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Oral and sublingual immunotherapy for food allergy: current progress and future directions

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Abstract

Food allergies are increasing in prevalence and present an emerging epidemic for westernized countries. Strict dietary avoidance is the only approved management for food allergy, but accidental exposures regularly occur, leading to significant patient anxiety and decreased quality of life. Over the past decade, oral and sublingual immunotherapies have emerged as potential treatments for food allergy. While several small clinical trials have demonstrated that immunotherapy can desensitize food-allergic individuals, strategies for further enhancing safety and definitively establishing long-term efficacy are needed. This review presents an overview of recent oral and sublingual immunotherapy trials, and provides a glimpse into what the next generation of food immunotherapy may entail.

Introduction

Food allergy (FA) is a serious disorder that has life-altering implications for afflicted individuals and their families. Although FA can encompass several different disease entities, here we use the term to denote an immunoglobulin E (IgE)-mediated hypersensitivity reaction that occurs after consuming a specific food [1]. FA affects up to 10% of the population with the highest rates in children [2–4], and incidence appears to be increasing along with other atopic disorders [3,5]. Clearly FA is a growing healthcare concern, yet effective treatment other than strict dietary avoidance remains elusive [1]. Over the past decade, several small clinical studies of two different therapeutic approaches, oral immunotherapy (OIT) and sublingual immunotherapy (SLIT), have shown promising results. In this review, we discuss recent findings of randomized controlled trials (RCT) evaluating the efficacy and safety of OIT and SLIT, and then present potential strategies for improving food immunotherapy.

Immunotherapy trials for FA

Immunotherapy involves manipulating the immune response directed against an antigen. Subjects who tolerate and successfully complete food immunotherapy protocols can experience two possible outcomes. The first is desensitization, where continuous allergen exposure increases the threshold of clinical reactivity to the food. The second and more ideal outcome is clinical tolerance, which is defined as the ability to consume a food without allergic symptoms after treatment is ceased indefinitely. It is unknown whether ‘tolerance’

after immunotherapy resembles the natural tolerance that occurs spontaneously for some FA patients, or if therapeutic tolerance is mechanistically similar to classical immune tolerance. For this reason, the term ‘sustained unresponsiveness’ has been introduced into the literature to avoid confusion [6•]. How such a change develops in humans is incompletely understood, but possibly involves the generation of allergen-specific regulatory T cells (Treg) or deletion of effector T cells [7,8]. Other immunological changes described in desensitized patients include decreased allergen-specific IgE but increased specific IgG4, and diminished mast cell and basophil activity [6,9,10,11•,12•].

OIT

OIT comprises the daily consumption of milligrams to grams of allergen, typically mixed with a food vehicle, which is incrementally increased over weeks to months with the goal of inducing desensitization and ultimately tolerance. Open-label pilot studies involving patients with milk, egg, and peanut allergies had suggested that OIT could increase the threshold of clinical reactivity to the culprit food [10,13–15]. Recent RCT have provided further compelling evidence that OIT can frequently induce desensitization in patients with FA [6,9,12•], although the effect varies across studies (Table 1).

There is evidence that OIT can also result in clinical tolerance or sustained unresponsiveness. In 2012, Keet *et al.* reported that 40% of subjects receiving milk OIT passed an OFC when treatment was ceased for 6 weeks [16•], although it is possible that some may have naturally outgrown their FA. That same year, a study by the Consortium for FA Research (CoFAR) found that of 30 patients desensitized with egg OIT, eleven (27.5% of the active treatment group) passed on OFC after halting therapy for 4–6 weeks [6•]. These individuals continued to consume egg regularly without problems when surveyed 12 months later. The likelihood of spontaneous FA resolution was very low in this study, and none of the control subjects exhibited evidence of outgrowing their egg sensitivity. This landmark article was the first to suggest that OIT could be a truly disease-modifying treatment.

SLIT

SLIT involves placement of micrograms to milligrams of allergen under the tongue with doses that are up to 1000-fold less than OIT. A few RCT have investigated allergen-specific SLIT for patients with milk [16•], peanut [11•,17•], hazelnut [18] and peach allergies [19], demonstrating varying degrees of efficacy (Table 1). One of the most informative studies to date was a CoFAR-sponsored multicenter RCT for peanut SLIT involving forty subjects. After 44 weeks of therapy, 70% of patients receiving SLIT developed partial desensitization to peanut, compared to only 15% of the placebo group ($P < 0.001$). These findings were slightly inferior to a prior single center study of peanut SLIT [11•], indicating the importance of performing multicenter trials to more accurately assess treatment effect.

One randomized study attempted to directly compare the efficacy of OIT and SLIT for the treatment of cow’s milk allergy [16•]. After an initial dose escalation with SLIT, 30 subjects were randomized to continue either daily SLIT or begin OIT at two different maintenance doses. Sixty weeks later, 70% of subjects in the OIT group passed a milk OFC, compared to only 10% in the SLIT group. The apparent superior efficacy of OIT was mitigated by a higher rate of systemic reactions during therapy. A retrospective comparison study of peanut-allergic individuals treated with either peanut OIT or SLIT also found greater efficacy associated with the former [20]. Thus, OIT may prove to be more efficacious than SLIT, but this could come at the expense of safety.

Summary of clinical trials

Some general conclusions can be drawn from the few published RCT for OIT and SLIT. First, a very small number of individuals have been subjected to rigorous study, thus restricting the generalizability of reported findings. Of those treated with OIT, greater than 80% experience at least partial desensitization to the food allergen while on therapy. Complete desensitization, which can be conservatively defined as passing a 5 g OFC without symptoms [21], occurs in 45–75% of OIT subjects. The rate is even lower for SLIT, with few subjects reaching full desensitization during the blinded phases of the trials. Only a minority of OIT subjects (25–40%) develops a state that resembles clinical tolerance; thus, prolonged and potentially indefinite therapy may be needed to provide adequate protection for most patients. The safety profile of OIT and SLIT is also less than ideal. Treatment-related adverse events are relatively frequent and reactions requiring epinephrine appear to occur more often when compared to the practice of dietary avoidance [22]. There have also been isolated reports of new eosinophilic gastrointestinal disorders developing in individuals receiving OIT [23]. Lastly, nearly all studies have excluded patients with severe food-induced anaphylaxis, which is the population in most need of effective interventions. Given these limitations, it is not surprising that two recent Cochrane reviews of OIT for milk [24•] and peanut [25] allergies found insufficient evidence to support its clinical implementation, which is in accordance with current clinical guidelines [1]. With the many uncertainties surrounding the long-term efficacy and safety of OIT and SLIT, we share the opinion of other leading researchers that food immunotherapy remains in a state of clinical equipoise [26•].

Strategies for enhancing food immunotherapy

OIT and SLIT are promising treatments for FA, but it is unlikely that current protocols will be effective for all patients, especially those with a more severe phenotype. The next generation of food immunotherapy should seek to further increase the likelihood of developing long-term tolerance while minimizing adverse events associated with treatment. Three general strategies for improving immunotherapy include firstly modifying the immunological characteristics of the food allergen, secondly adjunct treatment with immunomodulatory agents, and lastly utilizing alternative antigen delivery schemes (Figure 1). A variety of interventions that address these areas have been proposed, many of which are already being tested in the clinical setting.

Modification of food allergens

Altering the molecular structure of food allergens to decrease their allergenicity, while maintaining their immunotherapeutic effect, is an attractive approach for improving the safety of immunotherapy. Extensive heating is a straightforward method for changing the allergenicity of some foods (e.g. milk and eggs), as it results in the loss of conformational epitopes recognized by IgE [27]. A large proportion of patients allergic to milk or eggs tolerate the foods in baked forms [28,29], and two recent studies suggest that routine consumption of extensively heated food allergens can accelerate allergy resolution. In the first study, milk-allergic subjects able to add baked milk to their diets were 16-fold more likely to develop complete milk tolerance compared to a matched observational cohort that avoided all milk products [30•]. Similar results were observed for egg-allergic patients who incorporated baked egg into their diets [31]. The use of heat-denatured allergens in OIT and SLIT could lead to fewer treatment-related adverse events, a notion that requires further investigation.

A more targeted approach for decreasing allergenicity is to genetically alter the immunodominant B cell epitopes. Point mutagenesis of specific amino acids within the

major peanut allergens Ara h 1–3 substantially decreased recognition when blotted with pooled peanut-specific IgE from allergic human volunteers [32]. Treatment of peanut-sensitized mice with heat-killed *Escherichia coli* expressing these engineered recombinant peanut allergens was protective against peanut-induced anaphylaxis [33]. On the basis of these encouraging animal studies, a phase I clinical trial was performed using rectal administration of a similar product. Unfortunately, 5 of 10 subjects had to withdraw from the study due to treatment-related adverse events [34]. Successfully engineering recombinant hypoallergenic food allergens for use in immunotherapy trials might require individualized approaches, a labor-intensive process that may limit clinical feasibility.

Adjunct therapy with immunomodulatory agents

Altering the immune environment to prevent Th2-mediated responses directed against immunotherapeutic agents is another approach for reducing adverse events during OIT and SLIT. In this regard, agents that inhibit IgE-mediated signaling pathways, such as the monoclonal antibody omalizumab, could improve the safety of food immunotherapy. Anti-IgE monotherapy for peanut allergy could increase the sensitivity threshold for a subset of patients [35], but was associated with an unacceptably high rate of severe adverse reactions in a recent phase II trial [36]. Therefore, using omalizumab as an adjunct to OIT or SLIT may be a safer and more effective strategy. Accordingly, Nadeau and colleagues investigated the utility of using omalizumab to facilitate desensitization in a small group of children undergoing high-dose milk OIT [37•]. After 9 weeks of pretreatment with omalizumab, 9 of the 11 patients initially enrolled were able to rapidly reach maintenance dosing with minimal adverse events. Several small trials combining omalizumab treatment and OIT for other food allergens are currently underway ([ClinicalTrials.gov](https://clinicaltrials.gov), NCT01510626, NCT01157117, NCT00932282).

An herbal formulation (FAHF-2) containing nine herbs used in traditional Chinese medicine is being evaluated as a possible treatment for FA. In preclinical studies, FAHF-2 had multiple immunomodulatory effects and protected mice from peanut-induced anaphylaxis [38,39]. Subsequent phase I trials in patients with FA have shown FAHF-2 to be well tolerated with minimal side effects [40,41]. Whether FAHF-2 would have synergistic effects when combined with OIT or SLIT is currently unknown.

Other immunomodulatory strategies for improving FA immunotherapy include the use of Th1-promoting adjuvants [42], helminth therapy [43], and monoclonal antibodies directed against cytokines associated with Th2-mediated inflammation [44]. While it is possible that biological agents alone will be efficacious treatments for FA, combining them with allergen-specific immunotherapy protocols may be a more effective approach that warrants further investigation.

Alternative allergen delivery strategies

It is possible that the gut mucosa in FA patients is fundamentally altered to promote allergic responses against ingested antigens, and therefore delivering allergens to other tissues may prove more effective for generating tolerance. Accordingly, epicutaneous immunotherapy (EPIT), which involves the application of an allergen-loaded patch on intact skin, was shown to modestly desensitize milk allergic patients in a small RCT [45]. These findings have prompted further clinical inquiries into the efficacy of EPIT for the treatment of FA ([ClinicalTrials.gov](https://clinicaltrials.gov), NCT01170286, NCT01197053).

The use of nanoparticles for allergen delivery is a developing area that could be directly applicable to OIT and SLIT. Nanoparticles can be designed to target dendritic cells, which are important for inducing regulatory T cells. They can also be engineered to provide a

sustained release of antigen, thus obviating the need for daily dosing [46]. Nanoparticles containing peanut proteins were recently generated and tested in mice, and induced a greater Th1 response than protein alone [47]. These preliminary findings will hopefully lead to more extensive studies regarding the use of nanotechnology for allergen immunotherapy.

Conclusions

The past decade has been an exciting period in the area of FA research, as studies regarding OIT and SLIT provide hope that an effective therapy for FA is within reach. Given the encouraging results from small clinical trials, it is understandable why some are advocating strongly for immediate implementation of OIT and SLIT for the treatment for FA. However, definitive evidence of safety and efficacy are lacking with the current immunotherapeutic strategies for FA, and more research is needed before these therapies can be offered to patients in routine clinical practice. The next generation of food immunotherapies will hopefully build upon the early success of OIT and SLIT, and help make an emerging treatment into the standard of care.

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•• of outstanding interest

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Figure 1.

Strategies for improving food immunotherapy. Modification of food allergens to reduce recognition by IgE can be accomplished by extensive heating or molecular alteration of immunodominant epitopes. Incorporation of food allergens into nanoparticles or epicutaneous delivery of antigen could improve immunotherapy efficacy while reducing treatment-associated adverse reactions. Finally, adjunct use of immunomodulatory agents may prevent allergic responses mediated by allergen-specific T helper (T_H) cells, and promote tolerance through induction of T cell anergy or development of regulatory T cells.

Table 1

Summary of randomized controlled trials for OIT and SLIT

Study [Ref]	Type of therapy	Food	Subjects	Clinical outcomes	Safety/compliance	Comments
Skripak 2008 [9]	OIT	Milk	20 (ages 6–17 years) - 13 OIT - 7 placebo	100-Fold increase in median threshold dose with OIT; placebo unchanged Desensitization ^a : - Full: 46% - Partial: 46%	Symptoms with 45% of OIT doses Epinephrine given 4 times for OIT 8% dropout rate	Excluded subjects with severe FA Tolerance ^b not assessed
Pajno 2010 [48]	OIT	Milk	30 (ages 4–13 years) - 15 OIT - 15 placebo (soy)	Desensitization: - Full: 67% - Partial: 7%	OIT-related symptoms in 80% of subjects; 30% stopped treatment Epinephrine given 2 times for OIT 10% dropout rate	Weekly dose increases in clinic (no daily home dosing) Patients not blinded to treatment Tolerance not assessed
Varshney 2011 [12•]	OIT	Peanut	28 (ages 2–10 years) - 19 OIT - 9 placebo	OIT median threshold dose 18-fold higher than placebo Desensitization: - Full: 84%	Symptoms with 1.2% of OIT doses during buildup Epinephrine given 2 times for OIT (1 time for placebo) 16% dropout rate	Excluded subjects with severe FA No baseline OFC performed Tolerance not assessed
Burks 2012 [6••]	OIT	Egg	55 (ages 5–11 years) - 40 OIT - 15 placebo	OIT median threshold dose 100-fold higher than placebo Desensitization: Full: 55% Tolerance: 28%	Symptoms with 25% of OIT doses No epinephrine given 12.5% dropout rate (during blinded phase)	Excluded subjects with severe FA No baseline OFC performed
Keet 2012 [16•]	OIT/SLIT	Milk	30 (ages 5–11 years) - 10 SLIT - 20 OIT (high and low dose)	SLIT desensitization: - Full: 20% Partial: 80% OIT desensitization: - Full: 85% - Partial: 5% Tolerance: - SLIT: 10% - OIT: 40%	11-fold higher rate of systemic reactions with OIT vs. SLIT Epinephrine given 2 times for SLIT and 4 times for OIT Dropout rates: - SLIT: 0% - OIT: 20%	Excluded subjects with severe FA Not powered to detect differences between high and low dose OIT
Enrique 2005 [18]	SLIT	Hazelnut	23 (ages 19–53 years) - 12 SLIT - 11 placebo	5-fold increase in median threshold dose for OIT; unchanged for placebo Desensitization: - Full: 42%	Symptoms with 7% of SLIT doses No epinephrine given 4% dropout rate	55% of subjects had oral allergy syndrome High baseline median threshold dose for all subjects Included subjects with history of anaphylaxis Tolerance not assessed
Fernandez-Rivas 2009 [19]	SLIT	Peach	56 (adults, mean age 29 years) - 37 SLIT - 19 placebo	>3-Fold increase in tolerable dose in OIT group, but not significantly different from placebo Desensitization: unable to determine	89% of SLIT subjects had mild symptoms with treatment No epinephrine given 11% dropout rate	At least 60% of patients had oral allergy syndrome Lower SLIT dosing compared to other studies Tolerance not assessed
Kim 2011 [11•]	SLIT	Peanut	18 (ages 1–10 years) - 11 SLIT - 7 placebo	SLIT median threshold dose 20-fold higher than placebo Desensitization:	Symptoms with 12% of SLIT doses No epinephrine given	Excluded subjects with severe FA No baseline OFC performed

Study [Ref]	Type of therapy	Food	Subjects	Clinical outcomes	Safety/compliance	Comments
Fleischer 2013 [17•]	SLIT	Peanut	40 (ages 12–37 years) - 20 SLIT - 20 placebo	unable to determine 18-fold increase in median threshold dose with SLIT; placebo unchanged Desensitization: - Full: 0% - 70% had 10-fold increase in threshold dose	Symptoms with 44% of SLIT doses Epinephrine given once for SLIT 8% dropout rate (during blinded phase)	Tolerance not assessed Excluded subjects with severe FA Tolerance not assessed

^aPartial desensitization defined as significantly increased threshold dose during posttreatment OFC but total consumption of <5 g of food protein; patients able to consume 5 g of food protein during posttreatment OFC are considered fully desensitized.

^bTolerance defined as ability to pass an OFC after ceasing therapy for 4 weeks.