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Future therapies for food allergy

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Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; OIT, oral immunotherapy; SLIT, sublingual immunotherapy

Food allergy affects 3.9% of US children and is increasing in prevalence. The current standard of care involves avoidance of the triggering food and treatment for accidental ingestions. While there is no current curative treatment, there are a number of therapeutic strategies under investigation. Allergen specific therapies include oral and sublingual immunotherapy with native food protein as well as recombinant food proteins. Allergen non-specific therapies include a Chinese herbal formula (FAHF-2) and the use of anti-IgE monoclonal antibody therapy. Although none of these treatments are ready for clinical use, these therapeutic strategies present promising options for the future of food allergy.

Introduction

Food allergy affects approximately 3.9% of US children with a reported increase in prevalence of 18% from 1997–2007.[1] Other allergic conditions such as asthma, allergic rhinitis and atopic dermatitis have increased in prevalence over the same time period.[2,3] The explanation for this rise in allergic disease is unknown and may reflect a combination of genetic and environmental factors. The major allergenic foods that account for about 90% of food allergies in the US are milk, egg, peanut, tree nuts, soybeans, wheat, fish and shellfish.[4]

Although there are different forms of food allergy, this review will focus specifically on IgE mediated food allergy, which results in symptoms immediately after ingestion of the offending antigen. IgE mediated food allergy is thought to result from a defect in oral tolerance, although the mechanism of this breakdown is not completely understood. Oral tolerance is the process by which the mucosal immune system suppresses immunity to benign allergens encountered in the gastrointestinal tract.[5] This process involves multiple mechanisms including deletion of antigen-specific T cells, induction of anergy (non-response) in antigen-specific T cells and production of regulatory T cells (Tregs).[6,7]

With a defect in oral tolerance, patients develop a Th2-predominant allergen-specific immune response with the production of immunoglobulin IgE antibodies specific to the food allergen. Th2 cells secrete interleukin (IL)-4 and IL-13, which encourage the production of IgE by B cells. Once the offending food allergen is ingested, IgE bound to mast cells in mucosal tissues can recognize the antigen and degranulate, releasing mediators such as histamine, leukotrienes and prostaglandins. These mediators lead to allergic symptoms, including anaphylaxis.

Patients with food allergy remain at risk of a significant life-threatening reaction if the antigen is ingested. While many children with egg, milk, wheat and soy allergy will outgrow their food allergy, the majority of patients affected with peanut or seafood allergy will not. Without a curative treatment, the current standard of care focuses on strict avoidance of the offending dietary protein. Despite education on avoidance of triggering foods protein, many patients will still have accidental ingestions. Due to this risk of accidental ingestions, patients are educated on how to manage anaphylactic reactions and are instructed to carry epinephrine at all times. Unfortunately, food allergy is the most common cause of anaphylaxis evaluated in the emergency department[8] and occasionally results in fatalities with more than 90% of deaths in the US caused by reactions to peanuts or tree nuts.[9,10] Given the increasing prevalence of food allergy and the high risk for accidental reactions, there has been a focus on new therapies to treat food allergic patients.

The use of allergen specific and allergen non-specific therapies has been explored recently to treat food allergy patients and reduce the risk of life threatening reactions. Allergen specific therapies rely on either gradually increasing exposure to an unmodified allergen or administration of a modified allergen in an attempt to induce oral tolerance. Non-specific therapies rely on broad immunologic changes to decrease the pathogenic response to the allergen.

Allergen Specific Therapies

Immunotherapy for food allergy. Allergen immunotherapy involves the treatment of allergic disease by modulating the immune response.[11] Most trials have assessed desensitization, a temporary loss of reactivity to the protein due to continuous exposure. Few studies have demonstrated tolerance, which is defined as a permanent immunologic non-response to the offending allergen and can only be assessed by removing the allergen from the diet for a period of time prior to challenge. In this context, the ultimate goal of immunotherapy for food allergy is to achieve a permanent state of tolerance.

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Subcutaneous immune therapy. Subcutaneous immunotherapy (SCIT) has been used for over a century and is a successful therapeutic approach for treatment of hay fever and hymenoptera sensitivity.[12-14] Treatment is associated with an initial increase in allergen-specific IgE followed by eventual decrease and an increase in allergen-specific IgG4. The first report of successful SCIT for food allergy was published in 1930. Interestingly, no new reports appeared until the early 1990s when SCIT for peanut allergy was reported. In that study, three treated subjects displayed a 67–100% decrease in symptoms induced by double-blind, placebo-controlled food challenge (DBPCFC).[15] These subjects also demonstrated a 2–5-log reduction in end-point skin prick test reactivity to peanut. One placebo-treated subject died of anaphylaxis following accidental administration of peanut extract due to a pharmacy formulation error, resulting in premature termination of the study.

In another study, six subjects were treated up to a maintenance dose of 0.5 ml of 1:100 wt/vol peanut extract and six were followed as an untreated control group for 12 mo.[16] At the end of 12 mo, the six treated subjects demonstrated increased tolerance to double-blind, placebo-controlled peanut challenge and decreased skin prick test reactivity to peanut. The untreated controls had no improvement in those parameters. Significant adverse events were recorded in the treatment group even during maintenance injections, suggesting that this may be an unfavorable treatment approach.

Oral immunotherapy. Oral immunotherapy (OIT) for food allergy dates back to 1908, when Schofield successfully used capsules of increasing amounts of raw egg to desensitize a 13 year-old boy with egg allergy.[17] Subsequently, several studies using similar oral immunotherapy methods provided evidence that successful desensitization to milk, egg, fish and fruit is possible.[18,19]

Recently, OIT has been used for milk, egg and peanut allergy (**Table 1**). These trials have used widely differing dosing regimens and variable outcome criteria. Typically, oral immunotherapy protocols begin with an initial escalation day consisting of increasing doses of the food allergen (mixed with a food vehicle) until the subject has symptoms. Following the initial escalation day, the patient is begun on a therapy using the previously determined highest tolerated dose with a build-up period of dosing consisting of increasing doses of the offending allergen protein. These build-up doses are typically given for the first time in a clinical setting with home dosing continuing daily until the next increased dose. Once the subject has reached the goal maintenance dose for the trial, this daily dose is continued for a period of time, usually several weeks to months, followed by a DBPCFC.

Cow's milk OIT. Following Schofield's report, interval trials were conducted examining the efficacy of OIT in randomized clinical trials but the first double-blind, placebo-controlled report of OIT was not until 100 years following Schofield's report when Skripak et al. randomized 20 children to daily cow's milk or placebo therapy for a total of 13 weeks of treatment.[20] An entry DBPCFC established a threshold of reactivity, which was then compared with a post-therapy challenge to assess clinical desensitization. Subjects in the milk OIT group were able to tolerate 50 times higher doses of milk protein at the conclusion of the study, including patients initially on placebo treatment who were offered open label treatment following their post-treatment challenge. Milk specific IgE levels did not change significantly in either the treatment or placebo groups, however milk specific IgG4 levels did increase on active treatment. Food specific IgG_4 subclass antibodies are proposed to have a protective or blocking function.[21,22] A recent meta-analysis focused on OIT for IgE-mediated cow's milk allergy evaluated five randomized controlled trials and five observational studies.[23] Two hundred eighteen patients in the randomized controlled trials demonstrated the likelihood of tolerating 150 mL of cow's milk and the ability to eat dairy and milk-containing products was ten times higher in the OIT group as compared with elimination diet alone (95% CI: 4.1–24.2) suggesting efficacy in desensitizing patients through the use of OIT.

Egg OIT. Egg OIT published studies have been largely limited to open label clinical trials. In an open, uncontrolled study of egg OIT in children with egg allergy, seven children underwent a 24 mo egg OIT protocol involving modified rush, build-up and maintenance phase dosing consisting of 300 mg of powdered egg white.[24] All patients were able to tolerate significantly more egg protein at the post-therapy challenge. However, after following an egg restricted diet for 3–4 mo at the completion of the study, only two out of four patients were able to tolerate the doses previously tolerated at the completion of the study suggesting tolerance was obtained in only two of these patients.

Based on the results of this proof-of-concept egg OIT trial, the authors hypothesized that further dose escalation would improve OIT outcomes. Six patients completed a protocol with a maintenance phase consisting of conditional step-wise increases every 4 mo up to a maximum of 3,600 mg of egg white protein.[25] Maintenance doses were only increased if egg specific IgE levels were found to be greater than 2 kU/L. Once the egg specific IgE level was below 2 kU/L, a DBPCFC was performed. All six patients demonstrated a decrease in skin prick test wheal diameter and egg specific IgE levels. All six patients passed a DBPCFC one month after stopping OIT. None of the egg OIT studies included randomization or a placebo control, limiting interpretation of the results, as it is possible that these children naturally outgrew their allergy.

A multi-center randomized, double-blind, placebo-controlled trial of egg OIT is currently ongoing (Oral Immunotherapy for Childhood Egg Allergy; clinicaltrials.gov #NCT00461097) through the Consortium of Food Allergy Research. Following an initial escalation, build-up and maintenance (2000 mg of egg white) phase, 30/40 (75%) patients were desensitized at 22 mo.[26] Egg OIT was discontinued for 6–8 weeks and another OFC was conducted. 11/40 (27.5%) patients passed this OFC and were considered tolerant. A smaller skin prick test size at 22 mo was correlated with desensitization and tolerance in this study.

Peanut OIT. Following preliminary open label OIT trials, a double-blind, placebo-controlled study was conducted at Duke University Medical Center and Arkansas Children's Hospital consisting of 28 children with peanut allergy.[27] This protocol consisted of initial escalation day, a build-up dosing phase for 44 weeks and maintenance dosing phase of 4000 mg for 1 mo

Table 1. Results of completed clinical studies for therapy for IgE mediated food allergy

Author	Antigen/treatment	Type of therapy	Type of trial	Clinical outcomes	Immunologic outcomes in active treatment group	Reference
Skripak	milk	OIT	randomized, double-blind, placebo controlled trial	50x increase in milk protein tolerated at conclusion of study	no change in IgE; ↑ IgG4	20
Buchanan	egg	OIT	open, treatment only	All patients able to tolerate higher amounts of egg protein; 2/4 patients reacted to subsequent challenge 3 mo off treatment	no change in IgE; ↑ IgG	24
Vickery	egg	OIT	open, treatment only	All patients passed DBPCFC one month after stopping OIT	↓ IgE and skin prick test diameter	25
Varshney	peanut	OIT	randomized, double-blind, placebo controlled trial	All patients on OIT able to tolerate maximum dose (5000mg) vs. median cumulative dose of 280 in placebo patients	↓skin prick test size, IL-5 and IL-13; ↑ in IgG4 and peanut specific FoxP3 Tregs	27
Enrique	hazelnut	SLIT	randomized, double-blind, placebo controlled trial	Significant increase in mean quantity of hazelnut ingested to provoke symptoms in the treatment group with a non-significant increase seen in placebo group	no change in IgE; ↑ IgG4	30
Kim	peanut	SLIT	randomized, double-blind, placebo controlled trial	Treatment group able to ingest 20x more peanut protein than placebo group	↓ skin prick test size; initial rise in IgE followed by steady decline ; ↑ IgG4	31
Fernandez-Rivas	peach	SLIT	randomized, double-blind, placebo controlled trial	Treatment group able to tolerate significantly higher amount of peach (3–9 fold increase)	↓ skin prick test size, ↑ IgE and IgG4	32
Leung	recombinant humanized monoclonal anti-IgE (Hu-901)	IV infusion	randomized, double-blind, placebo controlled trial	Highest drug dose group with a signficantly higher threshold of sensitivity compared with placebo	n/a	47

followed by the first OFC at week 48. During the DBPCFC, all 16 peanut OIT patients completing the protocol were able to ingest the maximum cumulative dose of 5,000 mg (approximately 20 peanuts). The median cumulative dose tolerated by the nine placebo patients was 280 mg with a range of 0–1,900 mg. The peanut OIT patients showed reductions in SPT size, IL-5 and IL-13 with increases in IgG4 and FoxP3 regulatory T cells while these changes were not seen in patients receiving placebo.

Safety of OIT. In a comprehensive analysis of adverse reactions in one peanut OIT trial, initial escalation day symptoms included upper respiratory tract symptoms (79%) and abdominal (68%) affecting the majority of patients.[28] Symptoms rated as severe only occurred in the cutaneous category although mild and moderate symptoms were common. With escalations, 15% of patients required epinephrine. Reactions associated with build-up doses were less common, occurring in 46% with no patients requiring epinephrine dosing. 3.5% of total home doses of peanut OIT were associated with an adverse reaction including upper respiratory tract symptoms accounting for 1.2% and skin symptoms accounting for 1.1%. Two subjects out of 28 enrolled patients each received epinephrine once during the course of the trial following home doses.

Although asthma has clearly been identified as a risk factor for respiratory reaction,[28] other risk factors for adverse reactions have emerged through the course of OIT studies. Varshney et al. reported on five patterns associated with an increased risk of reaction to previously tolerated dose of peanut OIT including (1) concurrent illness, (2) sub-optimally controlled asthma, (3) timing of dose administration after food ingestion, (4) physical exertion after dosing and (5) dosing during menses.[29] As these risk factors emerged throughout the course of clinical trials, researchers modified their recommendations to address these risk

factors. Although OIT is generally well tolerated, it is important to note that these risks exist and understand that OIT is still under investigation to determine safety and efficacy prior to use in the clinical setting.

Sublingual immunotherapy (SLIT). Sublingual immunotherapy involves the administration of small amounts (micrograms to milligrams) of the allergen extract under the tongue. The first randomized double blind placebo controlled study using sublingual immunotherapy included 22 patients with hazelnut allergy.[30] Although all patients were skin prick test positive to hazelnut, the reported symptoms following ingestion included approximately 55% of patients reporting oral allergy syndrome as opposed to anaphylaxis or urticaria/angioedema. After 8–12 weeks of treatment, DBPCFC resulted in a significant increase in the mean quantity of hazelnut provoking symptoms increase from 2.29 g to 11.56 g in the active group ($p = 0.02$) and a non-significant increase from 3.49 to 4.14 g in the placebo group. Improvements were seen in patients with history of local symptoms as well as those with history of systemic symptoms. Systemic reactions were observed in 0.2% of doses and were only seen with build-up dosing, requiring only antihistamines for control. Local reactions, mostly in the form of immediate oral itching were observed in 7.4% of doses.

In the first double-blind, placebo-controlled trial for peanut allergy, 18 children completed 6 mo of dose escalation and 6 mo of maintenance dosing with 2,000 μg of peanut protein.[31] At the conclusion of the trial, the treatment group was able to ingest 20 times more peanut protein than the placebo group. Decreased skin prick test wheal size was only seen in the treatment group. Peanut specific IgE levels increased steadily over the initial 4 mo and then steadily decreased over the remaining 8 mo and an increase in peanut specific IgG4 levels over 12 mo were seen in the treatment group. Side effects in the treatment group were primarily oropharyngeal (9.3% of doses), which were also seen in the placebo group (1.5%).

Additionally, a randomized double-blind, placebo-controlled SLIT trial was conducted for peach allergy.[32] 49 patients completed the 6 mo SLIT trial (33 on active treatment, 16 on placebo). The active group tolerated a significantly higher amount of peach (3–9 fold increase) with a decrease in SPT and significant increase in peach specific IgE and IgG4. The placebo group demonstrated no significant changes. Side effects consisting of local reactions (mostly oral symptoms) were common in the active treatment group during the build-up phase. Mild systemic reactions were seen in both the active treatment and placebo groups with roughly the same frequency (13.5% in the active group and 16.7% in the placebo group) and subsided spontaneously or with antihistamines.

These positive results suggest successful desensitization with SLIT for three different food allergies. Safety reporting in these three trials reveals SLIT to be a safe therapy with the most common side effect consisting of local oropharyngeal symptoms.

Immunotherapy with pollen allergens. The oral allergy syndrome (OAS) is characterized by an immunoglobulin E (IgE) mediated immediate hypersensitivity reaction limited to the mouth and throat that occurs after ingestion of fresh fruits and vegetables in pollen sensitized individuals. Given that pollen allergen is responsible for the cross reactivity with food allergens in OAS, sublingual and subcutaneous immunotherapy have been tried. Since the early positive case report of fresh fruit tolerance after a year of pollen immunotherapy reported by Kelso et al. many studies have examined the effects of immunotherapy on OAS and the results have been mixed.

Randomized clinical trials of birch pollen immunotherapy in patients with apple allergy suggest that a subset of birch allergic patients with apple allergy show improvement in apple tolerance after SCIT.[34-36] However, one trial of sublingual immunotherapy for birch pollen allergy did not show efficacy for alleviating OAS symptoms.[37] In a small study comparing injection and sublingual forms of immunotherapy for OAS, complete tolerance to raw apple was achieved in two of eight and one of seven patients receiving injection and SLIT, respectively.[38] Also, an increase in the provocative dose was found in three of the SCIT-treated and two of the SLIT-treated patients.

Hence, immunotherapy for treatment of oral allergy syndrome appears to benefit a subset of patients only.

Modified recombinant vaccines. Immunotherapy with modified recombinant proteins is an attractive approach that should reduce the incidence of adverse effects. While these recombinant food proteins retain the ability to generate a T-cell response, they have a reduced IgE binding capacity.[39] The modified food allergens can be combined with bacterial adjuvants to enhance the Th1 and Treg skewing effects and decrease the Th2 effect.

Heat-killed *Escherichia coli* producing engineered (mutated) recombinant peanut proteins have been shown to induce long-term "downregulation" of peanut hypersensitivity in a murine model of peanut allergy.[40]

An ongoing clinical trial at Johns Hopkins University and Mount Sinai Medical Center is evaluating the safety and side effects of a product containing recombinant modified peanut proteins (EMP-123) in healthy and peanut-allergic participants (Peanut Allergy Vaccine Study in Healthy and Peanut Allergic Adults; clinicaltrials.gov #NCT00850668).

Promising allergen specific therapies. Several additional approaches have been evaluated in animal models and are very promising. Synthetic peptides representing T-cell epitopes of food allergens have been shown to induce milder allergic reactions in murine models of peanut allergy and egg allergy.[41,42] Plasmid DNA containing a recombinant peanut antigen (Arah2), was shown to modify the immune system in mice and protect against food allergen-induced hypersensitivity.[43] While both approaches are promising in murine models, safety, optimal dosage and efficacy remain to be determined in humans.

Allergen Non-specific Therapies

FAHF-2. An herbal formula based on traditional Chinese medicine, consisting of nine herbs, has been shown to be an effective treatment in preventing anaphylaxis in murine models of peanut allergy.[44] Mice allergic to peanut treated with FAHF-2 for 7 weeks were challenged post-therapy. After challenge, all sham treated mice developed signs of severe anaphylaxis while no signs of

anaphylaxis were seen in mice treated with FAHF-2. These protective effects continued for up to 6 mo following therapy suggesting a long-term immunologic effect.[44,45] Based on multiple immunomodulatory effects seen, including a dose dependent decrease in Th2 cytokine production with an increased interferon-γ, it is thought to be a general immunosuppressive agent.[45] Based on these promising results, FAHF-2 is now in clinical trials, phase II in patients aged 12–45 y old with allergies to nuts, fish and/or shellfish (Therapeutic Effect of Chinese Herbal Medicine on Food Allergy (FAHF-2); clinicaltrials.gov #NCT00602160).

Anti-IgE therapy. Recombinant humanized monoclonal anti-IgE treatment has been suggested as a therapy for food allergy. A double-blind, randomized trial was performed in 84 peanut allergic patients in which patients either received Hu-901 or placebo once a month for four months.[46] Patients were administered varying doses of the drug with results indicating the highest dose (450 mg) elicited the greatest increase in median dose tolerated from 178 mg to 2.8 g of peanut protein. In this group, 25% of the patients had improvement whereas 25% had no change in their reactivity, suggesting variability in response to anti-IgE therapy. Incidences of local and systemic reactions were similar between the active treatment and placebo group. Hu-901 was not selected for further clinical development; however studies with an alternative humanized anti-IgE molecule, omalizumab (Xolair; Genentech), have been initiated.

A controlled trial of omalizumab in patients with peanut allergy was terminated because of 2 severe anaphylactic reactions that occurred during the initial peanut DBPCFC.[47] Twenty-six patients had been randomized 2:1 to omalizumab or placebo and completed 24 weeks of therapy followed by a second DBPCFC by the time the study was terminated. The patients in the omalizumab group had a greater increase in tolerability of peanut protein than the placebo group ($p = 0.054$).

Combining omalizumab and OIT has been initiated as a therapy for cow's milk allergy and peanut allergy (Omalizumab with Oral Food Immunotherapy in Children and Adults With Food Allergies Open Label Safety Study in a Single Center; clinicaltrials.gov #NCT01510626 and Peanut Oral Immunotherapy and Anti-Immunoglobulin E (IgE) for Peanut Allergy; clinicaltrials.gov #NCT00932282). This combination has been proposed to decrease adverse reactions to immunotherapy and improve outcomes. No data from controlled clinical trials has been published to date.

Markers of Efficacy

Investigators conducting food allergy trials have studied various serum markers for a biomarker for efficacy of treatment. With desensitization, serum allergen specific IgE levels decline in some studies, yet rise in others. Antigen specific IgG4 levels tend to increase with desensitization; consistent with their known blocking function,[21,22] however these increases have not yielded cut-off values associated with successful desensitization induction. While antigen specific FoxP3 T regulatory subsets increase with the attainment of tolerance,[48] these levels have not been assessed in many of the food allergy trials. In the studies which evaluate these levels in conjunction with additional immunologic and clinical outcome measures, allergen specific FoxP3 Tregs increase with successful desensitization, suggesting this may be useful marker for efficacy in the future.[27,31] However, this remains a research tool without established values for efficacy. Currently, the gold standard for measure of efficacy is the DBPCFC.

Conclusions

Food allergy is an increasingly prevalent disorder with no curative therapy. Due to the high rate of accidental exposures, there is an urgent need to develop effective and safe therapies. While OIT and SLIT have been studied for several years with encouraging results, we still do not know if they can achieve a permanent state of tolerance. Additionally, side effects may limit the utility of this treatment to the research setting. Other therapies are in the initial stages of investigation but show promise for long-term treatments. As with immunotherapy, safety will continue to be a concern. Currently, the standard of care remains avoidance and immediate access to epinephrine, however these promising therapies give us hope for the future treatment of patients with food allergy.

Disclosure of Potential Conflicts of Interest

Dr. Burks has received grant support from the Food Allergy and Anaphylaxis Network, the National Institutes of Health, and the Wallace Research Foundation; has served on boards for the American Academy of Allergy Asthma and Immunology, Food Allergy and Anaphylaxis Network, US Food and Drug Administration, *Journal of Allergy and Clinical Immunology*, and National Institutes of Health HAI; and has received other support from the Food Allergy Research Project Fund, Food Allergy and Anaphylaxis Network, National Institutes of Health, and the Wallace Research Foundation. Dr. Burks has served as a consultant for ActoGeniX NV, Dannon Co. Probiotics, Intellijet, McNeil Nutritionals, Novartis, Nutricia, Pfizer and Schering-Plough Corp., and owns stock/stock options in Allertein Therapeutics and MastCell. Laurie McWilliams is a Fellow of the Pediatric Scientist Development Program and is supported through a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Dr. Mousallem reported no potential conflicts of interest relevant to this article.

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