# Oral Immunotherapy for Food Allergy

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Current management of food allergy involves strict avoidance, education on recognizing and managing allergic reactions, and carrying an adrenaline autoinjector. This approach is burdensome and associated with reduced quality of life. Patients with food allergy would benefit greatly from a treatment that could achieve desensitization or long-term tolerance. Recent studies have shown that oral immunotherapy (OIT) can induce desensitization and modulate allergen-specific immune responses; however, it remains uncertain whether OIT can induce long-term tolerance. Nevertheless, successful desensitization provides a major advance in management by reducing the risk of reaction to low amounts of allergen. Allergic reactions during OIT are common, although severe reactions are less common. Therefore, OIT should be performed in specialist centers under close medical supervision and would ideally be conducted as part of ongoing research studies. OIT holds promise as a novel approach to managing food allergy.

## Introduction

Rates of allergic disease have risen exponentially in the past three decades. Although 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]. In the United Kingdom, hospital admissions for food allergy and anaphylaxis increased 500% and 700%, respectively, between 1991 and 2005 [1••]. Similar trends have been reported in Australia for anaphylaxis admissions between 1993–1994 and 2004–2005, with food anaphylaxis in children 0 to 4 years old accounting for most of this rise [3••]. In particular, the prevalence of peanut allergy increased approximately threefold over a 5-year period in the United Kingdom (1989 to 1994–1996) and the United States (1997–2002) [4,5]. Food allergy is now estimated to affect 3% to 6% of children and 2% of adults [6•,7], and the cumulative incidence of peanut allergy was estimated to be 1.8% by the age of 4 to 5 years for children born in the United Kingdom in 1999 and 2000 [8•].

Allergic reactions to foods can range in severity from mild to severe; however, foods are the most common triggers of anaphylaxis [9] and the second most common cause of death from anaphylaxis [10••]. Among the common food allergens, peanuts and tree nuts are especially significant in that allergies to these foods generally persist into adulthood, reactions are often severe, and allergy to these foods is a strong risk factor for death from food anaphylaxis. Whereas most cases of allergy to milk and egg resolve by later childhood, allergies to peanut, tree nut, fish, and shellfish usually persist. Only 18% [11] to 21% [12] of children outgrow their peanut allergy (spontaneous development of tolerance), and there are no reliable predictors for resolution [5,13]. Peanut allergy is the most common cause of food anaphylaxis [14], and 42% of reactions to peanut involve respiratory symptoms [15]. Accidental ingestion of peanut in children with peanut allergy is also common (50% within 1 year, 75% within 5 years) [13], and most reactions from accidental peanut ingestion are severe [16]. Furthermore, nuts (peanut or tree nuts) were reported to cause 81% and 38% of deaths from food-induced anaphylaxis in recent US and UK series, respectively [10••,17••]. Therefore, children who fail to outgrow their food allergy often have peanut or tree nut allergy and are at greatest risk for severe allergic reactions and fatal anaphylaxis. Consistent with this, adolescents with peanut or tree nut allergy are overrepresented among food-induced anaphylaxis fatalities, with the incidence of fatal anaphylaxis among 15- to 24-year-olds with nut allergy in the United Kingdom estimated to be 10 times higher than the overall population rate of fatal anaphylaxis (2.3 cases per 100,000 population vs 1–3 cases per 1 million population) [18••]. A treatment that could modify the natural history of food allergy by inducing long-term tolerance (ability to tolerate any quantity of allergen in the absence of ongoing regular administration) would be of

great benefit to individuals who fail to outgrow their food allergy in childhood.

## Current Management of Food Allergy

There is currently no effective long-term treatment for food allergy. Management involves avoiding the food in question, recognizing symptoms of an allergic reaction early, and initiating appropriate emergency treatment of allergic reactions (particularly anaphylaxis) [18••]. This approach is fraught with difficulties, and the burden of living with food allergy and its management is significant. For example, children with peanut allergy are reported by their parents to have a poorer quality of life than children with rheumatologic conditions [19].

Avoiding food allergens is difficult, particularly with commercially prepared foods. Accidental exposures to food allergens occur in 58% of patients within 5 years and 75% within 10 years [16]. Furthermore, in reports of fatal food-induced anaphylaxis, most patients knew that they were allergic to the food in question but were not aware that the allergen was present within the food ingested, and approximately 40% of deaths involved ingestion of foods catered or prepared outside the home [10••,17••].

Adrenaline is the first-line therapy for anaphylaxis. Several available self-injectable devices can be administered if accidental exposure to a food allergen results in a severe reaction (anaphylaxis). However, the provision of such devices is only the first step toward optimizing management of anaphylaxis. The use of an EpiPen epinephrine autoinjector (DEY, Napa, CA) is not intuitive and requires specific training [20]. Most patients who were prescribed an EpiPen failed to use it at the time of a severe allergic reaction. In one study, only 71% of patients prescribed an EpiPen had it with them, 10% of these had expired, and only 32% could demonstrate its correct use [21]. Inadequate education and failure to use an adrenaline autoinjector even when prescribed were prominent among cases of fatal anaphylaxis, with 10 of 19 fatalities involving failure to carry or use the device correctly [10••]. Patients with anaphylaxis generally are reluctant to seek medical attention, and physicians seem similarly reluctant to administer adrenaline for severe symptoms. In a survey of Food Allergy & Anaphylaxis Network conference participants, only 35% of patients with severe symptoms sought medical attention, and only 6% received prehospital adrenaline [22]. Even for repeat severe episodes, although 73% of patients sought medical attention, only 33% received prehospital adrenaline [22]. Adrenaline may not always be sufficient to prevent death, as early and repeated administration of adrenaline failed to prevent death in 12% to 14% of anaphylaxis fatalities [10••,17••].

The many limitations of current management of food allergy highlight the need for treatment options that can induce long-term tolerance.

## Failure of Oral Tolerance as a Cause of Food Allergy

The mechanisms leading to the development of food allergy remain poorly understood. Food allergy is considered to be caused by a failure or loss of oral tolerance [23••]. Oral tolerance can be induced by a single high-dose exposure or by repeated low-dose exposures to antigen. High-dose tolerance involves Fas-mediated apoptosis or anergy, whereas low-dose tolerance is mediated by T regulatory cells (Tregs). Recent studies suggest that anergy and induction of Tregs may not be distinct mechanisms for tolerance, and most studies now focus on the role of Tregs [24••]. Several Treg subsets have been identified, including T-helper type 3 (Th3) cells, Tr1 cells, and $CD4^+CD25^+$ Tregs. Th3 cells produce transforming growth factor-β (TGF-β) and variable amounts of interleukin (IL)-4 and IL-10 [25]. Tr1 cells secrete IL-10 [26]. $CD4^+CD25^+$ Tregs express the transcription factor forkhead box P3 and mediate their suppressive effects in part by cell surface–bound TGF-β and, to a lesser extent, IL-10 [27]. $CD4^+CD25^+$ Tregs arise predominantly in the thymus but also may develop in mesenteric lymph nodes, Peyer's patches, and peripheral lymph nodes, where they play a role in mucosal tolerance [27].

Tregs TGF-β and IL-10 have been shown to play important roles in oral tolerance induction and food allergy. In a murine model of food allergy, mice tolerized to β-lactoglobulin had higher numbers of antigen-specific IgA-secreting cells in Peyer's patches and higher levels of fecal IgA, as well as increased TGF-β and IL-10 production by Peyer's patch T cells, compared with sensitized mice [28]. Children with food allergy have fewer $TGF\text{-}\beta^+$ lymphocytes in the duodenal epithelium and lamina propria [29] and show reduced TGF-β expression by milk-specific duodenal lymphocytes [30]. Similar findings have been reported for patients with non–IgE-mediated food allergies (food protein–induced enterocolitis) [31]. In patients with cow's milk allergy, resolution of allergy was associated with increased numbers of $CD4^+CD25^+$ T cells and reduced β-lactoglobulin–induced proliferation compared with those with ongoing allergy [32]. In vitro depletion of these $CD4^+CD25^+$ cells led to increased β-lactoglobulin–induced proliferation, suggesting that oral tolerance induction was related to increased $CD4^+CD25^+$ cells [32]. Oral tolerance is also associated with Th1-skewed responses, whereas food allergy is associated with Th2-skewed responses [33]. Comparison of peanut-specific immune responses in normal children, children with peanut allergy, and peanut-allergic children who had outgrown their allergy showed Th2-skewed responses in children with peanut allergy and Th1-skewed responses in oral tolerance (healthy children without food allergy and children who outgrew their peanut allergy) [33]. These findings suggest that food allergy is associated with failure or loss of tolerance, reduced Tregs and TGF-β, and reduced Th1 and increased Th2 responses.

## Allergen Immunotherapy as a Treatment for Allergic Disease

Immunotherapy is used for long-term treatment of asthma, allergic rhinitis, and insect venom anaphylaxis. Subcutaneous immunotherapy (SCIT) has been shown to reduce clinical symptoms and induce prolonged tolerance to allergens by modulating immune responses [34,35].

Mechanistic studies have shown that SCIT induces Tregs and restores the disturbed balance of Th1/Th2 effector cells in allergic patients. SCIT leads to reduced allergen-specific IgE, elevated allergen-specific IgG4, reduced Th2 cytokine expression (IL-4, IL-5), and in most studies increased Th1 cytokine expression (interferon-γ) [34,35]. These effects have been shown to be mediated by increased numbers of $CD4^+CD25^+$ Tregs and induction of antigen-specific $CD4^+CD25^+$ Tregs with suppressive activity that is mediated by production of IL-10 and/or TGF-β. Other immunologic effects of SCIT include increased apoptosis of allergen-specific Th2 cells, reduced tissue mast cell numbers, and reduced serum levels of tumor necrosis factor-α and IL-1β [34]. Sublingual immunotherapy (SLIT) has also been shown to be effective in reducing clinical symptoms in respiratory allergy (asthma, rhinitis); however, immunologic effects are less well characterized. Increased specific IgG4 and reduced specific IgE have been reported in some studies [34]. Oral immunotherapy (OIT) has not been consistently effective when used to treat respiratory allergy and was largely abandoned for treating these conditions. More recently, however, studies have suggested an exciting potential for OIT as a treatment for food allergy, and renewed interest exists in the application of OIT in this setting.

## Allergen Immunotherapy for Food Allergy

### Subcutaneous immunotherapy

Various allergen immunotherapy approaches have been attempted for treating food allergy. SCIT for peanut anaphylaxis was first attempted more than a decade ago and was effective in inducing desensitization (ability to tolerate an allergen with continued regular administration), increasing the threshold dose required to induce a reaction from 178 mg to 2805 mg (from half a peanut to 9 peanuts) in patients who could continue on maintenance therapy [36]. However, serious systemic reactions were frequent (39% during maintenance), so this approach was abandoned. Peptide and mutated protein SCIT are being investigated to avoid systemic reactions. However, translation to the clinical setting has been slow.

### Oral immunotherapy

Studies of OIT to treat food allergy have yielded promising results. OIT has been reported to consistently induce desensitization and in most studies to modulate allergen-specific immune responses; however, long-term tolerance is achieved only occasionally. Case reports describe desensitization with OIT in milk allergy [37,38]. A 12-year-old girl was desensitized to cow's milk and remained on OIT indefinitely [37]. A 6-year-old girl with cow's milk allergy was desensitized to milk after 4 months of milk OIT and experienced dramatic immunologic changes, including complete loss of skin prick test reaction to cow's milk, reduced serum levels of milk-specific IgE, increased serum levels of milk-specific IgG4 and IgA, and increased interferon-γ and decreased IL-4 production in β-lactoglobulin–stimulated peripheral blood mononuclear cell cultures [38].

In a recent case series, 39 children with confirmed IgE-mediated cow's milk allergy underwent cow's milk OIT, with doses increasing to 200 mL over 9 weeks, followed by daily intake of the maximum achieved dose thereafter [39]. Preliminary findings showed that after a median of 12 weeks, 36 children were successfully desensitized and could drink milk normally. Six months later, 33 patients demonstrated good tolerance. During OIT, 76.3% of patients suffered allergic reactions, although only two children discontinued treatment due to severe adverse reactions. Serum cow's milk–specific IgE decreased at OIT completion and 6 months after OIT [39]. A large case-control study of OIT in 51 patients 3 to 55 years old with various food allergies showed successful desensitization in 83% (45 of 54) of patients who remained on daily OIT [40]. Reduced peanut-specific IgE and increased peanut-specific IgG4 were demonstrated [40]. A double-blind, randomized, controlled trial of milk OIT (200-mL maintenance dose) for 6 months in 21 children with milk allergy reported successful desensitization to milk in 71% (15 of 21 tolerated 200 mL of milk on a daily basis) and partial desensitization in 14% (3 of 21 tolerated 40–80 mL of milk); however, none of the children demonstrated reduced milk-specific IgE [41]. In a pilot study of peanut OIT, 13 children with peanut allergy completed OIT at a daily maintenance dose of 300-mg peanut protein and underwent open food challenge to peanut after 4 months of maintenance dosing [42]. Preliminary findings showed that all patients tolerated the maximum dose of peanut flour (7.8 g): eight patients had no symptoms, and five experienced mild symptoms, with four requiring treatment with diphenhydramine. Most patients experienced mild allergic symptoms during treatment, and two experienced significant systemic allergic symptoms on day 1 of the OIT protocol. Peanut-specific IgE increased at 3 and 6 months but declined thereafter, whereas peanut-specific IgG and IgG4 increased significantly at 3 months and at 6 to 8 months [42]. Although many of these previous studies have demonstrated modulation of allergen-specific immune responses, suggesting the possibility of tolerance induction, it is uncertain whether OIT was effective in inducing long-term tolerance, as

food challenges were not performed after immunotherapy was discontinued. Indeed, Rolinck-Werninghaus et al. [43] described two patients in whom discontinuation of milk or egg OIT after 37 weeks and 41 weeks of OIT, respectively, resulted in loss of desensitization, indicating that tolerance had not been achieved. These patients were successfully desensitized again with recommencement of OIT [43].

Formal assessment of long-term tolerance was undertaken in two studies of OIT [44•,45••]. In a study of egg OIT in seven children with egg allergy, a modified rush phase was followed by maintenance OIT (300-mg daily dose) for 2 years. A double-blind, placebo-controlled egg challenge was performed at 2 years, and if this was passed, a second challenge was performed after patients had been off egg OIT and on an egg elimination diet for 3 to 4 months. All patients completed the treatment protocol. One child experienced hypotension during the rush induction phase, but none experienced lower respiratory symptoms. No patients experienced symptoms with home maintenance dosing. All patients completed an oral egg challenge (8 g of egg protein) at 24 months without reaction, indicating successful desensitization. A total of 29% (two of seven) of patients tolerated the second oral egg challenge after 3 to 4 months off OIT, indicating development of tolerance. However, there was no placebo group, so it is possible that these two children experienced spontaneous resolution of their egg allergy (expected in 50% over 3 years) rather than this representing OIT-induced tolerance. Consistent with this, OIT was associated with increased egg-specific IgG; however, egg-specific IgE was unchanged.

A randomized, controlled study of cow's milk and egg OIT also included a double-blind, placebo-controlled food challenge (DBPCFC) after a period of food elimination to assess for the development of long-term tolerance [45••]. Forty-five children with cow's milk or egg allergy as confirmed by food challenge were randomized to receive OIT or to remain on an elimination diet. A DBPCFC was performed at 15 to 59 months (median, 21 months), and children in the OIT group were placed on an elimination diet for 2 months before the food challenge. Twenty-five children received OIT (14 to cow's milk, 11 to egg) with maintenance doses of 200 mL of cow's milk (or 150 mL + deliberate intake) and one half of a hen's egg (or one quarter of a hen's egg + deliberate intake). Twenty children were allocated to elimination diets (10 cow's milk, 10 hen's egg). In the OIT group, 9 of 25 (36%) achieved long-term tolerance (tolerated food challenge after 2 months of elimination), 3 of 25 (12%) were desensitized (failed food challenge after a period of elimination but could tolerate the maximum dose with regular daily intake), 4 of 25 (16%) achieved partial desensitization (could tolerate reduced amounts of the food while on regular daily intake), and 9 of 25 (36%) were nonresponders (could not reach maintenance dosing). In the control group, a similar proportion (7 of 20 [35%]) of individuals acquired tolerance (tolerated food challenge). All those receiving OIT experienced allergic reactions during treatment, with most (21 of 25) being mild, and 4 experienced moderate reactions involving airway symptoms. Six of 20 children in the control group experienced allergic reactions after accidental exposure to foods: 5 were mild reactions, whereas 1 child developed severe anaphylaxis with cardiovascular involvement. Allergen-specific IgE levels were reduced in children who outgrew their allergy spontaneously (tolerant control) and in children who achieved tolerance and/or desensitization during OIT, although it was not stated whether levels were lower in the children with OIT-induced tolerance compared with the children with OIT-induced desensitization.

The findings from these two studies suggest that OIT can induce desensitization, allowing patients to tolerate significantly larger amounts of a food than they could tolerate before treatment, and can modulate immune responses to allergen. This is a significant outcome, as it reduces the risk of severe allergic reaction to accidental exposure, thereby improving quality of life for patients and their families. However, OIT's ability to induce long-term tolerance is not certain and would seem limited in the setting of current protocols. Longer duration of treatment, use of higher maintenance doses, or addition of adjuvant agents may enhance standard OIT's ability to induce tolerance.

OIT appears to be safe even in highly allergic children with a history of anaphylaxis, although response rates may be reduced [46•]. Sixty children 5 to 17 years old who were highly allergic to cow's milk, with milk-specific IgE levels greater than 85 kU/L, a history of at least one severe allergic reaction (anaphylaxis) after accidental exposure to milk or dairy products that required emergency treatment, and who developed symptoms during a DBPCFC performed at study entry to less than 0.8 mL of whole milk, were randomized to receive cow's milk OIT or to remain on a milk-free diet for 12 months [46•]. In the OIT group, 11 of 30 (36%) could tolerate the maximum dose (150 mL) and consume milk products freely in their diet, whereas 16 of 30 (54%) achieved partial desensitization (could tolerate 5–150 mL of cow's milk), and 3 of 30 (10%) failed to complete the OIT course due to severe symptoms. Cow's milk OIT was associated with significantly reduced cow's milk–specific IgE at 6 and 12 months in 50% of patients (15 of 30). All patients who received OIT experienced allergic reactions during treatment, with 4 requiring intramuscular adrenaline and 18 requiring nebulized adrenaline. Most reactions involved cutaneous and/or abdominal symptoms. There were no severe reactions involving marked dyspnea and/or hypotension. Among the control group, 20% experienced mild

allergic reactions after accidental exposure to cow's milk products. These response rates are lower than those typically reported for OIT in unselected populations [39–41]. Nevertheless, it is encouraging that despite being highly allergic to cow's milk, most patients could remain on OIT and attain partial desensitization, thereby reducing their risk for severe reactions to low amounts of allergen. A similar pilot study of peanut OIT in patients at high risk for severe reactions to peanut is under way: six peanut-sensitized children with peanut-specific IgE greater than 85 kU/L and asthma who are at high risk for peanut-induced anaphylaxis have commenced peanut OIT [47]. Results are pending.

It is possible that selected subgroups of children with food allergy will be more amenable to immunomodulation and tolerance induction after OIT than others. It was recently reported that a subgroup of children with cow's milk allergy who could tolerate baked but not fresh cow's milk demonstrated progressive reduction in cow's milk skin prick test and an increase in cow's milk–specific IgG4 with regular ingestion of baked milk [48•]. This raises the possibility that in this subgroup of children, OIT with baked cow's milk may hasten the development of tolerance. Cow's milk–allergic children who tolerate baked milk are considered to have a less severe phenotype than those who do not, as they presumably have antibodies directed to conformational rather than sequential allergenic epitopes, have lower milk-specific IgE and smaller milk skin prick test, and are more likely to outgrow their milk allergy. OIT in this group of cow's milk–allergic children therefore may be more likely to promote tolerance. This study is ongoing and will formally assess for development of tolerance and further investigate immunologic effects. Although there is no randomized placebo group, findings will be compared with a parallel group of children whose families refused to participate in the study. The outcomes from this study are awaited with interest, as they will help to clarify whether specific patient population characteristics will assist in selecting candidates who are more likely to benefit from OIT.

**Sublingual immunotherapy**

There have been fewer reports of SLIT for treatment of food allergy. Nevertheless, results are encouraging. A double-blind, placebo-controlled study of SLIT with hazelnut extract for 4 months in 41 adults with hazelnut allergy resulted in an increased threshold for reaction in the active treatment group (from 2.29 to 11.56 g) but not in the placebo group (from 3.49 to 4.14 g) [49]. Fifty percent of the treatment group—compared with 9% of the placebo group—could tolerate 20 g of hazelnut during an oral challenge performed 8 to 12 weeks after immunotherapy had been discontinued, indicating long-lasting tolerance. As further evidence of immune tolerance, the active treatment group demonstrated increased serum levels of IL-10 and hazelnut-specific IgG. However, when interpreting these findings, it should be noted that 1) more than 50% of study participants had oral allergy syndrome (OAS) rather than typical food allergy, and OAS may be more amenable to SLIT, as SLIT is known to be effective for treating pollen allergy; and 2) four of the six patients who developed tolerance had OAS rather than typical food allergy, whereas only two (18%) in the active group with typical food allergy achieved tolerance with SLIT [49]. SLIT with fresh kiwi pulp in a 29-year-old woman also resulted in prolonged clinical tolerance to kiwi, with protective effects from SLIT even after it had been discontinued for 4 months [50]. These findings support the potential for SLIT as a treatment for food allergy, with demonstration of immunomodulatory effects and prolonged clinical protection in limited studies. An important consideration when administering SLIT in children is the need to hold the extract under the tongue for 1 to 3 minutes before swallowing or discharging [49,50]. Products such as slow-dissolving tablets are being developed to assist with retention of extracts under the tongue.

## Conclusions

Allergen-specific OIT has been shown to consistently induce desensitization; however, OIT's ability to induce long-term tolerance appears limited. Desensitization in the absence of long-term tolerance nevertheless provides significant benefit to patients with food allergy, as there is a reduced risk of reactions after exposure to small or hidden quantities of allergen in foods. OIT may be more effective in selected populations. Various OIT protocols have been reported, most including an initial rush/ultra rush phase, followed by updosing and maintenance phases. Allergic reactions during treatment are common. Thus, 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. Further studies to confirm the safety and feasibility of OIT and to clarify whether selected populations are more likely to benefit from OIT or may be at greater risk for adverse reactions during OIT are required before such treatment can be implemented into routine clinical practice. SLIT may provide an approach to long-term tolerance induction; however, further studies are required to confirm clinical effects.

## Disclosure

Dr. Tang serves on the medical advisory board for the Nestlé Nutrition Institute.

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