

Is oral immunotherapy the cure for food allergies?

Anna Nowak-Węgrzyn^a and Alessandro Fiocchi^b

^aJaffe Food Allergy Institute and Department of Pediatrics, Mount Sinai School of Medicine, New York, USA and ^bDepartment of Child & Maternal Medicine, University of Milan Medical School at the Melloni Hospital, Milan, Italy

Correspondence to Anna Nowak-Węgrzyn, MD, Mount Sinai School of Medicine, Department of Pediatrics, Box 1198, One Gustave L. Levy Place, New York, NY 10029, USA
Tel: +1 212 241 5548; fax: +1 212 426 1902;
e-mail: anna.nowak-wegrzyn@mssm.edu

Current Opinion in Allergy and Clinical Immunology 2010, 10:214–219

Purpose of review

To review current evidence on food oral immunotherapy (OIT).

Recent findings

Desensitized state, defined as the ingestion of a substantial amount of food in the home diet that protects from severe reactions to accidental exposures, can be achieved by approximately 50–75% of the children treated with OIT. The rate of permanent tolerance is unknown; the longer duration of OIT may result in permanent tolerance. Side effects are common both during the initial dose escalation and during home dosing. Most reactions are mild (oral pruritus, abdominal discomfort, and rashes) and decrease in frequency with the longer duration of OIT. Severe reactions treated with epinephrine have been reported during home dosing. Factors associated with increased risk of reactions to previously tolerated doses during home dosing include exercise, viral infection, dosing on empty stomach, menses, and asthma exacerbation.

Summary

These preliminary data on OIT are encouraging. Additional studies must answer multiple questions including optimal dose, ideal duration of oral/sublingual immunotherapy, degree of protection, efficacy for different ages, severity and type of food allergy responsive to treatment and need for patient protection during home administration. Until these questions are answered in rigorous multicenter randomized and placebo-controlled trials, OIT remains an experimental approach with not sufficiently well established risk-to-benefit ratio.

Keywords

food allergy, milk immunotherapy, oral desensitization, oral immunotherapy, oral tolerance, peanut allergy, peanut immunotherapy

Curr Opin Allergy Clin Immunol 10:214–219
© 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins
1528-4050

Introduction

Food allergy prevalence is increasing worldwide. In the US, the Centers for Disease Control (CDC) reported an increase by 18% in the past two decades [1]. The prevalence of peanut allergy doubled in the recent years and now reaches 1–2% in young children in the US, UK, Canada, and Australia [2]. In parallel, food-induced anaphylaxis is also increasing [3]. Currently the only treatment for food allergy is strict dietary avoidance and thus therapies for food allergy are urgently needed. The promising therapies under investigation are both allergen-specific and nonspecific [4]. Not surprisingly, these therapies focus on the foods most frequently inducing severe anaphylactic reactions (peanut, tree nuts, shellfish) and the most common food allergens such as cow's milk and egg. Nonspecific therapies for food-induced anaphylaxis include monoclonal anti-IgE antibody, which increased the threshold dose for peanut in peanut-allergic individuals and Chinese herbal medications, which prevented peanut anaphylaxis in an animal model, for which human studies are ongoing. Allergen-

specific therapies include oral, sublingual, and cutaneous immunotherapy (desensitization), mutated recombinant proteins, which are deficient in their IgE-binding activity, co-administered with heat-killed *Escherichia coli* to generate maximum immune response. Table 1 summarizes the therapies other than OIT that are being currently investigated in the human trials [5–9].

An approach that attracts a significant interest of the public and media as well as scientific community, is the food oral immunotherapy (OIT) [10•]. A successful OIT was first reported in the early 20th century in a boy with severe anaphylactic allergy to egg [11]. At present, OIT to food is a subject of many ongoing studies. As food allergy most likely results from the failure of development or the breakdown of normal oral tolerance (such as following a gastrointestinal infection or sensitization to the cross-reactive allergen via inhalation), the oral route of administration takes advantage of the cells and immune pathways involved in the induction of oral tolerance. Animal studies suggest that the high-dose feeding of an antigen results in the state of nonresponsiveness due to anergy or deletion of

Table 1 Allergen-nonspecific therapy for food allergy

Therapy	Mechanism of action	Effects	Comments
Monoclonal anti-IgE [5]	Binds to circulating IgE and prevents IgE deposition on mast cells, blocks degranulation, affects facilitated antigen uptake by B cells and dendritic cells.	Improves symptoms of asthma and allergic rhinitis, provides protection against peanut anaphylaxis in 75% of treated patients.	Subcutaneous at monthly intervals, unknown long-term consequences of IgE elimination; food nonspecific; may be utilized in the combination with specific allergen OIT; studies of milk OIT under the coverage of anti-IgE are currently ongoing.
Traditional Chinese herbs [6]	Down-regulation of Th2 cytokines (IL-4, IL-5, IL-13), up-regulation of Th1 cytokines (IFN- γ produced by CD8+ T cells [7], IL-12), decreased T-cell proliferation to peanut, decreased allergen-IgE production.	Reverses allergic inflammation in the airways, protects mice from peanut anaphylaxis.	Oral, generally well tolerated, current studies focus on identification of the crucial active herbal components in the multiherb formulas and establishing optimal dosing in human phase I and II clinical trials.
Heat-killed bacteria mixed with or expressing modified peanut proteins [8]	Up-regulation of Th1 and T-regulatory cytokine responses.	Protection against peanut anaphylaxis in mice, lasting up to 10 weeks after treatment.	Concern for toxicity of bacterial adjuvants, excessive Th1 stimulation, and potential for autoimmunity; heat-killed <i>E. coli</i> expressing modified peanut allergens administered rectally viewed as the safest approach for future human studies; phase I clinical trials in adults ongoing.
Monoclonal anti-IL-5 antibody (mepolizumab) [9]	Reduced tenascin C ($P = 0.033$) and transforming growth factor beta-1 ($P = 0.05$) expression in the esophageal epithelial layer 13 weeks after initiation of treatment.	Limited improvement of symptoms was seen, although a trend was seen between 4 and 13 weeks after initiation of mepolizumab treatment.	Mepolizumab was well tolerated and had an acceptable safety profile, even at the high 1500 mg dose level. Mepolizumab is being currently evaluated in children with EoE.

antigen-specific T lymphocytes, whereas continuous low-dose ingestion may induce protective suppressive responses from regulatory T cells [12]. In contrast, intermittent feedings or nonoral exposures (e.g. cutaneous or inhalational) may induce IgE sensitization and allergic symptom upon food ingestion [13].

Desensitization versus permanent oral tolerance

A distinction should be made between approaches that induce 'desensitization' versus permanent oral tolerance. In a desensitized state the protective effect depends on the daily, uninterrupted ingestion of the food allergen; however, when the dosing is interrupted, the protective effect may be lost or significantly decreased. In addition, any factors that increase intestinal permeability such as exercise, viral gastroenteritis, stress or menses may cause loss of protection to the previously tolerated dose, even when the maintenance dose has been achieved. Possible mechanisms of oral desensitization include increased food-specific IgG₄ and decreased food-specific IgE antibodies, and decreased activation of mast cells and basophils. In contrast, when permanent oral tolerance is established, the food may be ingested without allergy symptoms despite periods of abstinence. The mechanism of persistent tolerance likely involves development of regulatory T cells and immunologic deviation away from the pro-allergic Th2 response. The permanence of protection is tested with intentional interruption of dosing for at least 4 weeks followed by a supervised oral food challenge [14]. At this time it is unclear whether permanent tolerance is a function of the duration of OIT and may be achieved in any allergic individual if the OIT is continued long enough or whether some allergic individuals will never become truly tolerant.

Oral immunotherapy trials

During OIT, the concentrated food is mixed in a vehicle and ingested in gradually increasing doses. The dose escalation occurs in a controlled setting; regular ingestion of a maximal tolerated dose (maintenance) occurs at home. Early studies were limited to case series and uncontrolled trials; nevertheless they provided evidence that at least a subset of food-allergic patients could be 'desensitized' to a variety of foods, including milk, egg, fish, fruit, peanut, and celery. These studies did not distinguish the effects of oral desensitization versus the natural resolution of food allergy and did not evaluate the permanency of the desensitized state. In some patients who ultimately tolerated a maintenance dose, even for a significant period of time, allergic symptoms re-developed if the food was not ingested on a regular basis, highlighting a concern that permanent tolerance was not achieved [14]. The review of the largest

Table 2 Summary of the most important studies of oral food desensitization for IgE-mediated food allergy

Study	Foods	Patients	Starting dose	Time to maintenance	Success rate ^a	Comments
Patriarca <i>et al.</i> [15]; open clinical trial	CM (8); egg (8); fish (2)	N = 19; age: 5–55 years	Milk: 10 drops of CM in 10 ml of water; 4 drops/day; egg: 10 drops of beaten egg in 100 ml of water; 4 drops/day; fish: 10 ml of mixed fish commercial extract (eel, sardine, codfish, anchovy) in 90 ml of water, 4 drops/day	Milk: 100 ml of undiluted CM/day in 104 days; egg: 120 drops of pure beaten egg/day in 90 days; Fish: 200 g of cooked fish/day in 120 days	CM 5/8; egg 6/8; fish 2/2	Side effects in 11/19 patients: urticaria, pruritus, emesis, angioedema, abdominal pain, rhinitis, dyspnea; patients followed for 3–12 months; patient with orange allergy reported resolution of allergy to plums and peaches. No insight into mechanism of desensitization.
Patriarca <i>et al.</i> [16]; clinical trial	CM (29); egg (15); fish (11)	N = 59; age: 3–55 years	Modification of previously published protocol [15]	Modification of previously published protocol [15]	45/54 (83.3%)	51% of patients experienced urticaria, emesis, diarrhea, or abdominal pain; in nine patients (16.7%) protocol was stopped due to side effects; no differences between children and adults; SPT became negative after 18 months in 78%; food-IgE decreased and food-IgG4 increased after 18 months.
Meglio <i>et al.</i> [17]	CM	N = 21; age: 5–10 years	1 drop of CM diluted 1 : 25 in water	200 ml undiluted CM per day over 180 days	15/21 (71.4%)	3/21 reacted to minimal dose of diluted CM; 3/21 tolerated only 40–80 CM/day; 15/21 tolerated 200 ml CM/day for 6 months; side effect rate 13/21; SPT to BLG and CS significantly decreased at 6 months ($P < 0.001$), CM-IgE levels not significantly different.
Rolnick-Werninghaus <i>et al.</i> [14]	CM (1); egg (2)	N = 3; age: 4–12 years	0.0006 ml of CM per day; 0.01 mg egg per day at home	100 ml CM per day over 37 weeks, 2.5 g egg per day (1/2 egg) over 41–52 weeks	3/3	All patients had acute symptoms to food re-exposure following discontinuation of food for 2–14 days. The first study to re-challenge patients to food following a period of avoidance while on maintenance.
Buchanan <i>et al.</i> [18]	Egg	N = 7; mean age 4 years (patients with history of egg-induced anaphylaxis were excluded)	0.1 mg of powdered egg white followed by doubling doses every 30 min until the highest tolerated dose was determined	Modified rush and build-up phase in the hospital, maintenance dosing once a day at home. Increases by 25 mg every 2 weeks until 150 mg then by 50 mg until reaching maintenance of 300 mg	4/7	Four patients tolerated egg challenge at the end of 24 months. Two of them reacted to a subsequent egg challenge done 3 months after treatment was stopped. Egg-specific IgG increased significantly from baseline to 24 months ($P = 0.002$). Five patients showed an overall decrease in egg-specific IgE.
Morisset <i>et al.</i> [19] randomized clinical trial	CM (57); egg (84)	N = 141 mean age: CM: 2.2 years; egg: 3.5 years	CM: 1 ml/day; egg: 1 g of hard boiled egg yolk	CM: home build-up over 6 weeks, up to a dose of 250 ml/day; egg: home build-up over 4 weeks to 4 g of yolk and 4 g of egg white once a day, every other day	CM: 89%; egg: 69%	Only children tolerating at least 60 ml of CM or 965 mg o raw egg white on a baseline food challenge were included. SPT sizes and specific IgE levels were significantly decreased in children that developed tolerance to CM or egg.
Staden <i>et al.</i> [20]	CM; egg	CM-14; egg-11; control group-20	CM-0.02 mg protein; egg-0.006 mg protein	Slow induction phase at home, median duration 7 months, then maintenance phase CM 100 ml and egg 1/2 egg; median duration 9 months	9/25 (36%) permanent tolerance; 3/25 (12%) tolerant with regular intake (desensitization); 4/25 (16%) partial responders	The first randomized clinical trial of OIT and to test the permanence of the therapeutic effect following 2 months of strict elimination. The rate of spontaneous food allergy resolution in the control group (7/20, 35%) was similar to the treatment group.

Longo <i>et al.</i> [21]	CM	CM-60; mean age 7.9 years; (5–17)	Five drops of a solution of one drop of CM in 10 ml of water	10 day rush phase in the hospital; goal 150 ml of CM for 1 year	11/30 (37%) tolerated >150 ml CM and 16/30 (53%) tolerated 5–150 ml	The first study to include children with history of anaphylaxis to CM. 17/30 reported side effects at home, 17 received oral steroids, 6 received nebulized epinephrine, and 1 received intramuscular epinephrine.
Skripak <i>et al.</i> [22**]	CM	N = 20, active to placebo ratio 2 : 1	0.4 mg CM protein	Dose increase every 1–2 weeks, 12 mg minimum tolerated dose to proceed to home dosing	13 weeks to repeat double-blind placebo-controlled food challenge	The first double-blind, placebo-controlled clinical trial; after OIT median cumulative dose of milk inducing a reaction in the active group increased from 40 mg to 5140 mg; there was no change in placebo group.
Jones <i>et al.</i> [23**]	Peanut	N = 29	0.1 mg peanut protein	Initial day escalation phase 0.1 mg peanut protein doubled every 30 min, up to 50 mg. Build-up phase: increase by 25 mg every 2 weeks, up to 300 mg	27/35 (77%)	Open-label study, 29 patients completed, 27 ingested 3.9 g peanut protein during the final food challenge. Four patients withdrew due to the side effects. Most symptoms noted during OIT resolved spontaneously or with antihistamines. By 6 months, titrated skin prick tests and activation of basophils decreased significantly. Follow-up for 30 months.

BLG, beta-lactoglobulin; CM, cow's milk; CS, casein; SPT, skin prick test.

* Success rate defined as regular ingestion of the tested food for at least 6 months.

published OIT studies is included in Table 2 [15–21, 22**, 23**]. It appears that a large subset of children, even those with severe milk allergy, may be desensitized to tolerate a significant amount of food in the daily diet that protects them from accidental ingestions and severe reactions.

Mechanism of oral immunotherapy

A recent study [23**] provided more insight into the mechanism of peanut OIT, and presumably these findings might be extended to other foods as well. Of the 29 children with peanut allergy who completed the protocol, 27 ingested 3.9 g peanut protein during the final food challenge. Most symptoms noted during OIT resolved spontaneously or with antihistamines. By 6 months, titrated skin prick tests and activation of basophils decreased significantly. Peanut-specific IgE antibody concentrations decreased by 12–18 months, whereas IgG₄ increased significantly. Serum factors inhibited IgE–peanut complex formation in an IgE-facilitated allergen binding assay. Secretion of the pro-allergic cytokines IL-10, IL-5, IFN- γ , and TNF- α from peripheral blood mononuclear cells increased over a period of 6–12 months. Peanut-specific forkhead box protein-3 (Fox P3) – positive regulatory T cells increased until 12 months and decreased thereafter. In addition, T-cell microarrays showed down-regulation of genes involved in the apoptotic pathways.

Safety of oral immunotherapy home dosing

Among the children who participated in a trial of peanut OIT, 20 completed all phases of the study [23**]. During the initial escalation, the risk of mild wheezing was 18%. The probability of having any symptoms after a build-up phase dose was 46%, with a risk of 29% for upper respiratory tract and 24% for skin symptoms. The risk of reaction with any home dose was 3.5%, upper respiratory tract (1.2%) and skin (1.1%) symptoms being most common. Treatment was given for 0.7% of home doses. Two patients received epinephrine after one home dose each. Allergic reactions during home dosing were more common in the open-label maintenance after milk OIT, from 2.55 to 96.4% of doses per patient in the first 3 months compared with 0–79.8% in the subsequent 3 months [24]. Local and multisystem reactions decreased, whereas all other reactions remained unchanged. Several systemic reactions occurred at previously tolerated doses in the setting of exercise or viral illness. As highlighted by a recent study from Jones' and Burks' groups, the risk of an allergic reaction to a previously tolerated dose of food is associated with physical exertion after dosing, dosing on empty stomach, dosing during menses, concurrent febrile illness, and suboptimally controlled asthma [25,26]. It is unclear whether these precautions are necessary only during

Table 3 Risks of the food oral immunotherapy

Side effects	
Peanut [23 ^{••} ,25,26]	Milk [22 ^{••} ,24]
Build-up	
Mild wheezing 18%	
Maintenance	
Upper respiratory symptoms 29%	
Cutaneous 24%	
Treatment given for 0.7% of home doses, two patients received one dose of epinephrine	
	Blinded study
	Local (oral pruritus) median 16% doses per child
	Gastrointestinal median 2% doses per child
	Epinephrine was used in 0.2% of total doses
	Open-label home study
	2.5–96.4% of doses per patient in the first 3 months, compared with 0–79% in the subsequent months
	% Reactions/total numbers of doses
	Local reactions (oral pruritus): 17
	Gastrointestinal: 3.7
	Respiratory: 0.9
	Cutaneous: 0.8%
	Multisystem: 5.5%
	Epinephrine was used for six reactions (0.2%; four patients)
	In one patient, apparent clinical reactivity to milk recurred, primarily manifesting with gastrointestinal symptoms, suggesting possible eosinophilic disease
Factors associated with increased risk of reactions to previously tolerated doses during home dosing ^a	
Exercise	
Viral infection	
Dosing on empty stomach	
Menses	
Asthma exacerbation	

Success rate is defined as ability to ingest the significant amount food on a regular basis for at least 6 months = desensitized state.

^a May require dose adjustment; avoid dosing on empty stomach and exercise within 1–2 h following the dose.

the 'desensitized' state or whether they would also apply after the permanent tolerance was established. Table 3 reviews the risks of OIT.

Conclusion

These preliminary data on OIT are encouraging; however, at this time, these treatments are considered investigational and additional studies must answer multiple questions including optimal dose, ideal duration of oral/sublingual immunotherapy, degree of protection, efficacy for different ages, severity and type of food allergy responsive to treatment and need for patient protection during home administration. In view of the recent studies of the reactions to the tolerated doses of OIT at home, it may be necessary to hold doses during acute febrile illness, avoid exercise within 2 h following dosing, and take a daily OIT dose with a meal or snack. Rhinitis and asthma have to be maintained under optimal control. Finally, as a subset of children with food allergies develops tolerance spontaneously, the future studies must address diagnostic tests that would distinguish among those with transient and persistent food allergies to identify the patients that will benefit from therapy.

Until these questions are answered in rigorous multicenter randomized and placebo-controlled trials, OIT

remains an experimental approach with not sufficiently well established risk-to-benefit ratio.

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

- 1 Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009.
- 2 Sicherer SH, Sampson HA. Food allergy: recent advances in pathophysiology and treatment. *Annu Rev Med* 2009; 60:261–277.
- 3 Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax* 2007; 62:91–96.
- 4 Skripak JM, Sampson HA. Towards a cure for food allergy. *Curr Opin Immunol* 2008; 20:690–696.
- 5 Leung DY, Sampson HA, Yunginger JW, *et al.* Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003; 348:986–993.
- 6 Srivastava KD, Kattan JD, Zou ZM, *et al.* The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J Allergy Clin Immunol* 2005; 115:171–178.
- 7 Srivastava KD, Qu C, Zhang T, *et al.* Food Allergy Herbal Formula-2 silences peanut-induced anaphylaxis for a prolonged posttreatment period via IFN- γ -producing CD8⁺ T cells. *J Allergy Clin Immunol* 2009; 123:443–451.
- 8 Li XM, Srivastava K, Grishin A, *et al.* Persistent protective effect of heat-killed *Escherichia coli* producing 'engineered,' recombinant peanut proteins in a murine model of peanut allergy. *J Allergy Clin Immunol* 2003; 112:159–167.
- 9 Straumann A, Conus S, Grzonka P, *et al.* Antiinterleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010; 59:21–30.

- 10 Scurlock AM, Burks AW, Jones SM. Oral immunotherapy for food allergy. *Curr Allergy Asthma Rep* 2009; 9:186–193.
• Very interesting review discussing OIT.
- 11 Schofield AT. A case of egg poisoning. *Lancet* 1908; 1:716.
- 12 Chehade M, Mayer L. Oral tolerance and its relation to food hypersensitivities. *J Allergy Clin Immunol* 2005; 115:3–12.
- 13 Strid J, Hourihane J, Kimber I, *et al*. Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. *Clin Exp Allergy* 2005; 35:757–766.
- 14 Rolinck-Werninghaus C, Staden U, Mehl A, *et al*. Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? *Allergy* 2005; 60:1320–1322.
- 15 Patriarca C, Romano A, Venuti A, *et al*. Oral specific hyposensitization in the management of patients allergic to food. *Allergol Immunopathol (Madr)* 1984; 12:275–281.
- 16 Patriarca G, Nucera E, Roncallo C, *et al*. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003; 17:459–465.
- 17 Meglio P, Bartone E, Plantamura M, *et al*. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 2004; 59:980–987.
- 18 Buchanan AD, Green TD, Jones SM, *et al*. Egg oral immunotherapy in non-anaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007; 119:199–205.
- 19 Morisset M, Moneret-Vautrin DA, Guenard L, *et al*. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases: a randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. *Allerg Immunol (Paris)* 2007; 39:12–19.
- 20 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.
- 21 Longo G, Barbi E, Berti I, *et al*. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol* 2008; 121:343–347.
- 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.
•• The largest open study of peanut OIT in children that discusses efficacy, safety and mechanism of OIT.
- 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.
•• The largest open study of peanut OIT in children that discusses efficacy, safety and mechanism of OIT.
- 24 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.
- 25 Varshney P, Steele PH, Vickery BP, *et al*. Adverse reactions during peanut oral immunotherapy home dosing. *J Allergy Clin Immunol* 2009.
- 26 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; 124:286–291.