

Vaccines and Immunomodulatory Therapies for Food Allergy

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Abstract The apparent increase in food allergy prevalence has led to a surge in the amount of clinical and basic science research dedicated to the field. At the current time, allergen avoidance remains the cornerstone of treatment; however, recent clinical trials investigating various forms of immunotherapy have opened doors to the possible future application of an active treatment strategy in everyday practice. In addition, improvements in molecular biology have allowed researchers to purify, clone, and modify allergens, thus laying the groundwork for research on vaccines using modified proteins of decreased allergenicity. Finally, various allergen-nonspecific immunomodulatory therapies are also being investigated as a means to alter the immune response to food allergens. With these emerging therapeutic strategies, it is hoped that practitioners will have options in caring for their food-allergic patients in the near future.

Keywords Food allergy · Immunotherapy · Immunomodulatory · Treatment · Therapy · Vaccine · Peptide · Epitope · Chinese herbal therapy · Omalizumab · Sublingual · Peanut

Introduction

As with other atopic conditions, the prevalence of food allergy appears to be increasing in developed nations. A recent report by the Centers for Disease Control and

Prevention estimates the prevalence of food allergy to be 3.9% in children younger than 18 years of age in the United States, representing an increase of 18% from 1997 to 2007 [1]. This increase was mirrored in a recent follow-up survey of self-reported peanut and tree nut allergy in the United States, in which the prevalence of self-reported nut allergy increased from 0.6% in 1997, to 1.2% in 2002, and finally to 2.1% in 2008 in children younger than 18 years of age [2]. The high prevalence is also seen in other nations, as a recent prevalence study in Australia showed that more than 10% of 1-year-old infants had challenge-proven food allergy [3]. This increasing prevalence, along with advances in molecular biology have spurred a surge in research devoted to the development of novel therapeutic approaches for food allergy, as well as to the re-examination of classic desensitization techniques using rigorous clinical trials.

In this review, we describe current vaccines and immunomodulatory therapies being researched for the treatment of food allergy both in humans and animal models (summarized in Table 1). We look briefly at more classic immunotherapy (IT) techniques such as subcutaneous, oral, sublingual, and epicutaneous IT, and review novel forms of IT using modified forms of allergens, peptide vaccines, and gene therapy. In addition, we review some forms of allergen-nonspecific immunomodulatory treatments under investigation. For the purposes of this review, we focus only on treatments of IgE-mediated food allergy.

Traditional Forms of Immunotherapy

Subcutaneous Immunotherapy

The earliest report of subcutaneous IT (SCIT) as a treatment of food allergy appeared in 1930, when Freeman [4]

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Table 1 Summary of immunomodulatory therapies for food allergy

Therapy	Prophylaxis or treatment schedule ^a	Foods/allergens studied	Stage of research
Allergen-specific immunotherapy			
Subcutaneous immunotherapy [5, 6]	Treatment •Build-up: 5-d rush protocol •Maintenance: weekly injections for up to 1 y	RDBPC: peanut	No trials conducted after 1997 due to serious adverse effects of therapy
Oral immunotherapy [7–19, 20••]	Treatment •Build-up: 44 wk for peanut and up to 14 wk for milk •Maintenance: daily ingestion for 4 wk for peanut and 13 wk for milk	RDBPC: peanut and milk Open: milk, egg, peanut, fish, fruits	RDBPC trials ongoing Not an approved treatment in the United States currently
Sublingual immunotherapy [25–28, 29••]	Treatment •Build-up: 14 biweekly visits •Maintenance: daily dose for 6 mo	RDBPC: peanut Open: kiwi, hazelnut, peach, and milk	Large RDBPC trial ongoing Not an approved treatment in the United States currently
Epicutaneous immunotherapy [30]	Treatment •Build-up: none •Maintenance: 3 mo	RDBPC: milk	Only data from pilot study published to date
Peptide immunotherapy [38, 39]	Treatment	Animal model: egg and peanut	No human trials initiated yet Identification of appropriate immunogenic peptides for peanut under way
Modified allergens			
•Engineered allergens to reduce allergenicity [41–46]	Treatment	Animal model: egg Development of modified allergens: milk, peanut, fish, peach, and apple Animal model: BSA	No published therapeutic trials in humans to date Reduced allergenicity of recombinant allergens has been shown in vitro and in vivo
•Sugar moieties added to allergen [47]	Prophylaxis		
Bacterial adjuvants			
•With native allergen [48]	Treatment	Animal model: peanut	Animal model only
•With modified allergen [49, 50]	Treatment	Animal model: peanut	Phase 1 trial in humans ongoing
Gene therapy [53, 54]	Prophylaxis	Animal model: peanut	No human trials initiated yet
Allergen-nonspecific therapy			
Anti-IgE therapy [55, 56•]	Treatment: 20–22 wk of therapy	RDBPC: peanut	Human trial halted due to adverse events during screening oral food challenges
Traditional Chinese medicine [58–61•]	Treatment	Human study: safety established	Extended safety and efficacy human phase 2 trial ongoing
Helminth therapy (<i>Trichuris suis</i> ova) [65]	Prophylaxis: treatment	Animal model: peanut	No published human trials in food allergy to date

^a Treatment schedules provided are from RDBPC trials only

BSA bovine serum albumin; RDBPC randomized, double-blind, placebo-controlled trial

reported successfully treating a 7-year-old fish-allergic child with a vaccine protocol “using as antigen the juices expressed from the cod fish.” Little was published on this topic from that time until the method was re-examined in the 1990s. In 1992, the first double-blind, placebo-controlled trial

of peanut SCIT using an aqueous peanut extract showed a 67%–100% decrease in symptom scores from pretreatment challenge to post-treatment challenge in the actively treated group, while the placebo-treated group showed no change in symptoms [5]. Unfortunately, due to a pharmacy error, one

individual in the placebo group died after accidentally receiving a maintenance dose of peanut extract, thus leading to the early termination of the study.

Given the optimistic results prior to the dosing error in the first peanut SCIT trial, a follow-up trial was conducted and published in 1997 [6]. In that trial, 12 individuals were enrolled, and 6 were randomly assigned to active treatment. All of those in the active treatment group were able to ingest more peanut at the 1-month post-rush treatment challenge, and this desensitized state was maintained at 1 year in the three patients who were able to continue on maintenance IT at the goal dose. No improvement was seen at any time point in the placebo-treated individuals. Unfortunately, systemic reactions were common in the actively treated group. During build-up, the median number of systemic reactions was 9 in the actively treated group, and all actively treated individuals required epinephrine, with 1 requiring 30 doses over the 4-day rush build-up. During maintenance, five of six of the actively treated individuals required epinephrine, and only three of six were able to continue on the goal maintenance dose.

Although these studies showed that desensitization to foods, or at least to peanut, was possible with SCIT, it was evident that the risk of systemic reaction is great, and this has halted further investigation into SCIT for food allergy.

Oral Immunotherapy

Over the past 15 years, many open clinical trials of oral IT (OIT) have been published, typically focusing on milk, egg, and peanut [7–19, 20•]. The first randomized, double-blind, placebo-controlled trial of OIT was performed in milk-allergic children and published in 2008 [13]. In this study, 19 children and adolescents 6–17 years old were randomly assigned 2:1 to milk or placebo OIT. The median threshold dose for reaction during oral challenge increased from 40 mg pretreatment to 5,140 mg post-treatment in the active group. No change was seen in the placebo group. More recently, the first double-blind, placebo-controlled trial of peanut OIT was published in 2011 [20•]. In this trial, 28 children and adolescents 1–16 years of age were randomly assigned 2:1 to peanut flour OIT or placebo in a three-step treatment protocol over 1 year. After 1 year of treatment, all the actively treated individuals who remained in the study were able to ingest the goal dose of 5,000 mg of peanut at the post-treatment oral challenge, as compared with those in the placebo arm, who reacted to a median dose of 280 mg of peanut after 1 year of treatment. This clinical effect was associated with a decrease in titrated skin prick test size, an increase in peanut-specific IgG₄ levels, an initial increase in peanut-specific IgE levels at 2 months that decreased back to baseline at 12 months, and a decrease in interleukin (IL)-5 and IL-13 levels in the

supernatants of cultured peripheral blood mononuclear cells. Interestingly, 3 of 19 individuals randomly assigned to the active group did not complete the study. Two could not reach the 1.5-mg dose on the initial day escalation phase and were deemed treatment failures; one withdrew due to gastrointestinal symptoms during the build-up phase. The gastrointestinal side effects of the therapy are a concern, as they have been shown to be a limiting side effect in the open peanut OIT trials, in which 20% of the participants withdrew (70% of withdrawals were due to gastrointestinal symptoms related to OIT) [21].

The data from these trials suggest that OIT can lead to desensitization in most individuals. Unfortunately, no convincing data to date suggest that permanent tolerance can be established with OIT. Due to this and the fact that the treatment is associated with frequent adverse events (some of which required withdrawal from studies), OIT is not yet considered to be ready for everyday clinical practice, although this has been a subject of debate.

Perhaps an alternative to OIT with crude allergen is OIT to extensively heated allergen, at least for milk and egg. Two clinical trials to date have shown that approximately 80% of children with milk and egg allergy tolerate the allergens if they have been extensively heated and baked into other products (e.g., a muffin) [22, 23]. Those who tolerated the heated allergen and incorporated it into their diet developed immunologic changes consistent with desensitization. In addition, preliminary findings suggest that the individuals ingesting the baked products may experience accelerated tolerance [24]. With this background, there is an ongoing large-scale trial to determine the safety and efficacy of baked goods as a form of IT for milk and egg allergy.

Sublingual Immunotherapy

The first report of sublingual IT (SLIT) for food allergy was published in 2003 in a patient with anaphylactic reactions to kiwi [25]. Since then, there have been clinical trials published with data on SLIT to hazelnut, peach, milk, and most recently peanut [26–28, 29•]. Perhaps the most intriguing and clinically relevant of these trials was the peanut SLIT trial [29•]. In this double-blind, placebo-controlled trial, 18 individuals 1–11 years of age were randomly assigned to crude peanut extract solution or matching placebo, which they held under the tongue for 2 min and then swallowed. The initial dose escalation phase took the 11 actively treated individuals from 0.25 µg of peanut protein up to 2,000 µg over a 6-month period, with dose increases occurring at the study center every other week. In between dose escalation visits, individuals self-administered their prescribed daily dose at home. Once on maintenance, they continued daily home maintenance

dosing for approximately 6 months longer, and then returned to the study center for a follow-up blinded peanut challenge. After treatment, those in the active group were able to tolerate more peanut than those in the control group (1,710 mg vs 85 mg, $P=0.01$) at the post-treatment challenge. This clinical improvement in the active group was accompanied by immunologic changes consistent with desensitization, such as a smaller peanut skin test wheal size, an increase in peanut IgG₄ levels, and an initial increase in peanut-specific IgE levels at 4 months that steadily decreased.

The minimal side effect profile of the treatment was perhaps more impressive than the positive clinical results. Only 11.5% of the peanut doses caused symptoms (as compared with 8.6% of the placebo doses). In addition, only 11 (0.3%) of all active doses required treatment with an oral antihistamine, and only 1 active dose required treatment with albuterol for an adverse event. No adverse event required epinephrine in the study.

Food-specific SLIT may offer a beneficial and safe treatment option for food allergies in the future, and it is hoped that data from ongoing larger trials will answer remaining questions regarding its use. Until that time, however, SLIT remains an investigational treatment in the United States. A comparison of OIT and SLIT double-blind, placebo-controlled trials is summarized in Table 2.

Epicutaneous Immunotherapy

To date, there has been one published trial of epicutaneous IT (EPIT) in humans [30]. In that double-blind, placebo-controlled trial of milk EPIT, investigators randomly assigned 19 children 3 months to 15 years of age to milk EPIT or matched placebo. The delivery devices (containing 1 mg of skim milk powder or 1 mg of glucose) were worn over the scapula in 48-hour applications 3 times per week for 3 months. After treatment, the tolerated dose of milk during oral food challenge increased from a baseline mean of 1.8 mL to 23.6 mL ($P=0.18$) in the active group, and from a baseline mean of 4.4 mL to 5.4 mL in the placebo group. There was no change in the milk IgE level in either group after treatment. Adverse events were mild and similar in both groups, with only a higher instance of local eczema and gastrointestinal symptoms seen in the actively treated group. Although conclusions on the efficacy of EPIT cannot be drawn from this single study, it appears to be safe and well-tolerated; it will be interesting to see data from future studies on this different IT delivery method.

Novel Forms of Immunotherapy and Vaccines

With advances in molecular biology and proteomics, researchers are now able to sequence, clone, and purify

recombinant allergens as well as peptide fragments of allergens, which may allow for safer and more effective vaccines for food allergy.

Peptide Immunotherapy

Peptide IT is a novel approach that utilizes only peptide fragments of the allergen in question rather than the whole allergen. Because these peptide fragments are small (~8–16 amino acids in length), they are too short to cross-link IgE on mast cells or basophils, thus eliminating the risk for these vaccines to elicit immediate-type adverse reactions such as those seen in earlier trials with peanut SCIT. This method has been studied in humans for cat allergy and bee venom allergy with some success but is still in its infancy for food allergy [31–33]. To design appropriate peptide IT vaccines, the immunogenic peptides that are able to stimulate a T-cell response and thus lead to immune regulation but yet are too short to be able to cross-link IgE on cell surfaces must first be defined. Works on defining these T-cell epitope peptide sequences for some food allergens, namely for peanut (Ara h 1 and Ara h 2) in humans and for egg (ovalbumin [OVA]) in mice, have now been reported [34–37]. In addition, there have been some reports of the use of peptide vaccines for peanut and egg in the murine model [38, 39]. In the most recent report, OVA-sensitized mice that were treated with T-cell epitope peptide vaccines after sensitization had lower anaphylactic scores upon OVA challenge as compared with sham-treated controls, a clinical change that was accompanied by a shift toward a T-helper type 1 (Th1) cytokine response and an increased expression of transforming growth factor (TGF)- β and forkhead box P3 genes in intestinal tissue [39]. At this point, peptide IT is limited to animal studies, but human studies are likely to be undertaken in the future.

Modified or Recombinant Allergen

Vaccines that incorporate allergens that have modified IgE-binding sites (via site-directed mutagenesis to alter IgE binding sites, or by altering tertiary protein structure) yet retain their T-cell epitopes theoretically allow for immunomodulatory responses by driving a regulatory or Th1 response without the concern of immediate-type reactions. Results from various human studies using such recombinant allergen vaccines for environmental allergies have been published [40]. As for food allergy, recombinant allergens have been synthesized for peanut (Ara h 1, 2, and 3), milk (casein), fish (parvalbumin), and peach (Pru p 3), and each has shown reduced or obliterated IgE-binding capability in vitro [41–44]. In addition, one report showed reduced allergenicity of an engineered apple allergen (Mal d 1) in vivo using skin prick testing and

Table 2 Randomized, double-blind, placebo-controlled trials of oral vs sublingual immunotherapy

Therapy	Treatment schedule	Clinical changes	Adverse events
Oral immunotherapy			
Milk [13]	Build-up	Increase in tolerable dose from 40 mg to 5,100 mg after 13 wk of treatment in active arm	45% of all doses in active arm led to reaction
•Ages 6–17 y	•0.4 mg up to 50 mg on day 1	No change in placebo arm	4 total reactions in active arm required epinephrine
•Active ($n=13$)	•Dose increases every 7–14 d to goal of 500 mg		
•Placebo ($n=7$)	Maintenance		
	•500 mg/d for 13 wk		
Peanut [20••]	Build-up	All individuals in active arm tolerated the goal of 5,000 mg of peanut upon completion (median time, 12.4 mo of treatment)	1.2% of all build-up doses in active arm led to a reaction (after day 1)
•Median age, 5.8 y (range, 2.3–10.5 y)	•0.1 mg up to 6 mg on day 1	No individual in placebo arm tolerated 5,000 mg (median tolerable dose, 280 mg) upon completion	2 individuals in active arm required epinephrine during day 1
•Active ($n=19$)	•Dose increases every 2 wk to goal of 4,000 mg		3 individuals withdrew from study due to adverse effects
•Placebo ($n=9$)	Maintenance		3 individuals could not reach goal maintenance dose
	•4,000 mg/d for 1 mo		
Sublingual immunotherapy			
Peanut [29••]	Build-up	Median tolerable dose in active arm was 1,710 mg after 6 mo of treatment	11.5% of all doses in active arm led to reaction
•Median age, 5.2 y (range, 1.6–10.5 y)	•0.2 µg once on day 1	Median tolerable dose in placebo arm was 85 mg after treatment	8.6% of all doses in placebo arm led to reaction
•Active ($n=11$)	•Dose increases every 3–4 d to a goal of 2,000 µg		No reaction required epinephrine
•Placebo ($n=7$)	Maintenance		
	•2,000 µg/d for 6 mo		

double-blind, placebo-controlled oral food challenge to a solution of both native Mal d 1 and recombinant Mal d 1 in apple-allergic patients (but did not use the recombinant Mal d 1 as a therapy) [45]. Although there have yet to be any published reports of the use of a therapeutic recombinant allergen vaccine in humans for food allergy, animal trials have been conducted. In a murine model sensitized to the third domain of ovomucoid, desensitization using three intraperitoneal injections of a modified form of the ovomucoid third domain led to decreased anaphylaxis scores, decreased histamine, and increased interferon- γ upon subsequent challenge with the native ovomucoid third domain, suggesting desensitization by shifting the immune response toward a Th1 phenotype [46].

In another approach, sugar moieties are added to create an allergen that mimics a pathogen through the immune system's recognition of the carbohydrate moieties, thus driving a Th1 or regulatory response to the allergen. This method was recently studied in bovine serum albumin (BSA)-sensitized mice that were either pretreated with a mannose-modified BSA or not prior to

sensitization with BSA [47]. Upon BSA challenge after sensitization, those mice pretreated with the mannosylated BSA had significantly reduced anaphylaxis scores and lower BSA-specific IgE levels. The mannose-modified BSA targeted lamina propria dendritic cells expressing SIGNR1 (a C-type lectin receptor) that induced expression of IL-10, which was thought to be the main mechanism of action leading to tolerance.

Bacterial Adjuvants

Bacterial adjuvants, such as heat-killed *Listeria monocytogenes* (HKL) or heat-killed *Escherichia coli* (HKE), can be added to vaccines to skew the immune response from a Th2 toward a Th1 response. This method has been studied in animal models with both native allergens and recombinant allergens [48–50]. In a canine model of food allergy, dogs with peanut allergy were immunized with 1×10^9 organisms of HKL with 1 mL of 1:10 weight: volume peanut extract. The mean dose of peanut required to elicit symptoms on challenge after vaccination was more than 13 g, as compared with a baseline mean

threshold dose of 0.63 g ($P=0.03$). This clinical change was accompanied by a decrease in skin test end point titration and appeared to be allergen specific. This group also showed similar effects in a canine model of multiple food allergies, including wheat and milk [48].

By combining bacterial adjuvants with recombinant allergens, as opposed to native allergens (as in the canine model above), one may theoretically be able to induce just as strong a protective response with less concern of immediate-type adverse effects. This method has been published in a murine model of peanut allergy using both HKL and HKE as adjuvants. The first report used modified peanut allergens (Ara h 1–3) plus HKL as a therapeutic vaccine given subcutaneously 10 weeks after sensitization. In this model, the actively treated group had lower histamine levels and lower anaphylactic scores as compared with sham-treated control mice upon intragastric peanut challenge [49]. As a follow-up to this study, the same group used HKE vector expressing the same modified peanut allergens Ara h 1 to 3 (termed *HKE-MP123* by the researchers) and administered this vaccine orally, subcutaneously, and rectally to assess the optimal route of therapy [50]. The rectal route was chosen for further study because it provided evidence of protection against peanut-induced anaphylaxis, while the oral route did not, and the subcutaneous route caused some skin irritation. The rectal route was also considered the safest mode of delivery for a vaccine containing *E. coli*. Optimal dosing was also assessed for the *HKE-MP123* given per rectum at 10, 11, and 12 weeks after sensitization. All three tested doses of *HKE-MP123* (0.9, 9, and 90 μ g) suppressed anaphylactic symptoms and decreased histamine levels as compared with sham-treated controls after the first peanut challenge (2 weeks after final vaccination). However, a prolonged therapeutic effect was only seen in the two higher doses during the post-6- and post-10-week vaccination peanut challenges [50]. Immune modulation consistent with desensitization was seen, as peanut-specific IgE levels were significantly lower in all treated groups throughout the study as compared with sham-treated mice, and IgG_{2a} levels were higher in the medium- and low-dose-treated groups throughout the study. A phase 1 clinical study assessing the safety of *HKE-MP123* in humans is currently under way.

An alternative approach to using bacterial adjuvants involves the use of probiotic bacteria (*Lactococcus lactis*) transfected with IL-10 or with IL-12 and β -lactoglobulin. Treatment with *L. lactis*-IL-10 prior to sensitization led to decreased anaphylaxis scores on challenge, and intranasal treatment with *L. lactis*-IL-12- β -lactoglobulin after sensitization led to decreased allergic response on intranasal challenge of β -lactoglobulin [51, 52].

Gene Therapy

By delivering genes of allergens encoded in plasmid DNA (pDNA), it is possible to express the gene of the allergen in the body and thus produce an immunomodulatory response to the protein/allergen of interest. This has been reported in a murine model of peanut allergy, in which pDNA of Ara h 2 complexed with chitosan (a natural polysaccharide) given once orally decreased anaphylaxis symptom scores upon peanut challenge as compared with sham-treated (empty vector) and non-treated control mice [53]. This was accompanied by increased levels of IgG_{2a} and decreased levels of histamine. More recently, orally administered pDNA of TGF- β complexed with chitosan was studied as a method of inducing oral tolerance in OVA-sensitized mice [54]. This strategy led to increased intestinal TGF- β expression, increased OVA-specific IgA, sustained decreased OVA-specific IgE, and an apparent shift toward Th1 cytokine expression. There were no OVA challenge data in this study, however.

Allergen-Nonspecific Therapies

Anti-IgE Therapy

The initial report for the use of anti-IgE therapy for food allergy was published in 2003 [55]. In that trial, the authors randomly assigned 84 peanut-allergic individuals (12–64 years of age) to placebo or to one of three doses (150, 300, and 450 mg) of a humanized, monoclonal murine IgG₁ anti-IgE antibody known as TNX-901 (also known as Hu-901). After 4 monthly doses, those treated with TNX-901 were able to tolerate more peanut protein over their baseline threshold dose as compared with those in the placebo group. The treatment was dose dependent, but the trend only reached statistical significance for the highest dose (450 mg). As expected, the clinical response was accompanied by a large decrease in free serum IgE in the TNX-901-treated individuals (no change was seen in the placebo arm).

Although TNX-901 never made it to market for clinical use, the results of this study led to a trial of the currently available anti-IgE, omalizumab, in peanut allergy [56•]. In this trial, 26 peanut-allergic individuals (6–75 years old) were randomly assigned to receive omalizumab ($n=17$) or placebo ($n=9$) in a 2:1, double-blinded fashion. The study was initially powered to randomly assign a total of 150 participants, but it was stopped early due to the severity of two anaphylactic reactions during the qualifying oral food challenge (prior to these individuals receiving any study drug).

Because the study was cut short, only 14 participants completed the trial (9 in the active arm, 5 in the placebo arm), and the data did not reach statistical significance. When comparing baseline tolerable peanut dose to post-24-week treatment tolerable dose, there was a trend toward increased peanut tolerability in the omalizumab-treated individuals compared with the placebo-treated individuals ($P=0.054$). In addition, 44% of the omalizumab-treated individuals were able to tolerate the goal dose of 1 g of peanut protein after 24 weeks of treatment, compared with only one in the placebo-treated arm. Unfortunately, because the study was stopped prematurely, the data are not strong enough to promote the use of omalizumab as a sole therapy for food allergy at this point.

Although anti-IgE may not be used in the near future as a sole therapy for food allergy, there are ongoing studies of the utility of using omalizumab in combination with OIT as a way to accelerate the desensitization phase of the IT through improved safety and/or a way to modulate the immune response to the IT by down-regulating facilitated antigen presentation. Preliminary results have been published for one such pilot study in milk-allergic patients, showing that treatment with omalizumab 7–11 weeks prior to initiating milk OIT allowed 9 of the 11 enrolled participants (7–11 years of age) to tolerate the 1-day rush desensitization protocol going from a 0.1-mg to a 1,000-mg dose of milk protein [57]. Although this was just a pilot study and thus lacked a placebo group and did not require baseline-blinded oral food challenge, it nevertheless points to the fact that there may be a role for omalizumab in conjunction with IT protocols in food allergy.

Traditional Chinese Medicine

Herbal remedies have been used for centuries in China for treatment of various autoimmune and inflammatory conditions. A mixture of 11 such herbs, termed the *Food Allergy Herbal Formula (FAHF)-1*, has been shown to eliminate anaphylaxis symptoms in a peanut-allergic murine model after challenge with peanut [58]. To refine the treatment to only the active compounds for human use, a simplified formula, FAHF-2, was designed and was shown to be just as effective [59]. Due to the apparent synergy, nine herbal compounds are necessary for the FAHF-2 effect. This effect was long-lasting (up to 36 weeks postvaccination) and correlated with lower peanut-specific IgE levels, higher peanut-specific IgG_{2a} levels, and higher CD8⁺ T-cell production of interferon- γ [60].

With the success of these murine studies, FAHF-2 has now entered into human trials. A phase 1 safety and dose

tolerability trial randomly assigned 19 food-allergic individuals 12–45 years of age to 1 of 3 FAHF-2 doses or to placebo in a blinded fashion [61•]. Overall, the treatment was well-tolerated, with one patient in the placebo group reporting vomiting and one patient in the active group reporting loose stools. In addition, one patient in the active arm withdrew due to a rash that was not deemed to be associated with the medication. With the initial safety now established in humans, a phase 2 extended safety and efficacy trial is currently ongoing.

To decrease the pill burden (4, 6, or 12 tablets 3 times daily in the phase 1 trial), a new butanol extraction technique has been demonstrated that can decrease the effective volume of the compound approximately fivefold in mice [62]. This may be a required step if this drug is ever going to be able to be used practically in the pediatric population. In addition, standardization of the active ingredients is crucial for regulation for use in humans, and ongoing studies hope to answer these questions.

Helminth Therapy

Various studies have demonstrated a negative association of chronic helminth infection and allergy [63]. Unfortunately, the best clinical study using a helminth (*Trichuris suis* ova) as treatment of allergic rhinitis did not show this treatment to be efficacious [64]. However, there is hope that enteric helminth therapy may prove to be beneficial in the treatment of food allergy based on data from murine models of food allergy [65] and from its use in inflammatory bowel disease [66], both of which point to the therapy's induction of immune suppression, mainly via IL-10.

Conclusions

At the present time, the standard treatment of food allergy continues to consist of avoidance of allergens and the use of emergency treatment in the case of any accidental ingestion. Clinicians and patients, however, may have active treatment options in the near future. Rigorous clinical trials of various forms of IT continue to demonstrate that desensitization is possible for food allergies, and the future question will be whether oral tolerance can be achieved. In addition, advances in molecular biology and immunology may allow for vaccines using modified allergens that can shift immune responses toward tolerance given either as prophylactic or therapeutic vaccines.

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- Of importance
- Of major importance

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