

Oral immunotherapy for food allergy

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Purpose of review

Food allergy is a difficult clinical problem for which no disease-modifying therapy currently exists.

Recent findings

The daily administration of graded allergen doses through oral immunotherapy (OIT) is one promising experimental approach to the development of a clinically available treatment. Although the concept of oral immunologic tolerance is not new, OIT as a treatment for food allergy is innovative. Over the last few years, several groups of investigators have begun to demonstrate safety and varying degrees of efficacy and immune modulation in uncontrolled pilot studies of OIT. Rigorously designed trials are currently underway and important unanswered questions remain.

Summary

OIT for food allergy holds promise for patients with food allergy but additional research is necessary before this approach is ready for clinical use.

Keywords

desensitization, food allergy, oral immunotherapy, tolerance

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Introduction

Food allergy is a common, serious, and growing problem in developed countries. Patients with IgE-mediated food allergy rapidly experience harmful adverse symptoms as a consequence of pathological immune responses to ingested food antigens. Although a recent meta-analysis identified variation in prevalence rates [1[•]], recent survey data from the Centers for Disease Control and Prevention indicate that the current prevalence of food allergy in US children is approximately 4%, an increase of almost 20% in the last decade [2^{••}]. Although there is slight variation in the magnitude of the effect, similar increases in food allergy prevalence have also been observed in several methodologically rigorous birth cohort studies around the world, including in geographically isolated populations [3]. The use of well defined outcome measures with precise sampling techniques suggests that rising prevalence is not simply due to increased recognition of the disorder. This is further supported by the continued increase in the prevalence of other allergic conditions such as asthma, allergic rhinitis, and atopic dermatitis [4].

No treatment currently exists to modify the natural history of the disease. Although patients with allergy to milk and egg are generally expected to eventually outgrow their condition, it may take much longer than previously recognized [5,6]. Allergy to peanut, tree nuts, and/or shellfish is not usually outgrown. All affected

patients must maintain a strict allergen-free diet and carry emergency medications to treat symptoms following accidental exposure. However, despite strict dietary adherence, these accidental allergic reactions occur frequently, typically due to occult exposure during processing or preparation. Although increased awareness has enhanced public understanding and resulted in improved food labeling, food allergy continues to be the leading cause of anaphylaxis among children seen in US emergency departments. Deaths are rare but do occur, especially among patients with allergy to peanut and tree nuts, and the persistent fear of accidental exposures and life-threatening reactions significantly disrupts social and educational activities [7[•]]. This profoundly impairs health-related quality of life, to an extent greater than that seen in chronic conditions such as diabetes mellitus [8]. Taken together, these observations indicate a great clinical need for an active treatment for food allergy. Although investigators are now actively developing different therapeutic approaches to this problem, this review will focus on oral immunotherapy (OIT). An increasing body of evidence suggests that OIT may yield promise as an interventional therapy for food allergy. Here we review the evolution and strength of some of this evidence from clinical and translational studies.

It is important to understand OIT-associated nomenclature when reviewing the primary outcomes of the clinical trials which follow. The oral administration of allergen is referred to in various publications as OIT and specific oral

tolerance induction (SOTI); for the purposes of this review, we will exclusively use the term OIT. 'Tolerance,' when discussed in the context of a suppressed immune response to oral antigen, refers to a specific set of critical immunologic mechanisms primarily directed by T-lymphocytes. The details of such pathways are beyond the scope of this paper but were recently summarized in an excellent review [9^{••}]. Tolerance may also refer to the clinical condition whereby an intervention persistently alters reactivity to an antigen, allowing discontinuation of therapy. In contrast, 'desensitization' is another clinical term which refers to a transient alteration in reactivity which returns upon discontinuation.

Early clinical studies

The idea of an allergen-specific immunotherapy for food allergy is not new. Freeman [10], who along with Noon pioneered subcutaneous immunotherapy for allergic rhinitis, described his successful experience in 1930 treating a boy with anaphylaxis to fish. The child was first treated with injections of an extract of fish protein followed by daily oral administration of fish oil, and subsequently was able to tolerate fish without symptoms. Clinical descriptions of successful cases of oral food desensitization began to appear in the literature, but were not widely accepted by a scientific audience because most did not incorporate rigorous methods.

In 1992, a placebo-controlled clinical trial of subcutaneous immunotherapy for peanut allergy was attempted at a major US medical center [11]. Although the approach was effective in changing reactivity to peanut in treated patients, adverse reactions were frequent and included severe anaphylaxis. An unblinded trial followed in 1997, which again showed some improvement in patients able to tolerate the injections, but the frequency and significance of side-effects led to abandonment of the subcutaneous approach and exploration of alternative strategies [12].

Pilot scientific trials with mechanistic data

The intestine contains a vast network of mucosal associated lymphoid tissue (MALT), which has long been understood to not simply ignore but rather actively suppress pathologic immunity to foreign proteins such as commensal microbes and food proteins. This persistent suppression of potentially adverse immune responses is referred to as oral tolerance and involves multiple regulatory pathways within the MALT. Functional redundancy ensures the robustness of oral tolerance, and failures of this system are thought to contribute to food allergy, celiac disease, and inflammatory bowel disease. Because of the intrinsic toleragenic potential of the MALT, investigators began to develop scientific

approaches towards treating food allergy through the graded oral application of food allergens.

Egg and milk

Initial OIT investigations focused on egg and milk allergy rather than nut allergy, presumably for safety reasons (Table 1). In one of the first controlled studies of OIT, Patriarca *et al.* [13] showed safety and proof-of-concept, documenting gradual clinical and immunologic changes in most treated patients but not controls. Meglio *et al.* [14] achieved similar success with milk desensitization and noted that the clinical response was inversely correlated with baseline milk-specific IgE levels. However, Longo *et al.* [15] showed that milk OIT was effective in a severely affected cohort with grade 4/5 anaphylaxis (laryngeal edema and/or hypotension) and very high IgE levels. In a randomized trial, Staden *et al.* [16] assessed the persistence of any treatment effect (i.e., clinical tolerance) by performing oral food challenges (OFC) after stopping OIT. Interestingly, the rate of permanent tolerance in the OIT group was the same as that of the control group, suggesting that treated patients had independently outgrown their allergy. However, one-third of the treated group also experienced clinical improvement which returned to baseline once treatment was stopped and was considered to be desensitized. Thus this study contrasted the transient nature of desensitization versus the permanence of tolerance, confirming a concept also demonstrated in an egg OIT study by Buchanan *et al.* [17]. Early clinical results from trials of OIT with baked milk and egg indicated that the majority of egg-allergic and milk-allergic patients can safely tolerate extensively heated foods (i.e., muffin) [18^{••},19,20]. Regular consumption of these thermally denatured allergens may act as a form of OIT, although this has not yet been formally proven. These studies have also provided important mechanistic insight into the development of tolerance, in particular the roles of regulatory T cells [21^{••}] and basophils [22[•]].

Peanut

Success in these proof-of-concept studies of egg and milk allergy prompted investigation into peanut OIT. Although isolated case reports of oral desensitization to peanut exist, Jones *et al.* [23^{••}] first reported a clinical trial of peanut OIT in which 39 peanut-allergic children (median age 57.5 months) were enrolled in an open-label study with three phases: an initial escalation day on a research unit, a build-up phase during which biweekly dose increases occurred on the research unit, and a maintenance phase. Desensitization was assessed with OFCs while on maintenance OIT. Ten patients withdrew from the study, six for personal/logistical reasons and four due to intolerable allergic side-effects. Whereas all patients reacted to 50 mg or less of peanut on the initial escalation day, after maintenance treatment all patients

Table 1 Interventional studies of food allergen immunotherapy

Year	Investigator	Allergen	N	Study design	Treatment results
2003	Patriarca <i>et al.</i> [13]	Milk Egg Fish Other	59	Open-label with observational controls	77% desensitized Decreased allergen-specific IgE Decreased skin test size Increased allergen-specific IgG4
2004	Meglio <i>et al.</i> [14]	Milk	21	Open label	71% desensitized Increased threshold dose
2007	Buchanan <i>et al.</i> [17]	Egg	7	Open label	57% desensitized 29% fully tolerant Increased egg-specific IgG No significant change in egg-specific IgE
2007	Staden <i>et al.</i> [16]	Milk Egg	45	Randomized, controlled	<i>Treatment group:</i> 36% fully tolerant 28% partially desensitized 36% failed treatment Increased threshold dose <i>Elimination diet group:</i> 35% fully tolerant 65% allergic Clinical improvement was associated with decreased allergen-specific IgE in both groups
2008	Longo <i>et al.</i> [15]	Milk	97	Randomized, controlled	<i>Treatment group:</i> 36% fully desensitized 54% partially desensitized 10% failed treatment Decreased milk-specific IgE in 50% of treated group <i>Elimination diet group:</i> No change in threshold or IgE
2008	Skipak <i>et al.</i> [24]	Milk	20	Double-blinded, placebo-controlled	<i>Treatment group:</i>
2009	Narisety <i>et al.</i> [18**]		15		21% initially fully desensitized; 46% with additional OIT ^a 74% partially desensitized 5% failed treatment Increased milk-specific IgG4 Decreased milk-specific IgE ^a Decreased skin test size ^a <i>Placebo group:</i> No change in threshold or antibody response
2009	Jones <i>et al.</i> [23**]	Peanut	39	Open label	81% fully desensitized 6% partially desensitized 13% failed treatment Decreased skin test size Decreased basophil activation Decreased peanut-specific IgE Increased peanut-specific IgG4 Increased peanut-specific serum inhibitory factor Increased FOXP3 ⁺ regulatory T cells Down-regulation of apoptosis genes
2009	Clark <i>et al.</i> [25*]	Peanut	4	Open label	75% fully desensitized 25% partially desensitized Increased threshold dose
2010	Blumchen <i>et al.</i> [26**]	Peanut	23	Open label	16% fully desensitized 58% partially desensitized 21% failed treatment Increased threshold dose Increased peanut-specific IgG4 Decreased skin test size Decreased T helper 2 cytokine response No change in peanut-specific IgE level

OIT, oral immunotherapy.

^aWith extended, higher-dose treatment during open-label extension.

were desensitized, with 27 of 29 (93%) ingesting all 3900 mg (approximately 16 peanuts) without symptoms during an OFC. Extensive immunologic changes were observed in this study, including: basophil hyporesponsiveness; a transient increase in peanut-specific regulat-

ory T cells; sustained decreases in peanut-specific skin tests and IgE and increases in peanut-specific IgG4; production of a serum inhibitory factor which blocks interaction of peanut allergen and IgE; and altered expression of apoptosis-associated genes. This study

represented a significant step forward because, in contrast to egg or milk allergy, peanut allergy persists in the vast majority of patients, and is commonly associated with severe reactions. In addition, extensive mechanistic analyses were performed and contributed several novel insights about the mechanism(s) of OIT.

Importantly, peanut OIT was shown to be well tolerated [27^{••}]. Allergic side-effects did occur, typically early in the protocol when doses were low and desensitization presumably had not occurred. These side-effects were generally mild, involved the skin and/or upper airway, and responded to conventional allergy treatment with antihistamines; however, as noted above, four of 39 (10%) of children withdrew from the study due to OIT-related allergic side-effects. Chest symptoms such as wheezing and cough occurred in children with a preexisting history of asthma and responded to bronchodilators. Systemic anaphylaxis was extremely rare. Of over 10 000 doses of OIT given at home during this trial, only one caused a reaction requiring epinephrine. Important cofactors were identified which increase the likelihood of an OIT reaction, such as intercurrent infection, exercise, and dosing on an empty stomach [28[•]].

Two other groups have now reported similar results with peanut OIT. Clark *et al.* [25[•]] published interim results of four boys aged 9–13 years. These children underwent an OFC at baseline to confirm the diagnosis and establish a pretreatment threshold for reactivity ranging from 5 to 50 mg. After a period of biweekly up dosing on a research unit, the patients consumed 800 mg of peanut protein daily for 6 weeks and the OFC was repeated. At the follow-up challenge, all patients were able to tolerate at least 2400 mg (10 peanuts), representing robust desensitization, with a median 50-fold increase in threshold. A similar safety profile to Jones *et al.* was observed.

Blumchen *et al.* [26^{••}] enrolled 23 peanut-allergic children (median age 5.6 years) and confirmed the diagnosis with an OFC at baseline, which established a 130-mg median threshold. Patients then underwent an inpatient 'rush' OIT protocol in which they received approximately four doses a day for 1 week. Only five patients with relatively low peanut-specific IgE at entry were able to reach the goal of at least 500 mg/day; side-effects prevented a successful rush phase in the remaining patients. All patients then proceeded to an up dosing phase and gradually built up to a maintenance dose of between 500 and 2000 mg/day, which was continued for 8 weeks and then stopped for 2 weeks before the final OFC. Fourteen of 23 (61%) of patients completed this protocol and experienced four-fold increases in threshold. Four asthmatic patients developed OIT-related pulmonary side-effects requiring discontinuation; the remainder withdrew for other reasons. Dosing

was otherwise well tolerated, and no patient required epinephrine. OIT was associated with reduced pro-allergic T-helper-2 cytokines and skin test wheal size, and increased peanut-specific IgG4 levels. Peanut IgE levels did not change.

Randomized controlled trials

Trials incorporating randomization and blinding have now begun to formally test the safety and efficacy of OIT for food allergy. In the only randomized, double-blinded, placebo-controlled trial published to date, Skripak *et al.* [24] enrolled 20 milk-allergic children (mean age 9.5 years) and established an average threshold of 40 mg at baseline with an OFC. An initial escalation day was followed by weekly or biweekly up dosing on the research unit. The maintenance dose of 500 mg (~15 ml milk) was continued for 13 weeks and the food challenge was repeated. Patients received powdered milk protein or matching placebo disguised in a vehicle food. In the active group, the median threshold increased 129-fold to 5100 mg (range 2540–8140), and milk-specific IgG4 levels increased over 700%; there was no change in the placebo group in either parameter. In both groups, skin test size improved and IgE levels did not change. Side-effects were more common in the active group and were primarily mild oropharyngeal or gastrointestinal symptoms. Over 90% of OIT-related reactions were transient and did not require treatment, although there were four reactions that did require epinephrine.

In contrast to Jones *et al.*, where virtually all patients tolerated the full amount without symptoms at follow-up challenge, 14 of 18 (78%) did experience some symptoms during the challenge, suggesting that this relatively short protocol was able to induce only a partial desensitization. In a follow-up study of 15 participants from this trial who were rolled over into an open-label extension phase of milk OIT, the daily dose was gradually increased to a median of 7000 mg [18^{••}]. During a follow-up OFC conducted a median 17 weeks after additional treatment, the median threshold increased to 10 000 mg and 10 of 15 (67%) tolerated the full 16 000 mg challenge dose without symptoms. Milk-specific IgE and skin prick test size were significantly decreased while milk-specific IgG4 continued to increase.

Double-blinded, placebo-controlled randomized controlled trials (RCTs) of egg [29] and peanut OIT [30] are currently underway. The results from these trials are expected in late 2010 or early 2011.

Conclusion

Pilot studies have shown OIT to be a promising approach to the development of an initial disease-modifying

treatment for food allergy. Although efficacy is variable primarily due to differences in protocol design (length of treatment, OFC dose, etc.) or population, OIT appears to be safe and effective in changing the threshold for clinical reactivity (i.e., desensitization) in most patients. Importantly, this increase in threshold is significantly greater than the dose expected to be encountered in most accidental ingestions and should thus be protective against anaphylaxis. Longer treatment and/or higher doses may be necessary in some patients. Although reported side-effects are generally mild, approximately 15% of patients are unable to continue treatment with OIT due to persistent allergic side-effects. Changes in the allergen-specific immune response are similar to those seen in subcutaneous immunotherapy. These observations are currently being examined in trials with rigorous scientific designs. Two recent meta-analyses [1*,31*] focusing on the diagnosis and treatment of food allergy concluded that there is a great need for high-quality evidence from RCTs, and as such the results of these studies are greatly anticipated.

However, before OIT can be implemented into clinical practice, several unresolved issues must be addressed. First, the risks of treatment with OIT must be compared with the risks of allergen avoidance. Second, patient selection and dosing regimens must be optimized. This is especially important given the potential for bias in food allergy trial volunteers. Third, the likelihood of permanent tolerance induction with OIT should be better defined. Until this is known, patients will be committed to indefinite daily treatment. Finally, on a more practical note, the logistics of this labor-intensive process, and the reimbursement which will support them, currently present obstacles to widespread clinical implementation. Though peanut OIT appears safer than subcutaneous peanut immunotherapy, we and others are troubled about published reports of clinical practitioners already offering OIT [32]. We feel strongly that OIT should only be attempted by experienced investigators in an International Review Board-approved and Food and Drug Administration-approved research setting in order to address the above concerns before clear clinical indications can be developed [33*]. In clinical allergy practices, including our own, the current standard of care for patients with food allergy remains strict allergen avoidance.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 837).

- 1 Chafen JJS, Newberry SJ, Riedl MA, *et al.* Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010; 303:1848–1856. This meta-analysis highlighted the inherent difficulties of making the proper diagnosis of food allergy, including overinterpretation of serological testing.
- 2 Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009; 124:1549–1555. Using data from the National Health Interview Survey and National Hospital Discharge Survey, Centers for Disease Control investigators documented the increasing prevalence of food allergy among US children over the period 1997–2007.
- 3 Venter C, Arshad SH, Grundy J, *et al.* Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy* 2010; 65:103–108.
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- 6 Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007; 120:1172–1177.
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- 9 Scurlock A, Vickery B, Hourihane J, Burks A. Pediatric food allergy and mucosal tolerance. *Mucosal Immunol* 2010; 3:345–354. This review describes the immunological mechanisms of oral tolerance and how these principles may be therapeutically exploited in the treatment of allergic disease.
- 10 Freeman J. 'Rush' inoculation, with special reference to hay-fever treatment. *Lancet* 1930; 215:744–747.
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- 16 Staden U, Rolinck-Werninghaus C, Brewe F, *et al.* Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 2007; 62:1261–1269.
- 17 Buchanan AD, Green TD, Jones SM, *et al.* Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007; 119:199–205.
- 18 Narisety SD, Skripak JM, Steele P, *et al.* Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2009; 124:610–612. Although the double-blinded RCT of milk OIT showed a convincing clinical effect, most patients remained incompletely desensitized and without significant immunologic changes. This study shows that extended treatment with higher doses may be necessary to achieve these endpoints.
- 19 Nowak-Węgrzyn A, Bloom KA, Sicherer SH, *et al.* Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol* 2008; 122:342–347; 347.e1–347.e2.
- 20 Lemon-Mulé H, Sampson HA, Sicherer SH, *et al.* Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol* 2008; 122:977.e1–983.e1.

- 21** Shreffler WG, Wanich N, Moloney M, *et al.* Association of allergen-specific regulatory T cells with the onset of clinical tolerance to milk protein. *J Allergy Clin Immunol* 2009; 123:43.e7–52.e7.

Although regulatory T cells are commonly implicated in the development of oral tolerance in mice, there is little high-quality evidence that this is true in humans. This study shows that tolerance of heated milk protein is associated with higher numbers of functionally active milk-specific T-regs.

- 22** Wanich N, Nowak-Węgrzyn A, Sampson HA, Shreffler WG. Allergen-specific basophil suppression associated with clinical tolerance in patients with milk allergy. *J Allergy Clin Immunol* 2009; 123:789.e20–794.e20.

The same group showed that basophils, key effector cells in allergic inflammation, are also suppressed in heated milk-tolerant patients.

- 23** Jones SM, Pons L, Roberts JL, *et al.* Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009; 124:292–300.

This landmark study was the first to show that OIT could be used in peanut-allergic patients to modify the immune response and induce clinical desensitization.

- 24** Skripak JM, Nash SD, Rowley H, *et al.* A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008; 122:1154–1160.

- 25** Clark AT, Islam S, King Y, *et al.* Successful oral tolerance induction in severe peanut allergy. *Allergy* 2009; 64:1218–1220.

This small clinical study adapted the protocol of Jones *et al.* and used a baseline food challenge to formally prove a desensitization effect in a British cohort.

- 26** Blumchen K, Ulbricht H, Staden U, *et al.* Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010; 126:83.e1–91.e1.

Like Clark *et al.*, this group used a food challenge at study entry to show desensitization with OIT in a European cohort. In addition, this group performed extensive immunologic analysis. These two studies lend significant scientific support to the OIT approach.

- 27** Hofmann AM, Scurlock AM, Jones SM, *et al.* Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol* 2009; 124:286.e6–291.e6.

Safety data from the trial by Jones *et al.*, show that, in contrast to subcutaneous peanut immunotherapy, OIT is generally well tolerated. Allergic side-effects are common but generally mild, and anaphylaxis is rare.

- 28** Varshney P, Steele PH, Vickery BP, *et al.* Adverse reactions during peanut oral immunotherapy home dosing. *J Allergy Clin Immunol* 2009; 124:1351–1352.

This study highlights the role of pro-allergic risk factors which interact with OIT and make dosing reactions more likely to occur. Accounting for these risk factors in dosing protocols has improved the side-effect profile.

- 29** National Institute of Allergy and Infectious Diseases; Consortium of Food Allergy Research. Oral immunotherapy for childhood egg allergy [Internet]. *Clinicaltrials.gov*. Bethesda: National Library of Medicine. <http://clinicaltrials.gov/ct2/show/NCT00461097>. [Accessed July 2010]

- 30** Duke University, University of Arkansas. Mucosal immunotherapy for peanut allergy [Internet]. *Clinicaltrials.gov*. Bethesda: National Library of Medicine. <http://clinicaltrials.gov/ct2/show/NCT00597675>. [Accessed July 2010]

- 31** Fisher HR, Toit GD, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance? A meta-analysis of published RCTs. *Arch Dis Child* 2010. [Epub ahead of print] OIT appears to be more effective than allergen avoidance in this small meta-analysis, although this did not reach statistical significance due to the small number of rigorous studies included. The inclusion of egg and peanut OIT studies in progress may change this result.

- 32** Sheikh A, Venderbosch I, Nurmatov U. Oral immunotherapy for peanut allergy. *BMJ* 2010; 340:c2938.

- 33** Thyagarajan A, Varshney P, Jones SM, *et al.* Peanut oral immunotherapy is not ready for clinical use. *J Allergy Clin Immunol* 2010; 126:31–32.

This editorial, co-authored by US food allergy experts, identifies the unresolved questions pertaining to OIT and calls for additional study prior to its clinical implementation.