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The Current State of Food Allergy Therapeutics

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Abstract

The prevalence of IgE mediated food allergy is an increasing public health concern. The current standard of treatment is strict avoidance of the offending food(s). There are no FDA approved treatments for food allergy. This review will provide an overview of strategies currently under investigation for the treatment of food allergy. The main focus of research has been directed at various forms of immunotherapy, including oral, sublingual and epicutaneous delivery routes. While oral immunotherapy (OIT) has shown the greatest promise for efficacy in terms of amount of protein that can be ingested, it has also demonstrated less tolerability and a less favorable safety profile as compared to sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT), which offers the least protection but has the best safety and tolerability profile. Investigation is also underway for modified antigens that may be used for immunotherapy and for adjuncts that may help facilitate immunotherapy, including biologics such as anti-IgE therapy, and also probiotics. There are also a number of preclinical concepts that are being evaluated to manipulate the antigens and/or the immune system that may one day be translatable to patients.

Keywords

Food allergy, Oral immunotherapy, Sublingual immunotherapy, Epicutaneous immunotherapy, Modified food allergens, Omalizumab, Traditional Chinese Medicine

Introduction

IgE mediated food allergy is an increasing public health concern with a rising prevalence in developed countries¹. The most common food allergies are milk, egg, peanut, tree nuts, wheat, soy, fish, shellfish and sesame. A major area of interest in the field of food allergy is the development of an effective treatment. Currently therapies for peanut, milk and egg allergies are under the most clinical investigation. Food allergies not only significantly impact quality of life for those affected but also create a significant financial burden to patients, families and society². This review will focus on recent research with respect to the treatment of IgE mediated food allergy, including various forms of allergen specific treatments (immunotherapy, modified food allergens, and additional preclinical basic science concepts that may be one day applied clinically), and allergen nonspecific treatments (biologics and traditional Chinese medicine)

Current Treatment

Treatment of food allergy in current clinical practice has been focused on strict avoidance of the offending food(s) and preparedness for as needed treatment in the event of accidental ingestions. The International Collaboration in Asthma, Allergy and Immunology has published a consensus document on food allergy outlining the recommended treatment in the event of accidental exposure with epinephrine and adjunctive treatment, including bronchodilators and antihistamines³. While strict avoidance is the current standard of care, the authors of this consensus document acknowledge the difficulty of maintaining strict avoidance. The majority of children with known IgE mediated food allergy to peanut will experience an accidental ingestion within a five year period⁴. Given the rate of accidental ingestions and the psychosocial and financial burden caused by food allergy, the future of treatment focuses on preemptive medical interventions.

Immunotherapy

Current immunotherapy research is directed at three routes of delivery. The most organic mechanism is oral immunotherapy (OIT), but due to issues with tolerability and safety, other routes are also under investigation, including sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT). Key studies are highlighted in Table 1. As with all forms of immunotherapy, food specific immunotherapy involves administration of increasing doses of the offending food over months and then a maintenance dose for years. Desensitization refers to the ability to tolerate the allergen with continuous exposure. Earlier studies focused on achieving long-term tolerance whereby patients are protected from reactions even after the exposure is discontinued. However, this endpoint has been difficult to achieve and to prove. Current studies are focused on measuring sustained unresponsiveness, whereby immunotherapy is discontinued for a variable amount of time (usually on the order of 1-2 months) and then patients are rechallenged to assess if they maintain their lack of reactivity⁵.

The immunologic mechanisms underlying immunotherapy are still being elucidated. Immunologic changes that have been observed include decreased mast cell and basophil reactivity, decreased levels of specific IgE and increased levels of specific IgG4 and decreased skin reactivity⁶⁻⁸. Some but not all studies have also observed changes in T lymphocytes, including increased T regulatory cells⁸⁻¹⁰. It should be noted that many of the immunologic effects appear to be transient.

OIT takes advantage of the natural route of ingestion for inducing oral tolerance. OIT utilizes the highest maintenance doses and appears to be the most efficacious; however, it is also associated with a greater likelihood of adverse reactions. SLIT employs lower maintenance doses as the volume of allergen that can be held under the tongue is limited. SLIT has an improved safety profile, but appears less efficacious than OIT. EPIT delivers antigen via the skin wherein it activates Langerhans cells and promotes

downregulation of effector cells. EPIT uses the lowest maintenance doses and also has an improved safety profile but appears to be the least efficacious.

Type	Year	Author	Food	Age	Total Subjects	Comments
SCIT ¹¹	1992	Oppenheimer, et al	Peanut	14-43	3	67-100% decreased symptom scores, 13% systemic reactions
SCIT ¹²	1997	Nelson, et al	Peanut	18-56	6	high rate of systemic reactions
OIT ¹³	2003	Patriarca, et al	Milk, egg, other	3-55	59	38/59 completed treatment
OIT ¹⁴	2008	Longo, et al	Milk	5-17	30	27/30 completed treatment
OIT ¹⁵	2009	Jones, et al	Peanut	1-16	39	29/39 completed treatment
OIT ¹⁶	2010	Blumchen, et al	Peanut	3-14	23	14/23 completed treatment
OIT & Probiotic ¹⁷	2015	Tang, et al	Peanut	1-10	62	82% achieved primary outcome
SLIT ⁸	2011	Kim, et al	Peanut	1-11	18	18/18 completed treatment
SLIT ¹⁸	2013	Fleischer, et al	Peanut	12-37	20	14/20 completed treatment
SLIT ¹⁹	2015	Burks, et al	Peanut	12-40	37	follow-up trial 10% desensitized at 3 years
EPI ²⁰	2016	Jones, et al	Peanut	4-25	74	46-48% achieved primary outcome

Subcutaneous Immunotherapy

Although subcutaneous immunotherapy is effective in treating allergic disease due to aeroallergens, efforts at evaluating subcutaneous immunotherapy directed against food allergens were halted due to safety concerns. One early small pilot study was conducted with 3 patients who underwent rush immunotherapy. They demonstrated a 67-100% decrease in symptom scores during double blinded placebo controlled peanut challenges with patients tolerating 8gm of peanut as the final dose of the challenge. However, the rate of systemic reactions with the immunotherapy group was 13.3% (16 reactions in 120 injections)¹¹. This study was terminated early due to a patient in the placebo arm who developed fatal anaphylaxis after accidentally receiving peanut extract. Another small pilot study evaluated 6 patients who underwent rush immunotherapy. Systemic reactions were again common and only 3 out of the 6 patients were able to continue full maintenance doses. These patients passed double blinded placebo controlled peanut challenges again with 8 gm of peanut. Patients who required dose reduction of their injections due to reactions could not tolerate the complete double blinded oral food challenge¹². Although the high rate of

systemic reactions led to waning interest in this form of immunotherapy for food allergy, it should be noted that those who were able to tolerate the therapy were able to tolerate a clinically significant amount of peanut. As we review other forms of immunotherapy, it is important to keep in mind the level of protection that can be derived from each form. Recently there has been some renewed interest in SCIT with recombinant food proteins, including a recombinant fish protein as part of the FAST (Food Allergy Specific ImmunoTherapy project) as discussed below, and a modified aluminum hydroxide adsorbed peanut extract (HAL-MPE1) (NCT02991885).

Oral Immunotherapy

As there have been many recent outstanding reviews on the individual OIT studies^{5,21-24}, we will focus briefly on a general overview of OIT, current challenges and clinical trials that are in progress.

With oral immunotherapy, patients ingest the food on a daily basis in between dose escalations. Of note, there is a wide range of dosing protocols in terms of both the buildup and maintenance phases. For example, in peanut trials, studies have used maintenance doses ranging from one peanut (approximately 200mg) to 17 peanuts²². Furthermore, there have been significant differences in reporting of outcomes, which is likely related to variable definitions used in differing studies, but also due to effects likely being dependent on time on therapy and dose of therapy.

Patients who are able to proceed through these desensitization protocols can oftentimes tolerate significant amounts of the food while on therapy, which would provide significant protection against accidental ingestions. The majority of patients will have some side effects of therapy, especially oropharyngeal symptoms and abdominal pain, but more severe reactions, including anaphylaxis occur. Side effects, especially gastrointestinal, often limit a patient's ability to achieve the target maintenance dose with studies reporting that up to 30% of patients fail to complete desensitizations²⁵. Furthermore, rates of sustained unresponsiveness have been lower^{6,26,27}. The optimal duration of immunotherapy is unknown but it is likely that treatment of longer duration promotes sustained unresponsiveness⁶.

Another key issue in food allergy immunotherapy is that approximately 30% of children are allergic to more than one food. A 2014 study evaluated OIT in up to five food allergens and found that while patients on multiple foods took longer to achieve an equivalent maintenance dose as single food OIT, they had a similar rate of reactions as compared to patients on peanut alone. There are ongoing clinical trials evaluating OIT for multiple foods (clinicaltrials.gov), including a trial evaluating the efficacy of omalizumab as an adjunct (NCT02643862), and a trial with Chinese herbal therapy and omalizumab (NCT02879006).

Oral immunotherapy has largely focused on trials for peanut, cow's milk and egg. There are multiple ongoing clinical trials for other allergenic foods (clinicaltrials.gov), including walnut (NCT01546753), hazelnut (NCT03048149), wheat (NCT01980992).

OIT with Probiotics

OIT with probiotics as an adjuvant has been evaluated. A double-blind, placebo-controlled randomized trial of *Lactobacillus rhamnosus* and peanut OIT was conducted in 62 children with peanut allergy¹⁷. The primary outcome was possible sustained unresponsiveness as evaluated by passing a 4gm peanut oral challenge 2 to 5 weeks after stopping OIT. Children were treated for approximately 18 months. 82.1% of patients in the OIT with probiotics group achieved the primary outcome as compared to 3.6% in the placebo group ($p = <0.001$). 89.7% of patients who received probiotics with OIT were successfully desensitized as compared to

7.1% of patients who received placebo ($p < 0.001$). Patients treated with OIT with probiotics also had decreased skin prick tests, lower peanut specific IgE levels and increased peanut specific IgG4 levels. Although this trial demonstrated efficacy of OIT with probiotics as compared to placebo, future trials will need to address the added value of probiotics with OIT as compared to OIT alone.

Sublingual Immunotherapy

SLIT delivers the antigen under the tongue in a liquid form. As with other forms of immunotherapy, patients receive gradually escalating doses until a maintenance dose is achieved. Dosing and thus efficacy is limited by the volume of liquid that can be held in the small space sublingually. The lower dosing does have the advantage of an improved safety and tolerability profile over OIT. SLIT is currently used for environmental allergen induced allergic rhinitis.

SLIT for the treatment of food allergy has largely focused on peanut, although other foods studied include milk and hazelnut as well as peach and kiwi. A double-blind, placebo-controlled study evaluated peanut SLIT vs. placebo for 12 months in 18 children⁸. The treatment group could tolerate 20 times more peanut protein than the placebo group with a median dose of 1710 mg as compared to 85mg ($p = 0.011$). SLIT was safe and relatively well tolerated; main side effects were largely oropharyngeal.

A randomized, double-blind, placebo-controlled study evaluated 40 patients comparing peanut SLIT vs. placebo¹⁸. After 44 weeks, 14 out of 20 patients who received active treatment were considered responders (defined as being able to consume 5gm of peanut powder or a 10-fold increase in the amount of peanut powder as compared to baseline). 3 out of 20 patients who received the placebo were considered responders. The active treatment group had a successfully median consumed dose that increased from 3.5 to 496 mg at 44 weeks and this increased further to 996 mg at 65 weeks.

A three year follow up for this trial showed that 50% of patients had discontinued therapy¹⁹. 4 out of 37 (10.8%) patients were desensitized to 10 gm of peanut powder, and these patients achieved sustained unresponsiveness as measured by an Oral Food Challenge (OFC) after 8 weeks off SLIT. There were no severe reactions or episodes requiring epinephrine.

OIT vs. SLIT

There have been two randomized studies that have compared SLIT vs. OIT. One study evaluated milk SLIT vs. milk SLIT followed by OIT with 60 weeks of maintenance therapy in 30 patients²⁸. 14 out of 20 patients who received OIT passed an OFC with 8gm of milk as compared to 1 out of 10 patients who received SLIT ($p = 0.002$). Patients who received OIT were more likely to have systemic adverse events as compared to patients who received SLIT.

Another double-blinded, placebo-controlled trial evaluated peanut SLIT vs. peanut OIT²⁹. SLIT maintenance dose was 3.7mg and OIT maintenance dose was 2000mg during a 12-month trial. 21 patients were initially enrolled but 5 discontinued therapy. All patients exhibited at least a 10-fold increase in the amount of peanut protein they could tolerate as compared to baseline. The OIT group demonstrated a much greater magnitude of change at 141-fold increase as compared to the SLIT group who had a 22-fold increase. Again, the OIT group were more likely to have more severe reactions as compared to SLIT.

Epicutaneous Immunotherapy

EPIT delivers the offending antigen via a patch through the skin. Langerhans cells that reside in the skin capture the antigen and present it to T cells in their respective regional lymph node with the goal of directing a regulatory immune response³⁰. EPIT delivers even smaller dosages of the antigen than SLIT. Furthermore, as patients are not ingesting the antigen as part of therapy, efficacy can only be assessed with oral food challenges.

Overall, EPIT appears to be a relatively safe form of immunotherapy. A double-blind, placebo-controlled pilot study of EPIT for cow's milk allergy evaluated safety in 19 patients. The majority of adverse events were local skin reactions at the patch site. Reactions were mild and did not interrupt treatment. A randomized, double-blind, placebo-controlled study of EPIT for peanut evaluated safety in 100 patients³¹. Non-localized adverse events occurred in about half of all patients in the two groups--42/80 (52.5%) of patients in the active group reported at least one non-local adverse event as compared to patients in the placebo group (45%; 9 of 20 patients). There were no anaphylactic events and no patients required epinephrine. Patients in the active group did report more local adverse reactions. 84% of patients in the active group experienced at least one local reaction compared to 60% in the placebo group ($p = 0.021$; relative risk 1.4, 95% CI 0.99-2.08).

A recent multicenter, double-blind, randomized, placebo-controlled study evaluated EPIT for the treatment of peanut allergy²⁰. This study included 74 patients. Patients were randomized to placebo or one of 2 doses of peanut patch (100 or 250 μ g). Patients were treated for 52 weeks. The primary outcome was passing an oral food challenge of 5044mg or an ability to tolerate a 10-fold or greater increase as compared to baseline. 48% of patients who received the higher dose patch and 46% of patients who received the lower dose patch achieved the primary outcome as compared to 12% of the patients who received placebo ($p = 0.003$ and $p = 0.005$, respectively). Patients in the lower dose patch group could tolerate 43mg more of peanut protein at the end of the trial and patients in the higher dose patch group could tolerate 130mg more of peanut protein as compared to 0mg in the placebo group ($p = 0.014$ and $p = 0.003$, respectively). They also found that the treatment was more efficacious in younger children (age 4-11 compared to >11 years). The patch was found to be relatively safe and recapitulated prior studies that demonstrated the majority of adverse reactions were local and mild. 79.8% of patients who received an active patch reported reactions as compared to 14.4% of patients who received placebo. There were no anaphylactic reactions.

Overall, epicutaneous immunotherapy appears to offer a better tolerability and safety profile as compared to other forms of immunotherapy with the majority of adverse reactions being local skin reactions. However, thus far it also appears to provide a lower relative degree of protection in terms of amount of ingested protein tolerated.

Perhaps after these individual therapies, OIT, SLIT and EPIT, are characterized and evaluated as monotherapy, studies will evaluate them in sequence. EPIT seems to be the most well tolerated and perhaps can be used in patients who did not otherwise tolerate OIT or SLIT; if EPIT provides enough efficacy then perhaps they would subsequently be able to better tolerate OIT or SLIT.

Intralymphatic Immunotherapy

Intralymphatic immunotherapy is in the earliest stage of development. It has largely been studied with respect to aeroallergens where there have been conflicting results regarding efficacy³²; however, some studies have been promising and studies are ongoing. Intralymphatic immunotherapy has not yet been applied to food allergy.

Baked Milk and Egg

Ingestion of extensively heated cow's milk and egg products has shown promising results for children with milk and egg allergies, respectively. Studies suggest that 70-75% of children who are milk or egg allergic can tolerate baked forms of these proteins³³. Heating these proteins is believed to change the epitopes recognized by specific IgE through denaturation³⁴. Furthermore, interactions with a food matrix is also thought to alter the allergenicity of these proteins^{35,36}.

Previous studies have demonstrated that children who are able to tolerate baked milk or egg are more likely to develop tolerance to regular cow's milk and egg^{37,38}. A study of 65 cow's milk allergic patients who tolerated and consumed baked milk regularly were 16 times more likely to develop tolerance to regular milk as compared to those who strictly avoided milk³⁹. A study of 70 egg allergic patients who tolerated and consumed baked egg regularly were 14.6 times more likely to develop tolerance to regular egg as compared to patients who strictly avoided egg. Furthermore, the baked egg consuming group developed tolerance to regular egg in a shorter interval at 50 months as compared to 78.7 months⁴⁰.

Baked milk and baked egg therapy appears to be largely well tolerated amongst those who demonstrate their tolerance with physician supervised oral food challenges. There have been reports of patients who initially tolerated the baked oral food challenge but then developed symptoms at home with consumption of baked products, including one patient who required epinephrine⁴¹. Few patients have also reported mild oral and abdominal symptoms at home^{39,42,43}. In some cases, there was concern about whether home baked products were adequately cooked, which highlights the importance of adequate guidance regarding the degree of heating required at home.

The risk in baked milk and baked egg therapy largely lies in the initial oral food challenge to assess tolerance of these baked products as studies have reported anaphylaxis requiring epinephrine during these initial challenges⁴².

Modified Food Allergens

Standard immunotherapy involves administration of whole allergenic extracts. Given the high rate of adverse reactions with food allergy immunotherapy, there has been interest in the development of modified food allergens and peptides for immunotherapy.

Work has been done evaluating whether sugar modified antigens (bovine serum albumin bearing 51 molecules of mannoside; Man₅₁-BSA) may induce oral tolerance in a mouse model⁴⁴. Administration of Man₅₁-BSA decreased the anaphylactic response by targeting a C type lectin receptor, SIGNR-1, which conditions dendritic cells in the lamina propria and favored generation of CD4+ type 1 regulatory like cells expressing IL-10 and IFN- γ . Another study employed a similar approach and evaluated glycosylated forms of ovalbumin⁴⁵. They found that treatment with these modified antigens decreased specific IgE and clinical signs after oral challenge. They also found a decrease in maturation and uptake by DCs and an increase in the percentage of T regulatory cells.

Peptide Immunotherapy

Peptides are also being researched for allergen specific immunotherapy. While these peptides contain T cell epitopes of the major allergens, they have a decreased capacity to cross link and activate IgE. This design will hopefully translate into better safety profiles.

Most of the work thus far has been directed at peanut. One study generated Ara h 2 (a major peanut component) specific CD4+ T cell lines from peripheral blood mononuclear cells (PBMCs) of peanut allergic patients⁴⁶. They identified 5 dominant CD4+ T cell epitopes and identified 3 short peptide variants that demonstrated HLA binding but not peanut IgE binding and could be used to target T cells for

immunotherapy. This group also identified Ara h 1 peptides that targeted specific T cells employing a similar strategy⁴⁷. Another study evaluated computer based predictive algorithms and in vitro analysis to identify Ara h 2 candidate peptides again using PBMCs from peanut allergic individuals. They identified 4 dominant regions of Ara h 2 that could serve as candidates for peptide immunotherapy. A similar study identified 4 Ara h 1 peptides as potential immunotherapy candidates⁴⁸.

A recent study showed the potential for a peanut peptide derived from Ara h 2 to be conjugated to a carrier derived from *Lactobacillus buchneri* to be used therapeutically⁴⁹. Although this fusion protein was recognized by IgE, it did not activate sensitized rat basophil leukemia cells.

While peptide research has largely been investigated in peanut, there has been interest in the search of relevant peptides in other food allergies. There has been evidence in milk allergy that hydrolyzed β -Lactoglobulin (β Lg) contains the necessary T cell epitope needed to be a novel candidate for peptide based oral immunotherapy⁵⁰. A recent pilot study evaluated oral immunotherapy with hydrolysed egg in children⁵¹. Although a 6-month treatment course in a small number of patients was not enough to demonstrate a statistically significant difference in the proportion of patients who became tolerant to egg, they found that patients treated with hydrolysed egg demonstrated increased specific IgG4 and decreased basophil activation as compared to patients treated with placebo, suggesting a trend toward tolerance.

Murine work in shellfish allergy has identified 6 immunodominant T cell epitopes of tropomyosin (major shrimp allergen of *Metapenaeus ensis*, Met e 1). Sensitized mice treated with these peptides demonstrated decreased allergic reactions on subsequent challenge and demonstrated a decrease in Th2 associated cytokines and an increase in T regulatory cell response⁵². Additional food specific T cell epitopes that have previously been described include peach, ovomucoid, and tree nuts⁵³.

Heat killed bacteria expressing modified recombinant food proteins

Previous studies have employed modified food proteins in concert with heat killed bacteria in mouse models to evaluate for protective effects. These modified proteins have an altered amino acid that significantly reduces IgE binding to the protein. In one study, peanut allergic mice were treated with heat killed *E. coli* expressing modified peanut proteins, Ara h1, 2, 3, (HKE-MP123) and were then subsequently challenged⁵⁴. Investigators found that the mice treated with HKE-MP123 demonstrated decreased anaphylaxis symptom scores upon challenges as compared to mice treated with sham reagents. They also found significantly reduced IgE levels, decreased expression of Th2 cytokines in the splenocytes of mice who received the highest doses of HKE-MP123, and increased expression of Th1 and T regulatory cytokines as compared to the sham group.

This group also studied peanut allergic mice treated with modified Ara h 1, 2, 3 proteins administered with heat killed *Listeria monocytogenes* as an adjuvant (HKLM-mAra h 1-3)⁵⁵. They found that mice treated with HKLM-mAra h 1-3 had decreased anaphylaxis symptom scores upon subsequent challenge as compared to mice in the sham treatment group as well as compared to mice who were treated with m Ara h1-3 alone. They similarly found decreased expression of Th2 cytokines in the splenocytes of mice who received HKLM-mAra h1-3, and increased expression of Th1 cytokines.

A phase 1 trial evaluated the safety of rectally administered modified Ara h 1, 2, 3 protein encapsulated in heat and phenol killed *E. coli*⁵⁶. Ten peanut allergic adults received weekly dose escalations for 10 weeks to a maximum of 3,063 micrograms and then biweekly administrations for 6 weeks. Five patients were unable to complete dosing due to adverse reactions (including 2 episodes of anaphylaxis), 1 patient had mild rectal symptoms and 4 patients tolerated dosing without any symptoms. They found that the patients who reacted had significantly higher baseline peanut and Ara h 2 IgE levels. After treatment, patients had decreased

peanut skin test titration and basophil activation but no changes in total IgE or peanut IgE. Given the high rate of allergic reactions, rectal administration of these modified peanut proteins with killed *E. coli* at this dose was deemed not suitable for further clinical investigation; however, great interest remains in modified allergens.

Research is ongoing for the development of other modified food proteins that can be expressed by *E. coli*, including recombinant mango allergen (Man I 1)⁵⁷ and recombinant hypoallergenic carp parvalbumin (Cyp c 1)⁵⁸ (NCT02017626).

Additional Preclinical Concepts

CpG Coated Peanut Nanoparticles

A mouse model of peanut allergy was used to evaluate peanut OIT in the form of CpG coated nanoparticles with peanut extract⁵⁹. Mice who were treated with these nanoparticles demonstrated lower anaphylactic symptom scores on subsequent oral challenges. Mice also demonstrated decreased T_H2 cytokines and increased IFN- γ levels.

Food allergen coupled cell transfer

Previous studies have shown the ability of antigens chemically linked to cells via 1-ethyl-2-(3'-dimethylaminopropyl)-carbodiimide (ECDI) to promote tolerance in Th1 and Th17 mediated autoimmune diseases. A group evaluated the effect of peanut antigen coupled cells to induce tolerance in sensitized mice⁶⁰. They found this approach prevented anaphylactic responses on oral challenge and this tolerance was dependent on CD25+ T regulatory cells.

Regulatory Dendritic and T Cells

Regulatory dendritic cell immunotherapy is being evaluated in murine models. Dendritic cells in the intestines present food antigens to naïve T cells and can induce differentiation of regulatory T cells that mediate tolerance. A recent study evaluated the ability of mature retinoic acid-skewed dendritic cells to reverse ovalbumin or peanut allergy⁶¹. They found that when these cells presenting specific food allergens were delivered in sensitized mice, there were decreased rates of anaphylaxis with subsequent allergen challenge by up to 90%. They were able to characterize induction of T regulatory cells. Investigators hope to translate this approach to patients and clinical food allergy.

Biologics

Omalizumab

Omalizumab is an anti-IgE biologic agent that is being evaluated for treatment in food allergy. Initial studies focused on the use of omalizumab as monotherapy to decrease reactions in patients with food allergy while more recent studies are evaluating the use of omalizumab in conjunction with OIT. A previous study assessing the amount of peanut patients could tolerate while on omalizumab was terminated early due to safety concerns about the peanut challenge prior to randomization⁶². Fourteen patients did reach the primary endpoint after 24 weeks of omalizumab treatment. The patients who were treated with omalizumab demonstrated a trend towards a greater change from baseline in terms of the amount of peanut tolerated. Another study of peanut allergic patients assessed after 6 weeks of therapy with omalizumab demonstrated an increase in the amount of peanut tolerated before a reaction was elicited (80mg at baseline increased to 6500mg, $p < 0.01$)⁶³. They also demonstrated a decreased basophil histamine release in these patients.

More recent studies have focused on omalizumab as an adjunct to immunotherapy. Studies have shown promising potential in conjunction with OIT trials with peanut and milk and also with multiple allergenic foods⁶⁴⁻⁶⁶. Two recent studies have evaluated omalizumab in cow's milk OIT and one recent study evaluated omalizumab in peanut OIT. One study performed a double-blind, placebo-controlled trial of omalizumab vs. placebo as pretreatment before open label milk OIT. In the study, 57 patients were pretreated for 4 months with omalizumab or placebo and continued to receive omalizumab or placebo until month 28. Patients who were able to tolerate OIT received treatment for 8 weeks and then discontinued OIT 4 weeks thereafter to assess sustained unresponsiveness. After 28 months, omalizumab and placebo patients passed OFCs at similar rates (88.9% vs. 71.4%, respectively; $p = 0.18$). Rates of sustained unresponsiveness were also similar (48.1% in the omalizumab group vs. 35.7% in the placebo group; $p = 0.42$). Despite similar efficacy outcomes, they did find a statistically significant difference in the rate of adverse events. Patients treated with omalizumab had a smaller proportion of doses per patient that provoked symptoms, fewer reactions requiring treatment and also required fewer doses to achieve the maintenance dose.

A recent study also evaluated the use of omalizumab to facilitate OIT in cow's milk and egg allergic patients who previously did not tolerate OIT due to anaphylactic reactions⁶⁷. Fourteen patients received 9 weeks of omalizumab followed by 12 months of cow's milk or egg OIT. Patients continued to receive omalizumab for 2 months after the induction phase of OIT. They reported 100% of their patients were able to achieve desensitization. They reported 4 patients had mild allergic reactions during the induction phase and 6 patients had anaphylactic symptoms after discontinuing omalizumab.

A double-blind, placebo controlled study evaluated omalizumab to facilitate rapid peanut desensitization⁶⁸. In the study, 37 patients were randomized to either omalizumab or placebo for 12 weeks. These patients then received rapid peanut OIT and had weekly increases up to the maintenance dose of 2gm at which time omalizumab was discontinued. Twelve weeks after discontinuation of omalizumab or placebo, they underwent an open challenge to 4gm of peanut protein. They found that patients who received omalizumab tolerated 250mg of peanut protein on the initial day of desensitization as compared to 22.5mg for patients who received placebo. They found that 23 of 29 patients (79%) who received omalizumab tolerated 2gm of peanut 6 weeks after omalizumab was discontinued as compared to 1 of 8 patients (12%) who received placebo ($p < 0.01$). Twenty-two patients who received omalizumab passed the 4gm peanut challenge as compared to 1 patient receiving placebo. They found similar rates of adverse reactions between the two groups despite the omalizumab group receiving higher doses of peanut.

While these studies suggest a promising role for omalizumab in the treatment of food allergy, especially as an adjunct to immunotherapy, the costs of the drug will also have to be weighed. Not all patients would need omalizumab to tolerate immunotherapy, therefore, appropriate patient selection will likely be a key issue. Further studies are also needed to evaluate the optimal omalizumab regimen and duration.

Other Biologics

The monoclonal antibody dupilumab targets IL-4 receptor α and modulates activity of IL-4 and IL-13. Dupilumab has been studied and shows promising efficacy in atopic dermatitis, asthma and sinusitis. It was recently approved by the FDA in the treatment of atopic dermatitis. Although, application of this drug has not yet been applied to food allergy, IL-13 variants have been associated with food sensitization in patients with atopic dermatitis, and mutations in IL-4 receptor α have also been associated with food sensitization, suggesting potential for this or similar drugs to play a future role in food allergy therapeutics^{69,70}. Multiple other biologic agents are under investigation and may have implications for the treatment of food allergy, including additional monoclonal antibodies and TLR agonists,⁷¹

Traditional Chinese Medicine

The field of complementary and alternative medicine has been growing in recent years. With respect to the field of food allergy, traditional Chinese medicine with herbal formulations have been evaluated. Food Allergy Herbal Formula-2 (FAHF-2) is composed of 9 herbs that were previously shown to mitigate anaphylaxis induced by peanuts in a mouse model⁷². A randomized, double-blind, placebo-controlled study wherein patients received therapy for 6 months showed no clinical efficacy for inducing tolerance; although patients treated with FAHF-2 did show increased regulatory T cells, and T cell studies showed an increase in production of IL-10 and a decrease in production of IL-5. This study was limited by poor drug adherence. Given evidence of potential immunomodulation in this clinical trial, it remains to be seen whether longer duration or different dosing of FAHF-2 may be more efficacious clinically, or if it can be used in combination with other therapies. As mentioned above, there is also an ongoing trial examining the use of adjunctive Chinese herbal therapy and omalizumab in OIT directed at multiple foods (NCT02879006).

Conclusion

The rise in prevalence of food allergy has led to significant interest in developing better therapeutics than the current standard of care, which involves strict avoidance and as needed medications for accidental ingestions. There are a number of both allergen specific and allergen non-specific mechanisms to treat food allergy currently under investigation. The field of food allergy therapy is continually advancing, and we can likely expect changes to clinical practice in the near future. Currently the most promising advances lie in OIT, which offers the best efficacy as compared to other routes of immunotherapy but also the highest likelihood for treatment related adverse effects. The use of omalizumab in conjunction with OIT offers the potential for an improved safety profile.

Abbreviations

(OIT) Oral immunotherapy

(SLIT) Sublingual immunotherapy

(EPIT) Epicutaneous immunotherapy

(FAHF-2) Food Allergy Herbal Formula-2

1. Sicherer SH. Epidemiology of food allergy. *Journal of Allergy and Clinical Immunology* 2011;127:594–602.
2. Toit du G, Tsakok T, Lack S, Lack G. Prevention of food allergy. *J Allergy Clin Immunol* 2016;137:998–1010.
3. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: food allergy. *J Allergy Clin Immunol* 2012;129:906–20.
4. BOCK S, ATKINS F. The natural history of peanut allergy. *Journal of Allergy and Clinical Immunology* 1989;83:900–4.
5. Wood RA. Food allergen immunotherapy: Current status and prospects for the future. *J Allergy Clin Immunol* 2016;137:973–82.
6. Jones SM, Burks AW, Keet C, Vickery BP, Scurlock AM, Wood RA, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol* 2016;137:1117–27.e1–10.
7. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral Immunotherapy for Treatment of Egg Allergy in Children. *N Engl J Med* 2012;367:233–43.
8. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: Clinical and immunologic evidence of desensitization. *Journal of Allergy and Clinical Immunology* 2011;127:640–1.
9. Syed A, Garcia MA, Lyu S-C, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *Journal of Allergy and Clinical Immunology* 2014;133:500–11.
10. Ryan JF, Hovde R, Glanville J, Lyu S-C, Ji X, Gupta S, et al. Successful immunotherapy induces previously unidentified allergen-specific CD4+ T-cell subsets. *Proc Natl Acad Sci USA* 2016;113:E1286–95.
11. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. *Journal of Allergy and Clinical Immunology* 1992;90:256–62.
12. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *Journal of Allergy and Clinical Immunology* 1997;99:744–51.
13. Patriarca G, Nucera E, Roncallo C, Pollastrini E, Bartolozzi F, De Pasquale T, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003;17:459–65.
14. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *Journal of Allergy and Clinical Immunology* 2008;121:343–7.
15. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *Journal of Allergy and Clinical Immunology*

2009;124:292–7.

16. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschoner J, de Oliveira LCL, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *Journal of Allergy and Clinical Immunology* 2010;126:83–91.e1.
17. Tang MLK, Ponsonby A-L, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. *J Allergy Clin Immunol* 2015;135:737–8.
18. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: A randomized, double-blind, placebo-controlled multicenter trial. *Journal of Allergy and Clinical Immunology* 2013;131:119–127.e7.
19. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, et al. Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial. *Journal of Allergy and Clinical Immunology* 2015;135:1240–3.
20. Jones SM, Sicherer SH, Burks AW, Leung DYM, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol* 2016;
21. Hussey Freeland DM, Fan-Minogue H, Spergel JM, Chatila TA, Nadeau KC. Advances in food allergy oral immunotherapy: toward tolerance. *Curr Opin Immunol* 2016;42:119–23.
22. MacGinnite A. Update on Potential Therapies for IgE-Mediated Food Allergy. *Curr Allergy Asthma Rep* 2017;17:4.
23. Albin S, Nowak-Węgrzyn A. Potential treatments for food allergy. *Immunol Allergy Clin North Am* 2015;35:77–100.
24. Gernez Y, Nowak-Węgrzyn A. Immunotherapy for Food Allergy: Are We There Yet? *J Allergy Clin Immunol Pract* 2017;5:250–72.
25. Yee CSK, Rachid R. The Heterogeneity of Oral Immunotherapy Clinical Trials: Implications and Future Directions. *Curr Allergy Asthma Rep* 2016;16:25.
26. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol* 2014;133:468–75.
27. Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2013;132:737–739.e6.
28. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2012;129:448–55–455.e1–5.
29. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol* 2015;135:1275–82.e1–6.

30. Tordesillas L, Mondoulet L, Blazquez AB, Benhamou P-H, Sampson HA, Berin MC. Epicutaneous immunotherapy induces gastrointestinal LAP+ regulatory T cells and prevents food-induced anaphylaxis. *Journal of Allergy and Clinical Immunology* 2017;139:189–201.e4.
31. Jones SM, Agbotounou WK, Fleischer DM, Burks AW, Pesek RD, Harris MW, et al. Safety of epicutaneous immunotherapy for the treatment of peanut allergy: A phase 1 study using the Viaskin patch. *Journal of Allergy and Clinical Immunology* 2016;137:1258–1261.e10.
32. Hoffmann HJ, Valovirta E, Pfaar O, Moingeon P, Schmid JM, Skaarup SH, et al. Novel approaches and perspectives in allergen immunotherapy. *Allergy* 2017;69:643.
33. Lemon-Mulé H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Węgrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol* 2008;122:977–983.e1.
34. Nowak-Węgrzyn A, Fiocchi A. Rare, medium, or well done? The effect of heating and food matrix on food protein allergenicity. *Current Opinion in Allergy and Clinical Immunology* 2009;9:234–7.
35. Miceli Sopo S, Greco M, Monaco S, Bianchi A, Cuomo B, Liotti L, et al. Matrix effect on baked milk tolerance in children with IgE cow milk allergy. *Allergologia et Immunopathologia* 2016;44:517–23.
36. Miceli Sopo S, Greco M, Cuomo B, Bianchi A, Liotti L, Monaco S, et al. Matrix effect on baked egg tolerance in children with IgE-mediated hen's egg allergy. *Pediatr Allergy Immunol* 2016;27:465–70.
37. Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of milk allergy in an observational cohort. *Journal of Allergy and Clinical Immunology* 2013;131:805–812.e4.
38. Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of egg allergy in an observational cohort. *Journal of Allergy and Clinical Immunology* 2014;133:492–8.
39. Kim JS, Nowak-Węgrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *Journal of Allergy and Clinical Immunology* 2011;128:125–131.e2.
40. Leonard SA, Sampson HA, Sicherer SH, Noone S, Moshier EL, Godbold J, et al. Dietary baked egg accelerates resolution of egg allergy in children. *J Allergy Clin Immunol* 2012;130:473–80.e1.
41. Bartnikas LM, Sheehan WJ, Schneider LC, Phipatanakul W. Predicting Food Challenge Outcomes for Baked Milk: Role of Specific IgE and Skin Prick Testing. *Journal of Allergy and Clinical Immunology* 2012;129:AB21.
42. Turner PJ, Mehr S, Joshi P, Tan J, Wong M, Kakakios A, et al. Safety of food challenges to extensively heated egg in egg-allergic children: a prospective cohort study. *Pediatr Allergy Immunol* 2013;24:450–5.
43. Nowak-Węgrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow's milk allergy. *Journal of Allergy and Clinical Immunology* 2008;122:342–2.
44. Zhou Y, Kawasaki H, Hsu S-C, Lee RT, Yao X, Plunkett B, et al. Oral tolerance to food-induced

systemic anaphylaxis mediated by the C-type lectin SIGNR1. *Nat Med* 2010;16:1128–33.

45. Rupa P, Nakamura S, Katayama S, Mine Y. Effects of ovalbumin glycoconjugates on alleviation of orally induced egg allergy in mice via dendritic-cell maturation and T-cell activation. *Mol Nutr Food Res* 2013;58:405–17.
46. Prickett SR, Voskamp AL, Dacumos-Hill A, Symons K, Rolland JM, OHehir RE. Ara h 2 peptides containing dominant CD4+ T-cell epitopes: candidates for a peanut allergy therapeutic. *J Allergy Clin Immunol* 2011;127:608–15.e1–5.
47. Prickett SR, Voskamp AL, Phan T, Dacumos-Hill A, Mannering SI, Rolland JM, et al. Ara h 1 CD4+ T cell epitope-based peptides: candidates for a peanut allergy therapeutic. *Clin Exp Allergy* 2013;43:684–97.
48. Ramesh M, Yuenyongviwat A, Konstantinou GN, Lieberman J, Pascal M, Masilamani M, et al. Peanut T-cell epitope discovery: Ara h 1. *Journal of Allergy and Clinical Immunology* 2016;137:1764–4.
49. Anzengruber J, Bublin M, Bönisch E, Janesch B, Tscheppe A, Braun ML, et al. *Lactobacillus buchneri* S-layer as carrier for an Ara h 2-derived peptide for peanut allergen-specific immunotherapy. *Mol Immunol* 2017;85:81–8.
50. Ueno HM, Kato T, Ohnishi H, Kawamoto N, Kato Z, Kaneko H, et al. T-cell epitope-containing hypoallergenic β -lactoglobulin for oral immunotherapy in milk allergy. *Pediatr Allergy Immunol* 2016;27:818–24.
51. Giavi S, Vissers YM, Muraro A, Lauener R, Konstantinopoulos AP, Mercenier A, et al. Oral immunotherapy with low allergenic hydrolysed egg in egg allergic children. *Allergy* 2016;71:1575–84.
52. Wai CYY, Leung NYH, Leung PSC, Chu KH. T cell epitope immunotherapy ameliorates allergic responses in a murine model of shrimp allergy. *Clin Exp Allergy* 2016;46:491–503.
53. Lozano-Ojalvo D, López-Fandiño R. Immunomodulating peptides for food allergy prevention and treatment. *Critical Reviews in Food Science and Nutrition* 2017;66:0–0.
54. Li X-M, Srivastava K, Grishin A, Huang C-K, Schofield B, Burks W, et al. Persistent protective effect of heat-killed *Escherichia coli* producing “engineered,” recombinant peanut proteins in a murine model of peanut allergy. *Journal of Allergy and Clinical Immunology* 2003;112:159–67.
55. Li X-M, Srivastava K, Huleatt JW, Bottomly K, Burks AW, Sampson HA. Engineered recombinant peanut protein and heat-killed *Listeria monocytogenes* coadministration protects against peanut-induced anaphylaxis in a murine model. *J Immunol* 2003;170:3289–95.
56. Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, et al. A phase 1 study of heat/phenol-killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. *Allergy* 2013;68:803–8.
57. Tsai W-C, Wu T-C, Chiang B-L, Wen H-W. Cloning, expression, and purification of recombinant major mango allergen Man i 1 in *Escherichia coli*. *Protein Expr Purif* 2017;130:35–43.
58. Zuidmeer-Jongejan L, Huber H, Swoboda I, Rigby N, Versteeg SA, Jensen BM, et al. Development of

a Hypoallergenic Recombinant Parvalbumin for First-in-Man Subcutaneous Immunotherapy of Fish Allergy. *Int Arch Allergy Immunol* 2015;166:41–51.

59. Srivastava KD, Siefert A, Fahmy TM, Caplan MJ, Li X-M, Sampson HA. Investigation of peanut oral immunotherapy with CpG/peanut nanoparticles in a murine model of peanut allergy. *Journal of Allergy and Clinical Immunology* 2016;138:536–543.e4.
60. Hsu C, Smarr CB, Byrne AJ, Miller SD, Bryce PJ. Rapid Induction of Tolerance To Peanut By Antigen-coupled Cell Transfer. *Journal of Allergy and Clinical Immunology* 2012;129:AB1.
61. Dawicki W, Li C, Town J, Zhang X, Gordon JR. Therapeutic reversal of food allergen sensitivity by mature retinoic acid-differentiated dendritic cell induction of LAG3+CD49b–Foxp3– regulatory T cells. *Journal of Allergy and Clinical Immunology* 2016;0:705–715.e1.
62. Sampson HA, Leung DYM, Burks AW, Lack G, Bahna SL, Jones SM, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *Journal of Allergy and Clinical Immunology* 2011;127:1309–1310.e1.
63. Savage JH, Courneya J-P, Sterba PM, MacGlashan DW, Saini SS, Wood RA. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. *Journal of Allergy and Clinical Immunology* 2012;130:1123–1129.e2.
64. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 2013;132:1368–74.
65. Nadeau KC, Schneider LC, Hoyte L, Borrás I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *Journal of Allergy and Clinical Immunology* 2011;127:1622–4.
66. Bégin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. *Allergy Asthma Clin Immunol* 2014;10:7.
67. Martorell-Calatayud C, Michavila-Gómez A, Martorell-Aragonés A, Molini-Menchón N, Cerdá-Mir JC, Félix-Toledo R, et al. Anti-IgE-assisted desensitization to egg and cow's milk in patients refractory to conventional oral immunotherapy. *Pediatr Allergy Immunol* 2016;27:544–6.
68. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol* 2017;139:873–8.
69. Zitnik SE, Rüschenhoff F, Müller S, Sengler C, Lee Y-A, Griffioen RW, et al. IL13 variants are associated with total serum IgE and early sensitization to food allergens in children with atopic dermatitis. *Pediatric Allergy and Immunology* 2009;20:551–5.
70. Liu X, Beaty TH, Deindl P, Huang S-K, Lau S, Sommerfeld C, et al. Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children. *Journal of Allergy and Clinical Immunology* 2004;113:489–95.
71. Bauer RN, Manohar M, Singh AM, Jay DC, Nadeau KC. The future of biologics: applications for food

allergy. J Allergy Clin Immunol 2015;135:312–23.

72. Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, Wallenstein S, et al. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. Journal of Allergy and Clinical Immunology 2005;115:171–8.