



Food immunotherapy for children with food allergies: state of the art and science

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Purpose of review

This review examines the current literature and provides insight into the role of food immunotherapy in the management of food-allergic children. Key food immunotherapy trials, benefits, and risks of the intervention, as well as areas requiring further study are all discussed.

Recent findings

Research studies have reported encouraging results regarding the efficacy of food immunotherapy in desensitizing food-allergic patients with an acceptable safety profile and a documented improvement in quality of life. The role of biologics and long-term effects of food immunotherapy are still under investigation.

Summary

The burden of food allergy is significant, multifaceted, and well documented. Food immunotherapy is a novel treatment option and an exciting area of research that has seen tremendous progress over the last decade, presenting encouraging results for the treatment of children with food allergies.

Keywords

desensitization, food allergy, immunomodulators, immunotherapy, tolerance

INTRODUCTION

Food allergy affects approximately 4% of children and its prevalence is increasing [1]. Common childhood food allergies such as milk, egg, and peanut are reported in 2, 8.9, and up to 3% of children, respectively [2–5]. The burden of food allergy is significant and multifaceted; it includes dietary and social restrictions, fear of accidental reactions, and high levels of anxiety related to risk of severe reactions and fatalities. As a result, food-allergic children and their parents often experience low quality of life [6,7].

Until recently, the only available management approach for food allergies was dietary avoidance, education on how to promptly recognize and treat reactions and use of emergency medication as needed, when allergic reactions occurred. The emergence of food immunotherapy as an active treatment option for food allergies has been a welcome addition to the limited landscape of treatments and is currently an area of intense research with a potential to be disease modifying.

REVIEW

Food immunotherapy presents significant benefits as a treatment option in common childhood food allergies

Immunotherapy consists of the administration of small, gradually increasing doses of the food that patients are allergic to, with the ultimate goal to enable them to eat varying amounts of the allergenic food without reactions. Most research studies include an initial up dosing phase (with or without a “rush” escalation) which usually lasts a few weeks or months and a long-term maintenance phase once the desired maintenance dose is reached. This phase

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KEY POINTS

- Food immunotherapy is a novel treatment for food allergies, potentially disease modifying.
- Various routes exist for food immunotherapy administration including oral, SLIT, and EPIT.
- OIT has better efficacy, but increased risk of systemic reactions compared with the other routes of immunotherapy.
- Most OIT-treated children will achieve desensitization, but long-term tolerance is less likely and still under investigation.
- Use of immune modulators alongside food immunotherapy decrease the risk of adverse reactions, but have not been shown to increase efficacy.

lasts for years and currently, ongoing regular ingestion is advised as maintenance therapy.

Multiple terms exist with regards to the effect of immunotherapy that may be confusing and require clarification. The term “desensitization” refers to a raise in the allergenic threshold of reactivity and implies ongoing (usually daily) dose ingestion. This increase in threshold is usually enough to provide protection from accidental ingestion and can be achieved after months of therapy by the majority of food-allergic children [8,9[¶]]. “Sustained unresponsiveness” refers to the ability of study participants who have completed an immunotherapy protocol, to take breaks off treatment (usually a few weeks or months) and then return to regular allergen consumption at their previous dose, without suffering any allergic reactions. Achieving sustained unresponsiveness requires years of therapy [8,9[¶]]. “Long-term or oral tolerance” is defined as the ability to eat the previously allergenic food *ad lib* (any amount and any period of food abstinence, however prolonged) without any problems or the need for ongoing treatment (daily dosing) and has only been reported in a small number of patients so far [8,9[¶]].

As expected, the acquisition of long-term tolerance would be the ultimate goal for individuals, but interestingly, for many families, desensitization to a level protective of accidental ingestion reactions is also actively pursued and accepted as a satisfactory outcome of oral immunotherapy (OIT). Studies have shown that approximately 25–50% study participants maintain their desensitization after “breaks” of OIT treatment [10–13] and results appear to be much more encouraging for younger children [14[¶]]. More data are needed and we are still missing a systematic, universally applied approach to this

important issue with well designed and multicenter studies.

Studies on food immunotherapy for milk, egg and peanut have shown promise in desensitizing food-allergic children with the majority achieving this goal [10,15–17] (see Table 1 for more information on key food immunotherapy studies). Systematic reviews on milk, egg, and peanut OIT reported that when compared to an elimination diet alone, food allergen immunotherapy increased the likelihood of achieving clinical tolerance to milk, egg, and peanut [18–20]. In addition to raising the threshold of reactivity, food immunotherapy has demonstrated a significant effect on improving the quality of life of children and their caregivers, following successful desensitization [17,21,22].

The encouraging results from food immunotherapy research studies have prompted pharmaceutical companies to develop biologic drug products for use in OIT. Results from a recent, phase 2, multicenter trial revealed peanut OIT-induced desensitization in 79% of participants. Interestingly, after just 6 months of treatment, participants experienced an 18-fold increase in the amount of peanut tolerated compared with pretreatment baseline levels [23[¶]].

Taking into consideration all the above benefits of food immunotherapy, recent guidelines were published from the European Academy of Allergy and Clinical Immunology recommending OIT as a treatment option to increase the threshold of reaction while on treatment for children age 4–5 years and above with persistent milk, egg, and peanut allergy [24[¶]].

Food immunotherapy may be administered via different routes and safety profiles vary

OIT for food allergy appears to be a popular option and has been studied more than other routes of administration. The safety profile is generally acceptable with most study participants experiencing mild or moderate reactions during treatment [25]. Frequency and number of reactions generally decrease during the maintenance phase and it has been suggested that adverse events are significantly associated with allergic rhinitis and skin prick test (SPT) wheal size [25]. Specifically, for milk OIT, a Cochrane systematic review reported adverse reactions in 97 of 106 milk OIT patients although most were local and mild. For every 11 patients receiving milk OIT, one required intramuscular epinephrine. One patient required it on two occasions [26]. For egg OIT, a systematic review including children between 4 and 15 years reported mild to severe adverse effects during OIT treatment in 69% of

Table 1. Key studies of food immunotherapy

Study reference	Study design	Route of immunotherapy (relevant food allergen) and top dose tolerated post immunotherapy	Study protocol	Study population	Study duration	Main results	Rate of systemic reactions
Longo <i>et al.</i> , JACI 2008	Randomized controlled trial	Oral (cow's milk) Top dose: 150 ml of cow's milk	Initial rush, buildup, and maintenance	60 children (all >5-year-old) with severe cow's milk allergy	12 months	36% in the active group were successfully desensitized None in the placebo group were desensitized	Three study participants (10%) in the active group
Clark <i>et al.</i> , Allergy 2009	Open, prospective	Oral Top dose: 2.38 g peanut protein	Buildup followed by maintenance	Four children with severe peanut allergy Median age: 12.5 years (9–13)	Not stated	100% successfully desensitized to 2.38 g peanut protein post-OIT (compared with 5–50 mg peanut protein pre-OIT)	None
Jones <i>et al.</i> , JACI 2010	Open, prospective	Oral Top dose: 3.9 g peanut protein	Rush, buildup and maintenance	39 children with peanut allergy Median age: 57.5 months (12–111 months)	36 months	Of 29 study participants who completed the protocol, 93% were successfully desensitized (tolerated 3.9 g peanut protein), 7% failed. There was a 25% withdrawal rate	15%
Blumchen <i>et al.</i> , JACI 2010	Open, prospective	Oral Top dose: 4 g peanut	Rush, buildup and maintenance	23 children with peanut allergy Median age: 5.6 years (3–14)	9 months	61% successfully desensitized to 0.5–2 g peanut 17% failed, 22% dropped out	None
Kim <i>et al.</i> , JACI 2011	Randomized controlled trial	Sublingual Top dose: 1710 mg peanut protein	Buildup and maintenance	18 study participants with peanut allergy (active group: 11, placebo group: 7) Median age: 5 years (1–11)	12 months	The active group ingested 20 times more peanut protein than the placebo group (1710 g versus 85 mg) post immunotherapy	None
Varshney <i>et al.</i> , JACI 2011	Randomized controlled trial	Oral Top dose: 5 g peanut protein	Rush, buildup, and maintenance	28 children with peanut allergy (active group: 19, placebo group: 9) Median age: 6 years (1–16)	12 months	84% of study participants who completed the study protocol were successfully desensitized to 5 g of peanut protein, 16% failed. There was a 32% dropout rate	21%
Anagnostou <i>et al.</i> , CEA 2011	Open, prospective	Oral Top dose: 6.6 g peanut protein	Buildup followed by maintenance	22 children with peanut allergy Median age: 11 years (4–18)	56 weeks	64% tolerated the top dose (6.6 g peanut protein), 22% tolerated a lower dose (800 mg peanut protein), and 9% failed	None
Burks <i>et al.</i> , NEJM 2012	Randomized controlled trial	Oral (egg) Top dose: 5 g of egg protein	Initial rush, buildup, and maintenance	55 children with egg allergy (active:40, placebo:15)	10 months	55% of active participants were successfully desensitized No placebo study participants were desensitized	None
Fleischer <i>et al.</i> , JACI 2013	Randomized controlled trial	Sublingual Top dose: 496 mg peanut protein	Buildup and maintenance	40 study participants with peanut allergy Median age: 15 years (12–37)	68 weeks	70% in the active group reached the top dose of 496 mg peanut protein, 30% failed	None
Schneider <i>et al.</i> , JACI 2013	Open, prospective	Oral (peanut) and anti-IgE (subcutaneous injection) Top dose: 2 g peanut protein	Initial rush, buildup, and maintenance	13 peanut allergic children with high peanut-specific IgE Median age: 10 years	32 weeks	92.3% successfully reached the top dose	15.3% (2 study participants)

Table 1 (Continued)

Study reference	Study design	Route of immunotherapy (relevant food allergen) and top dose tolerated post immunotherapy	Study protocol	Study population	Study duration	Main results	Rate of systemic reactions
Anagnostou <i>et al.</i> , Lancet 2014	Randomized controlled crossover trial	Oral Top dose: 1.4 g peanut protein	Buildup followed by maintenance	99 children with peanut allergy of any severity Median age: 12.4 years (7–16)	26 weeks	62% of study participants in the active group that completed the OIT protocol tolerated the top dose of 1.4 g peanut protein, 22% tolerated 800 mg peanut protein, 16% failed. There was a 10% dropout rate	1%
Begin <i>et al.</i> , Allergy Asthma Clin Immunol 2014	Open, prospective	Oral (peanut and other food allergens) Top dose: 4 g of protein for each allergen	Initial escalation, buildup, and maintenance	40 participants (4–46 years) 15 study participants mon allergic (peanut only), 25 polyallergic (peanut and other food allergies)	85 weeks	12/15 (80%) in the single OIT group and 22/25 (88%) in the multi-OIT group were successfully desensitized	10% (4 study participants, 2 in each group)
Begin <i>et al.</i> , Allergy Asthma Clin Immunol 2014	Open, prospective	Oral (peanut and other food allergens) Top dose: 4 g for each food allergen	Initial rush, buildup, and maintenance	25 children with multiple food allergies (including peanut) Median age: 7 years	18 weeks	22/25 (88%) of participants were successfully desensitized	4% (1 study participants)
Tang <i>et al.</i> , JACI 2015	Randomized controlled trial	Oral (peanut) and probiotic Top dose: 2 g peanut protein	Rush, buildup, and maintenance	62 children (1–10 years) with peanut allergy	18 months	89.7% in the active group (OIT and probiotic) were successfully desensitized 7.1% in the placebo group were desensitized	11.3% (7 study participants, 3 active and 4 placebo)
Vickery <i>et al.</i> , JACI 2017	Randomized controlled crossover trial	Oral: peanut Top dose: 3 g peanut protein	Initial rush, buildup, and maintenance	40 children with peanut allergy (9–36 months)	29 months	81% were successfully desensitized	1 study participant in the intervention group None in the control cohort
Bird <i>et al.</i> , JACI In Pract 2017	Randomized controlled trial	Oral (peanut) Top dose: 443 mg peanut protein	Initial rush, buildup, and maintenance	55 study participants (4–26 years old) with peanut allergy (29 active, 26 placebo)	6 months	79% of active study participants versus 19% of placebo study participants were successfully desensitized	4% in the active group 6% in the placebo group
Sampson <i>et al.</i> , JAMA 2017	Randomized controlled trial	Epicutaneous (peanut) – patch doses included 50 µg or 100 µg or 250 µg Top dose: 1 g peanut protein (or >10-fold increase in threshold)	Buildup and maintenance	221 patients (median age 11 years) with peanut allergy randomized (1:1:1:1); Number of study participants receiving an epicutaneous peanut patch containing 50 µg (n = 53), 100 µg (n = 56), or 250 µg (n = 56) of peanut protein or a placebo patch (n = 56)	12 months	Results for 250 µg patch only were significant; shown below Overall (both adults and children): 50% in the active group versus 25% in the placebo group were desensitized In children: 53.6% in the active group versus 19.4% in the placebo group were desensitized	1 study participant in the active group

Key studies of food immunotherapy are described in chronological order (based on publication date). Information presented includes the study reference (authors, journal, and date of publication), the study design, the route of immunotherapy used, the relevant food allergen studied (in brackets) and the top dose tolerated orally after immunotherapy treatment; the study protocol (rush, buildup, or maintenance), the relevant population (age range in brackets, shown in years), the duration of each study (in days, weeks, or months), and the main results (success rate of desensitization and rate of systemic reactions).

the participants with 5% requiring epinephrine [19]. As severe reactions can occur, it is of outmost importance that children have both an allergy action plan and epinephrine autoinjectors readily available to treat any allergic reactions. Families should also be educated on the fact that viral illnesses and other factors (exercise, tiredness, and menstruation) may lower the threshold of reactivity in patients undergoing OIT [27].

Concerns have been raised regarding the onset of eosinophilic esophagitis (EoE) as a result of this oral intervention, but it is not clear whether OIT incites EoE or unmasks a preexisting tendency. A published meta-analysis reports up to 2.7% of patients with immunoglobulin E (IgE)-mediated food allergies undergoing food OIT developing this complication, with EoE often resolving following discontinuation of OIT treatment. However, the available data are limited, the risk is considered minor at present [28], and a causal relationship between food OIT and EoE remains controversial [29,30].

In addition to OIT, alternative routes of immunotherapy such as sublingual (SLIT) and epicutaneous (EPIT) are being pursued. Clinical SLIT trials have been performed for cow's milk [31], egg [19], peanut [32,33], hazelnut [34], and other foods. SLIT is administered in a liquid form, held under the tongue for a few minutes and then spat out or swallowed. The typical starting dose for SLIT is lower than OIT (usually in micrograms rather than milligrams of food protein) as is the maintenance dose, making SLIT less effective when compared with OIT. The safety profile is also quite different with systemic reactions being rather uncommon with SLIT (reported in up to 2.3% of doses) [19,32,34,35]. Overall, SLIT has fewer side-effects when compared with OIT and symptoms are typically mild and localized to the oropharyngeal region [36]. EoE has not been observed with food allergen SLIT but has been reported in aeroallergen SLIT [37].

Unlike oral or SLIT, EPIT has provided an alternative route of desensitization to a food allergen via the skin. In EPIT, an adhesive patch is applied daily to the back or inner arm. The dose is fixed (250 mcg) and significantly lower than OIT doses. The safety profile for EPIT has so far been favorable. The epidermis is not vascularized and as a result, systemic effects are much less likely to occur. Mild local reactions at the patch site have been observed in over 90% of patients receiving the active treatment (peanut EPIT) and mild non-local reactions were observed in less than 20% of study participants. Systemic reactions have not been reported with EPIT as yet [38,39,40,41]. Recent findings from an industry-sponsored, phase 2b double blind, placebo-controlled trial of the peanut EPIT demonstrated a response rate difference of 34.2% after

12 months of treatment with EPIT versus placebo [39]. Further results from phase 3 peanut EPIT trials are still ongoing. Phase 1 and 2 EPIT trials for other food allergens such as cow's milk are also underway.

Food immunotherapy for multiple food allergies appears successful, but requires further study

For children with multiple food allergies, the simultaneous administration of a combination of food allergens compared with the administration of a single allergen has been studied. Multifood OIT has been shown, in small phase I trials, to be comparable in safety to single-food immunotherapy. Similar rates of adverse reactions, 3.3 and 3.7%, were observed in each group, most of which were mild [42,43,44]. This approach has the potential to minimize the number of hospital patient visits and the overall cost of treatment, as OIT to more than one food allergen can be time consuming and expensive, if the allergens are to be administered sequentially, one at a time.

Use of immune modulators alongside food immunotherapy decreases risk of adverse reactions, but does not increase efficacy

The use of immune modulators (such as anti-IgE) in combination with food immunotherapy has been suggested with the aim to facilitate this process and improve the safety profile of the intervention. The use of anti-IgE (omalizumab) as an adjuvant in milk immunotherapy was examined in a randomized, double-blind, placebo-controlled trial. Despite significant improvements in terms of safety, efficacy for the omalizumab and OIT-treated group compared with the group that received placebo and OIT was similar [45]. In a different study of peanut OIT in children, omalizumab was shown to be effective in facilitating rapid oral desensitization, but allergic reactions recurred once it was discontinued [46]. Omalizumab was also evaluated in oral OIT with multiple food allergens. After pretreatment with omalizumab, participants tolerated the initial rapid escalation day with minimal or no rescue therapy and the majority of reactions experienced by study participants were mild [42]. A recent trial has also confirmed that omalizumab enables well-tolerated and rapid desensitization in multiple food OIT. The study showed a significantly lower per participant percentage of OIT doses associated with any adverse events (27 versus 68%; $P=0.0082$) in the omalizumab group versus the placebo group. The most common adverse events reported were gastrointestinal [47]. Overall, the use of anti-IgE

in combination with OIT has shown a decrease in adverse events, but no significant increase in efficacy. Other immune modulators such as probiotics are also been examined alongside OIT [48,49].

Mechanism of food immunotherapy

Research studies have shown downregulation of the allergen-specific T helper cell (Th2) response, increase of the Th1 response, and induction of regulatory T cells, as a result of food immunotherapy. In particular, successful desensitization is associated with an allergen-specific IgE decrease, SPT decrease, allergen-specific IgG and IgG4 increase, as well as decreased IL-4, IL-5, and IL-13 and increased IL-10 and TGF- β cytokine production [11,16,33,50,51]. Microarray data have demonstrated downregulation of genes in several apoptosis pathways in patient T cells, although it is not clear whether these changes included apoptosis of antigen-specific cells as well as total peripheral blood T cells [50]. Clinical immune tolerance has been associated with demethylation of forkhead box protein 3 cytosine-phosphate-guanine sites in antigen-induced regulatory T cells [13]. Generally, most of the immunological changes seen are similar to those seen in patients receiving other forms of immunotherapy (for instance for environmental allergens), however, more research is needed in the area to clearly identify the underlying mechanisms of desensitization and long-term tolerance in food immunotherapy.

Existing practices and health economics in the context of food immunotherapy

As expected, practices vary in different countries and geographical areas with regards to food immunotherapy. Some countries have developed guidelines, whereas others are in the process of forming consensus documents for this novel treatment. In the United States, in an effort to understand existing practices of allergists who perform OIT, an online survey of members of the American Academy of Allergy Asthma and Immunology was performed. A total of 442 clinicians responded to the survey, with a minority (13.8%) providing OIT as a service or studying OIT under a research protocol. Some important differences in the practice of OIT between academic and nonacademic providers were highlighted, with academics obtaining institutional review board and Investigational New Drug approval more often than nonacademic clinicians [52].

With increasing healthcare expenditures in most developed countries, there is a need for economic evaluation and analysis of new medical therapies [53]. To characterize the cost-effectiveness of food immunotherapy, an economic analysis of peanut

OIT was performed, which revealed that peanut OIT may be cost-effective in a long-term economic model when compared with strict avoidance. Rates of accidental reactions, therapy-associated adverse events and likelihood of therapy-induced tolerance were all taken into account in the analysis [53]. Clearly, more studies are needed in this area, ideally examining different food allergens, for a better understanding of the cost-effectiveness of this novel treatment option for food-allergic patients.

CONCLUSION

Food immunotherapy presents an exciting, potentially disease-modifying treatment approach for food allergy, but is still facing challenges that require further study to optimize this intervention and unveil its full potential. Research has shown encouraging results regarding the efficacy of food immunotherapy in desensitizing food-allergic patients with an acceptable safety profile and a documented improvement in quality of life. Adverse reactions occurring during treatment are mostly mild to moderate, although episodes of anaphylaxis have also been recorded and the risk should be taken into account prior to undertaking this treatment. The optimal dosing schedule, duration, and long-term effects of food OIT, as well as health-related economics are still largely unknown requiring further investigation.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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