical symptoms in respiratory allergy (asthma and allergic rhinitis); however, immunological effects are less well characterized. Increased allergen-specific IgG4 and reduced allergen-specific IgE have been reported in some but not all studies [11]. Oral immunotherapy has not been consistently effective when used for the treatment of respiratory allergy; however, recent studies suggest an exciting potential for OIT as a treatment for food allergy, and there is renewed interest in the application of OIT in this setting.

### ORAL IMMUNOTHERAPY FOR FOOD ALLERGY

Oral immunotherapy protocols involve daily oral administration of allergen in gradually increasing doses during the build-up phase to reach a maintenance dose that is continued for a variable period (usually 6 months to 2 years) [12–

30]. Study outcomes have mostly focused on achievement of desensitization (the ability to tolerate an allergen while on immunotherapy), with only a few studies evaluating the acquisition of tolerance (the long-term ability to tolerate an allergen after immunotherapy is discontinued) (reviewed in [7]). Studies of OIT for the treatment of food allergy have consistently reported successful desensitization in the majority of subjects [12,14,16,17,22,24], and OIT has also been shown to induce modulation of allergen-specific immune responses [15,16,18,31]. However, effective induction of long-term tolerance with OIT has yet to be demonstrated.

### OIT AND INDUCTION OF DESENSITIZATION

The majority of early OIT studies focused on hen's egg and cow's milk allergies. Initial encouraging results of OIT in food allergy originated from case reports describing desensitization in patients with cow's milk allergy [14,15], and associated immunologic changes of resolution of cow's milk skin-prick test, reduced milk-specific IgE, increased milk-specific IgG4 and IgA levels, increased IFN $\gamma$  and decreased IL-4 production [15]. A case series of 39 children with confirmed IgE-mediated cow's milk allergy reported similar results: 36 children were successfully desensitized after 12 weeks of milk OIT, and 33 demonstrated ongoing desensitization 6 months later, with serum milk-specific IgE decreased at completion of OIT and 6 months after [28]. In an open-label case-control study of OIT in 54 patients (aged 3–55 years) with various food allergies, Patriarca et al. demonstrated successful desensitization in 83.3% of the participants (45/54), with reductions in food-specific IgE and increase in food-specific IgG4 [16]. Meglio and colleagues employed a 6 month milk OIT protocol in 21 children with proven IgE-mediated cow's milk allergy, and reported full desensitization to milk in 71% (15/21 who tolerated 200 ml) and partial desensitization in 14% (3/21 who tolerated 40–80 ml), with decreased milk-specific IgE and increased milk-specific IgG4 [17]. Follow-up at 4 years showed that all of these children remained desensitized while on daily milk consumption [18]. A desensitization milk OIT protocol used in an outpatient setting (weekly increases in doses over a 9–10 week period) demonstrated that 16 of 18 children with challenge-confirmed cow's milk allergy tolerated a daily dose of 200–250 ml, with 13 of 16 continuing to tolerate milk for more than a year [27].

The first randomized double-blind placebo-controlled trial of OIT was performed by Skripak et al. [19]. Nineteen children (12 completed active treatment and 7 received placebo) aged 6–17 years with IgE-mediated cow's milk allergy underwent milk OIT (an initial escalation day aiming for 50 mg, weekly updosings over 8 weeks to a final dose of 500 mg, and maintenance for 3–4 months), with double-blind placebo-controlled food challenges performed before and after 13 weeks of OIT. Following OIT, the

SCIT = subcutaneous immunotherapy  
IL = interleukin  
OIT = oral immunotherapy

IFN $\gamma$  = interferon-gamma

median threshold dose for reaction to milk increased from 40 mg to 5140 mg in the active group but remained unchanged in the placebo group ( $P = 0.003$ ). Although there were no changes in milk-specific IgE levels and SPT size in both groups, increased milk-specific IgG4 levels were observed in the active group [19]. In a follow-up study of 15 children from the original Skripak study, the median tolerated daily dose was gradually increased to 7 g, with 6 children tolerating 16 g without symptoms and 7 subjects reacting at 3–16 g during milk challenges conducted after 13–75 weeks. Milk-specific IgE levels and SPT wheal size were significantly decreased and milk-specific IgG4 increased [20]. In a randomized single-blind controlled study, Pajno et al. [32] evaluated 30 children (aged 4–10 years) with challenge-confirmed IgE-mediated cow's milk allergy who received milk OIT (15 children; 1 drop of milk diluted 1:25 and doubled every week until week 18 to achieve 200 ml) or matched soy formula (15 subjects), followed by a DBPCFC. Unlike other protocols, there were no "home doses" between clinic visits for updosing. In the active group, 10 of 13 children achieved full desensitization without adverse events, 1 child achieved partial desensitization at 64 ml, while 2 children discontinued therapy after experiencing severe reactions requiring epinephrine, and desensitization was associated with increased milk-specific IgG4, but milk-specific IgE remained unchanged. After 6 months, the desensitized children continued to tolerate regular milk ingestion without clinical reactions [32].

Longo and co-researchers [21] evaluated the safety and efficacy of OIT in highly milk-allergic children with a history of anaphylaxis. Sixty children (aged 5–17 years) with a history of at least one severe allergic reaction and significantly elevated ( $> 85$  kU/L) milk-specific IgE levels and who reacted to  $\leq 0.8$  ml during an initial oral milk challenge were randomized to receive milk OIT or a milk-free diet for 12 months. After 1 year 36% of children in the active group (11/30) were completely desensitized ( $\geq 150$  ml/day), 54% (16/30) achieved partial desensitization (tolerated 5–150 ml), and 10% (3/30) failed to complete the OIT protocol due to persistent symptoms. In contrast, all 30 children in the control group failed the DBPCFC after 1 year. Fifty percent of subjects in the OIT group had significantly decreased milk-specific IgE levels at 6 and 12 months, whereas in the control group milk-specific IgE remained unchanged. The response rates in this study were lower than those reported in unselected populations in the previous OIT studies [16,17]. Nevertheless, despite being highly allergic to cow's milk, the majority of children were able to remain on maintenance therapy and attained partial desensitization. Similar results were observed in a study using rush milk OIT protocol: 6 of 9 children with persistent cow's milk allergy achieved a maximal dose of 120 ml with only mild

to moderate reactions [26], indicating that desensitization can be achieved quickly through a rush protocol. In a recent rush hen's egg OIT study, all six children with severe egg allergy were able to ingest one whole cooked egg without adverse reactions and demonstrated decreased egg white-specific IgE and increased egg white-specific IgG4 and transforming growth factor-beta 1, but rather surprisingly decreased IL-10 [29]. Adding six cases to the first six reported cases above also revealed similar results [30]. Kaneko et al. [33] evaluated the efficacy of slow updosing OIT methods (1 daily drop of milk in 20 ml water, with dose increments every 2 weeks), followed by an oral food challenge in a pilot study involving 10 children with cow's milk allergy. Eight patients completed the protocol and were able to tolerate 100 ml while the other two did not complete the study because of persistent adverse reactions at 5 ml and 20 ml doses. The severity and frequency of adverse reactions were similar to previous OIT protocols [13,21]. However, no data were provided with regard to the duration of OIT and the outcomes of desensitization.

Since severe reactions can occur following accidental peanut ingestion or inhalation, peanut OIT has now become a major focus in food allergy treatment. Despite several isolated case reports of oral desensitization following peanut OIT, the first clinical trial of peanut OIT was conducted by Jones and colleagues [22], who enrolled 39 peanut-allergic children (aged 1–16 years) in an open-label uncontrolled study involving a 1 day modified rush escalation phase (0.1 mg increased to 50 mg), a build-up phase (daily doses increased by 25 mg every 2 weeks until reaching 300 mg), and a maintenance phase (300 mg daily for 4–22 months). During the initial day escalation, 26% of subjects (10/39) tolerated the highest dose of 50 mg, 38% (15/39) tolerated 25 mg, 15% (6/39) tolerated 12 mg, 13% (5/39) tolerated 6 mg, 3% (1/39) tolerated 3 mg, and 5% (2/39) tolerated 1.5 mg. Twenty-nine subjects completed the protocol followed by an open OFC; 27 children (93%) tolerated 3.9 g during a peanut challenge with 18 of them having no reaction. By 6 months, titrated peanut SPT responses and basophil activation to peanut antigen were significantly decreased. By 12–18 months, peanut-specific IgE decreased and peanut-specific IgG4 increased. Production of IL-10, IL-5, IFN $\gamma$  and TNF $\alpha$  by peanut-stimulated peripheral blood mononuclear cells increased over a 6–12 month period. Peanut-specific FoxP3 Treg cells increased until 12 months and decreased thereafter. In addition, T cell microarray gene expression analysis showed down-regulation of genes involved in the apoptotic pathways, and production of serum inhibitory factors that blocked IgE-peanut antigen complex formation were demonstrated [22]. This study provided evidence for the ability of peanut OIT to induce desensitization and modulate immune regulation. It

**Oral immunotherapy has been shown to consistently induce desensitization, but its ability to induce long-term tolerance appears limited**

SPT = skin-prick test  
 DPBFC = double-blind placebo-controlled food challenge

TNF $\alpha$  = tumor necrosis factor-alpha  
 OFC = oral food challenge

also contributed novel findings that provide insight into the mechanisms of OIT.

Clark et al. [12] reported a case series of four boys (aged 9–13 years) with challenge-confirmed peanut allergy who underwent peanut OIT with gradual escalation and higher doses of peanut protein (biweekly updosing increments from 5 to 800 mg daily). After 6 weeks, all patients tolerated at least 2.4 g (10 peanuts) with a median 50-fold increase in dose threshold for reactivity following a repeat OFC [12]. The follow-up data of these 4 subjects and another 18 children following the same protocol were evaluated in an uncontrolled clinical trial whereby OIT was administered in two phases: a gradual updosing phase with 2-weekly increments (8–38 weeks) to 800 mg/day and a 30 week maintenance phase, followed by an OFC at 6 and 30 weeks. After 6 weeks, 54% (12/22) completed a 2.6 g peanut challenge without reaction, and after 30 weeks 64% (14/22) tolerated 6.6 g. The median tolerated dose was increased by 1000-fold following peanut OIT [34]. This study used a higher maintenance dose of 800 mg peanut protein compared to 300 mg in the Jones study [22].

The first RDBPCT of peanut OIT in children with peanut allergy was recently reported by Varshney et al. [31], in which 28 children aged 1–16 years were randomized to receive a high dose of 4 g peanut flour (19 subjects) or placebo (9 subjects). The OIT protocol involved an initial one-day escalation phase (0.1 mg increased to 6 mg), a build-up phase (the highest tolerated dose on the initial day was increased by 50–100% until 75 mg, and then by 25–33% until 4 g was reached, every 2 weeks for 44 weeks), and a maintenance phase (4 g daily for 1 month), followed by an OFC at the completion of OIT. Sixteen of 19 participants in the peanut OIT group completed the one year OIT protocol and underwent peanut challenge with the maximum cumulative dose of 5 g (approximately 20 peanuts) without reaction, whereas placebo subjects ingested a median cumulative dose of 280 mg ( $P < 0.001$ ). The peanut OIT group showed reductions in SPT wheal size ( $P < 0.001$ ), IL-5 ( $P = 0.01$ ) and IL-13 ( $P = 0.02$ ) by peanut-induced PBMC, and increased peanut-specific IgG4 ( $P < 0.001$ ), but no changes in peanut-specific IgE as compared to the placebo group. Additionally, the ratio of FoxP3hi:FoxP3intermediate Treg cells increased at the time of OFC in peanut OIT subjects [31]. Follow-up of this study will determine the ability of OIT to induce long-term clinical tolerance after discontinuing OIT.

Taken together, these findings suggest that OIT can consistently induce desensitization, allowing patients to tolerate significantly larger amounts of food than before treatment,

and is also able to modulate allergen-specific immune responses in the direction of tolerance induction.

#### INDUCTION OF TOLERANCE WITH OIT

Although the above studies confirm the ability of OIT to induce desensitization, it remains uncertain whether current OIT protocols are effective in inducing long-term tolerance, since few studies included a formal evaluation for tolerance by performing food challenges after immunotherapy was discontinued for at least 2–4 weeks or more [35].

In a pilot study of egg OIT involving seven children with egg allergy, Buchanan and team [24] used a modified rush phase (doubling of hen's egg protein every 30 minutes until the highest tolerated dose was achieved) followed by daily maintenance therapy (300 mg) for 24 months. At the end of the treatment, a DBPCFC was performed to assess for desensitization, and a second OFC was performed 3 months after stopping OIT for tolerance assessment. All patients completed the treatment protocol, with one child experiencing hypotension during the rush induction phase and all subjects tolerating daily home maintenance doses. All patients passed the first oral egg challenge (8 g egg protein) at 24 months without reaction – indicating

successful desensitization, and 2 of 7 children (28%) tolerated the second challenge – suggesting possible development of permanent tolerance. Egg OIT was associated with increased egg-specific IgG, but egg-specific IgE was unchanged. Blumchen et al. [23]

#### **With OIT there is reduced risk of allergic reaction following exposure to small or hidden quantities of allergen in food, but patients continuing on maintenance doses of OIT can experience adverse reactions (in some cases anaphylaxis)**

conducted an open peanut OIT study (maintenance dose 125–500 mg, maintenance phase 2–22 months) in 23 children (aged 3–14 years) with severe challenge-confirmed IgE-mediated peanut allergy (the median peanut-specific IgE level was 95.6 kU/L, 65% had asthma, and > 80% had history of allergic reaction after accidental peanut ingestion). A DBPCFC performed 2 weeks after discontinuation of OIT revealed acquisition of tolerance in 4 of 23 subjects (17%). This study highlighted the safety of a long-term build-up protocol for children at high risk of peanut-induced anaphylaxis [23]. However, as there was no control group included in the two studies it is possible that those children had experienced spontaneous allergy resolution rather than OIT-induced tolerance.

In the only randomized controlled trial to date that included a control group and evaluated tolerance induction as a study outcome, Staden et al. [13] randomized 45 children with cow's milk allergy or hen's egg allergy confirmed by food challenge to either receive OIT or remain on an elimination diet: 25 children received OIT (14 to cow's milk, 11 to egg) with maintenance doses of 250 ml milk and half an egg, and 20 children were allocated to elimination diets (10 milk, 10 egg). A DBPCFC performed 2 months after OIT was discontinued

RDBPCT = randomized double-blind placebo-controlled trial  
PBMC = peripheral blood mononuclear cells

revealed acquisition of long-term tolerance in 36% of children in the OIT group (9/25) and 35% in the control group (7/20), suggesting that OIT may not modify the natural course of tolerance development. Interestingly, allergen-specific IgE levels decreased significantly in children who achieved OIT-induced tolerance and/or desensitization as well as those who naturally acquired tolerance [13].

A meta-analysis of specific oral tolerance induction in food-allergic children by Fisher and colleagues [36] included three randomized controlled trials [13,19,21] in their analysis, and concluded that SOTI can not yet be recommended in routine practice for the treatment of children with IgE-mediated food allergy, and that larger, higher quality randomized controlled trials assessing long-term efficacy and safety of SOTI are needed. Unfortunately, the meta-analysis does not clearly distinguish desensitization vs. tolerance as an outcome since two of the studies [19,21] did not perform a formal evaluation for tolerance by means of food challenges after discontinuing immunotherapy.

### OIT WITH HEAT-DENATURED PROTEINS

OIT with heat-denatured proteins offers a new therapeutic direction in this field. It has been shown that children with transient milk and egg allergy possess IgE antibodies directed against conformational epitopes that are disrupted by extensive heating or food processing, whereas the presence of IgE antibodies that bind sequential epitopes is a marker for persistent milk and egg allergy [37,38]. Recently, it was reported that a subgroup of children (75%) with cow's milk allergy who could tolerate baked milk products (e.g., muffins and waffles) but not fresh cow's milk demonstrated a reduction in milk SPT size and increase in milk-specific IgG4 with regular consumption of heated milk [39], suggesting that OIT with heated milk may hasten the development of tolerance in this subgroup of children. In selecting subjects for baked milk OIT, it will be important to first evaluate the ability to tolerate baked milk products by carefully supervised food challenges, since 35% of baked milk-reactive children needed epinephrine for anaphylactic reaction during the challenge with baked milk products [39]. Studies suggest that children who are able to tolerate baked milk foods have different milk-specific immune responses compared to those who cannot tolerate such foods. Children who were able to take heated milk had significantly lower basophil reactivity following stimulation with milk protein as compared to children who reacted to extensively heated milk [40]. In addition, higher percentages of casein-specific Treg cells were evident in extensively heated milk-tolerant children compared with children who reacted to extensively heated milk [41]. Another study demonstrated similar results in hen's egg-allergic children who

completed a baked egg OIT protocol with tolerance acquisition: decreased SPT reactivity and increased egg-specific IgG4 after OFC [42]. However, these two studies did not include a control group, so it remains uncertain whether the changes observed for the tolerant group related to the baked milk/egg intervention or simply reflected the natural resolution of food allergy.

The long-term effect of incorporating baked milk products into a patient's diet was evaluated recently by Kim et al. [43], who reported the outcomes of children from the Nowak-Wegrzyn study [39]. Eighty-eight children evaluated for tolerance to baked milk (muffin) underwent sequential food challenges to baked cheese (pizza) over a median of 37 months (range 8–75 months) followed by unheated milk challenge. In the initial baked milk challenges, 65 children passed (baked milk-tolerant) and 23 failed (baked milk-reactive). A comparison group consisting of 60 subjects who met the inclusion criteria but were not initially challenged to baked milk products were included in the study. Among the baked milk-tolerant group, 60% (39/65) tolerated unheated milk, 28% (18/65) tolerated baked milk/baked cheese, and 12% (8/65) chose to avoid milk completely. Among the baked milk-reactive group, 9% (2/23) tolerated unheated milk, 13% (3/23) tolerated baked milk/baked cheese, and the majority (78%) avoided milk strictly. Thirteen of 60 children (22%) in the comparison group tolerated unheated milk, 22% (13/60) tolerated milk/baked cheese, and 56% (34/60) continued to avoid all milk. Children who were baked milk-tolerant were 28 times more likely to become unheated milk-tolerant compared to the baked milk-reactive children ( $P < 0.001$ ). Children who incorporated baked milk products in their diet were 16 times more likely than the comparison group to develop tolerance to unheated milk ( $P < 0.001$ ). The levels of casein IgG4 were significantly increased in the baked milk-tolerant group, but milk-specific IgE levels were unchanged [43].

### SAFETY OF OIT

Safety considerations for OIT include the risks of inducing allergic reactions during the treatment protocol as well as during oral food challenges required to evaluate treatment outcomes. A large peanut OIT study discussed above [22] examined clinical reactions throughout all stages of the protocol and revealed that the frequency and severity of reactions were greatest on the initial rush induction day, and least during the home dosing phases: 93% of subjects experienced some symptoms during the initial rush induction, mostly upper respiratory (79%) and abdominal (68%) symptoms, although 4 withdrew because of persistent adverse reactions. During the subsequent build-up phase, adverse reactions occurred after 46% of the build-up doses, with 29% experiencing upper respiratory tract symptoms and 24% skin symptoms. The risk of an adverse reaction with any home dose

SOTI = specific oral tolerance induction

was 3.5%, and treatment was required for only 0.7% doses, including epinephrine injections in two participants [44]. Risk factors for developing reactions to a previously tolerated OIT dose are reported to be concurrent illness (especially fever), suboptimally controlled asthma, timing of dose administration after food ingestion, physical exertion after dosing, and dosing during menses [20,45]. Studies of egg and milk OIT also identified several “augmentation factors” – such as infection, exercise, pollen allergy, and irregular intake of OIT – that can predispose subjects to allergic reactions [13].

Cumulative findings from published OIT studies show that adverse reactions during OIT treatment are common, with the majority being mild allergic reactions involving the skin, perioral region, and gastrointestinal system, which respond to conventional treatments such as antihistamines [13,19,27]. More severe reactions involving the lower airways and/or cardiovascular system requiring treatment with bronchodilator and/or epinephrine (anaphylaxis reactions) were reported less commonly [13,19,20,22,31,45], while no epinephrine was needed for the treatment of adverse reactions in two OIT studies [12,23]. Even highly allergic subjects at increased risk of anaphylaxis appear to be able to complete the OIT protocol without severe adverse effects in most cases, and the incidence of severe reactions among these subjects is similar to that reported in other OIT studies that did not specifically enrol high risk subjects [21,23,29,30].

## SUMMARY

Various OIT protocols have been reported, and most include an initial rush/ultra-rush phase followed by up dosing and maintenance phases. Allergic reactions during treatment are common, and therefore OIT should be performed in specialist allergy centers under close medical supervision, ideally as part of ongoing research. Nevertheless, OIT appears to be safe in children and adults with a range of food allergies, including children with severe allergy who are at high risk for anaphylaxis. OIT has been shown to consistently induce desensitization, but the ability for OIT to induce long-term tolerance appears limited. It is controversial whether desensitization in the absence of long-term tolerance provides significant benefit to patients with food allergy. On the one hand, there is reduced risk of allergic reaction following exposure to small or hidden quantities of allergen in foods, which may lessen anxiety for the patient and their family. On the other hand, the safety of maintaining desensitization, particularly in the setting of peanut allergy, is of some concern given that patients continuing on a steady maintenance dose of oral immunotherapy have commonly been reported to experience adverse reactions (in some cases anaphylaxis). While some risk factors for reactions to a steady maintenance dose have been identified (e.g., intercurrent illness, menses,

exercise), the emergence of such reactions may not be reliably predicted and therefore represent a defined risk to subjects continuing on a daily desensitization program. Before such treatment can be implemented into routine clinical practice, further studies are needed to identify novel approaches that enhance the tolerogenic potential of OIT, to confirm the safety and feasibility of OIT, and to clarify whether selected populations are more likely to benefit from OIT or whether they are at greater risk of adverse reactions during OIT.

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