

Food allergies and hypersensitivity: a review of pharmacotherapy and therapeutic strategies

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Key words

Food allergy

Anaphylaxis

Allergy immunotherapy

Peanut allergy

Abstract

Food allergy is a major cause of life-threatening hypersensitivity reactions. Food-induced anaphylaxis is the most common reason for someone to present to the emergency department for an anaphylactic reaction. Currently, the avoidance of the allergenic food is the only method of preventing further reactions for allergic patients. With better characterization of allergens and an understanding of the immunologic mechanism involved in this reaction, investigators have developed several therapeutic modalities potentially applicable to the treatment and eventual prevention of food allergy. Among the therapeutic options currently under investigation, there is anti-IgE therapy, peptide immunotherapy, Traditional Chinese Medicine, mutated protein immunotherapy, DNA immunization and immunization with immunostimulatory sequences linked to allergens. These novel forms of treatment for allergic disease hold promise for the safe and effective treatment of food-allergic individuals and the prevention of food allergy in the future.

Food allergy is a major cause of life-threatening hypersensitivity reactions ^{(1) (2)}. Food-induced anaphylaxis is the most common reason for someone to present to the emergency department for an anaphylactic reaction ^{(3) (4)}. Currently, the avoidance of the allergenic food is the only method of preventing further reactions for allergic patients. Even with good educational information, 50% of allergic patients have accidental ingestions and allergic reactions over a 24-month period ⁽⁵⁾. With better characterization of allergens and an understanding of the immunologic mechanism involved in this reaction, investigators have developed several therapeutic modalities potentially applicable to the treatment and eventual prevention of food allergy ⁽⁶⁾. Among the therapeutic options currently under investigation, there is anti-IgE therapy, peptide immunotherapy, Traditional Chinese Medicine, mutated protein immunotherapy, DNA immunization and immunization with immunostimulatory sequences linked to allergens. These novel forms of treatment for allergic disease hold promise for the safe and effective treatment of food-allergic individuals and the prevention of food allergy in the future.

Desirable therapeutic strategies for the treatment and prevention of food allergies must be safe, relatively inexpensive, and easily administered. Our recent advances in the understanding of the immunological mechanisms underlying allergic disease and the better characterization of food allergens have greatly expanded the potential therapeutic options for future use.

Traditional Therapies

Immunotherapy for IgE-mediated disease has been used since its first description nearly a century ago⁽⁷⁾. Although injection immunotherapy has traditionally been employed in the treatment of inhalant allergies, such as allergic rhinitis, it has also been used with success in the treatment of food allergy. Injection immunotherapy was first used in the treatment of food allergy when a young child was successfully desensitized to fish⁽⁸⁾. In patients with allergic rhinitis experiencing oral allergy symptoms with the ingestion of cross-reacting allergens in fresh fruits, nuts, and vegetables, traditional injection immunotherapy has also been successful in many cases in ameliorating the oral allergy symptoms with minimal adverse reactions^(9;10).

Traditional injection immunotherapy for food allergy is currently not recommended because of the significant allergic side effects of the therapy⁽¹¹⁾. Studies have been conducted in a double-blind, placebo-controlled trial of rush immunotherapy for the treatment of anaphylactic hypersensitivity to peanuts⁽¹²⁾. Patients in the treatment group were able to tolerate increased amounts of peanuts in post treatment food challenges. Unfortunately, an unacceptably high rate of adverse systemic reactions was associated with the rush immunotherapy and maintenance protocols^(12;13). The actual peanut immunotherapy produced so many side effects of treatment that practically it would be impossible to perform on a routine basis.

While food desensitization in the oral allergy syndrome has been generally successful and well tolerated with cross-reacting pollen immunotherapy⁽¹⁴⁾, the practice of injection immunotherapy for food allergy has been largely abandoned due to the

associated risk of serious systemic reactions. Since traditional immunotherapy has been largely impractical for the treatment of most food allergies, several novel therapies are now being explored (Table 1).

Novel Therapies

Techniques under current investigation for the treatment of food allergy include: anti-immunoglobulin E (Anti-IgE) therapy, peptide immunotherapy, Traditional Chinese Medicine, mutated protein immunotherapy, allergen DNA immunization vaccination with immunostimulatory DNA sequences and sublingual immunotherapy.

Anti-IgE Immunotherapy: In general, the immune response to allergen immunotherapy is allergen specific, making treatment of multiple allergies complex and expensive. Often patients are allergic to more than one allergen. Ideally, one would prefer to utilize a single therapy to combat the entire allergic mechanism, one therapeutic option that would be effective for multiple inhalant allergies as well as food allergies. One such therapy, already in clinical trials, involves the use of anti-IgE antibodies ⁽¹⁵⁾. Immunoglobulin E (IgE) exists freely circulating or attached to mast cells and basophils. When two mast cell-bound IgE molecules are cross-linked by antigen, the cell is activated, and vasoactive mediators are released. Anti-IgE, a humanized mouse monoclonal IgG antibody, directed against the human IgE molecule, binds to freely circulating IgE and not to mast cell- or basophil-bound IgE. Once circulating IgE is bound by anti-IgE, it is unable to bind to its specific high-affinity receptor (FcεRI) on mast cells and basophils. These antigen-antibody complexes are then cleared from the circulation. Several clinical trials involving patients with allergic rhinitis ⁽¹⁶⁾ and

allergic asthma ⁽¹⁷⁾ have been completed. Statistically significant reductions in medication use, allergic symptoms, and airways hyperreactivity have been described following anti-IgE treatment. Reductions in total serum IgE levels to less than 1% of pretreatment levels were noted in addition to down-regulation of the high-affinity IgE-receptor (FcεRI).⁽¹⁸⁾

A recent study of 84 patients with peanut hypersensitivity treated with anti-IgE has been completed ⁽¹⁵⁾. A significant number of patients, receiving the highest dose of anti-IgE monthly for four months, had a significant decrease in their clinical symptoms following peanut challenge post treatment. Patients received 150 mg, 300 mg, or 450 mg of anti-IgE monthly for four months. After treatment the subjects had a peanut challenge. Those subjects receiving the highest dose had an increased tolerance of eight peanuts comparing the pre- and post-food challenge results. One problem with the study though is that 25% of the subjects even in the high dose group had no change of their tolerance to peanuts after treatment.

Although anti-IgE therapy is expensive and requires frequent administration to maintain the IgE-deficient state, it could theoretically be used quite effectively in conjunction or as an adjunct with other therapeutic modalities. For example, pretreatment with anti-IgE could potentially prevent the systemic reactions experienced with peanut immunotherapy ⁽¹²⁾ while achieving the beneficial effects of desensitization. This promising technique is currently under investigation in patients who have food allergy. It should be mentioned though the recent FDA alert in the US on the anaphylactic potential of omalizumab.

Peptide Immunotherapy: Peptide immunotherapy utilizes peptide fragments containing T-cell reactive epitopes rather than complete protein molecules. Theoretically, these peptide fragments are unable to cross-link two IgE molecules required to activate mast cells causing clinical allergic symptoms. These peptides do appear to render T-cells unresponsive to subsequent allergen exposure ⁽¹⁹⁾. In one study utilizing peptide immunotherapy, the investigators injected cat allergic patients with T-cell reactive peptide fragments of a dominant cat allergen ⁽²⁰⁾. Patients tolerated the injections with some both immediate and delayed adverse reactions. The investigators demonstrated that cat allergic patients treated with the peptide fragments had statistically significant improvement in nasal, lung, and total symptom scores when compared to placebo-treated subjects after exposure to cats ⁽²⁰⁾. A similarly related approach that has involved larger numbers of peptides from cat has also been shown to be effective.⁽²¹⁾ Cat-allergic patients treated with intradermal cat peptides developed a significant immune response, as well as clinical improvement in their symptoms.

Another study demonstrated that pepsin-digested peanut allergen containing T-cell epitopes but no IgE-binding epitopes induced interferon-gamma (IFN- γ), a T_H1 cytokine, in a concentration-dependent manner ⁽²²⁾. While peptide immunotherapy for food allergy has not yet reached clinical trials, studies utilizing the peptides of the peanut allergens are interesting and suggest a possible role for peptide immunotherapy in the future therapy of food allergy.

Traditional Chinese Medicine: Herbal remedies have been used in Asia for centuries for the treatment of allergic diseases ^(23;24). They have a favorable safety profile and the advantage of a low cost. Recent studies have utilized Traditional

Chinese Medicine in a mouse model of peanut allergy.^(24;25) IgE levels were significantly reduced by the food allergy herbal formula-2 (FAHF-2) treatment and remained significantly lower for as long as 5 weeks post-therapy. Splenocytes from FAHF-2–treated mice showed significantly reduced IL-4, IL-5, and IL-13, and enhanced IFN- γ production. Work is now underway to delineate the active ingredients in FAHF-2 and understand the mechanism of action for this compound.

Fusion Proteins: Utilizing another idea to prevent IgE-mediated symptoms, investigators have shown that cross-linking of Fc γ RIIb to Fc ϵ RI on human mast cells and basophils by a genetically engineered Fc γ -Fc ϵ protein (GE2) leads to the inhibition of mediator release upon Fc ϵ RI challenge⁽²⁶⁾. GE2 protein was shown to inhibit cord blood-derived mast cell and peripheral blood basophil mediator release *in vitro* in a dose-dependent fashion, including inhibition of human IgE reactivity to cat allergens. The mechanism of inhibition in mast cells included alterations in IgE-mediated Ca²⁺ mobilization, tyrosine kinase phosphorylation and the formation of downstream of complexes. Pro-allergic effects of Langerhan's like dendritic cells, and B-cell IgE switching were also inhibited by GE2. *In vivo*, GE2 was shown to block passive cutaneous anaphylaxis driven by human IgE in mice expressing the human Fc ϵ RI and inhibit skin test reactivity to dust mite antigen in a dose-dependent manner in rhesus monkeys⁽²⁶⁾. The balance between positive and negative signaling controls of mast cell and basophil reactivity is critical in the expression of human allergic diseases. This approach using a human Fc γ -Fc ϵ fusion protein to co aggregate Fc ϵ RI with the Fc γ RII holds promise as a new therapeutic platform for the immunomodulation of

allergic diseases and potentially other mast cell/basophil-dependent disease states. It's applicability to the treatment of food allergy remains to be seen.

Mutated Protein Immunotherapy: With greater understanding of the allergic mechanism and better characterization of allergens, we and our collaborators ^(6;27) are developing techniques that appear to be both safe and effective in the treatment of food allergy. This type of immunotherapy can be achieved through modification of the primary amino acid sequences of IgE-binding epitopes of the major allergens present in foods. Food-specific IgE typically binds to the linear amino acid sequences of food allergens, whereas IgE binds to the conformational sites of inhaled allergens.⁽²⁷⁾ By altering the primary amino acid sequence of the IgE epitopes, researchers have been able to substantially alter IgE antibody binding with the major peanut and shrimp allergens which resulted in either reduced IgE binding or complete abolishment of binding.

The major peanut allergens, Ara h 1, Ara h 2 and Ara h 3 have had mutations made to their cDNA and then the mutated less-allergenic proteins were expressed in *E. coli* ^(28;29). Mutating the IgE-binding sites did not significantly alter the T-cell epitopes, however, patients with peanut hypersensitivity had dramatically reduced IgE binding to the mutated proteins when compared to the wild type peanut proteins. In animal studies with peanut-allergic mice, the mutated proteins significantly reduced the amount of peanut-specific IgE antibody produced by the peanut-allergic animal, as well as reducing their clinical symptoms following a peanut challenge ^(30;31). The treated animals had a reduction in Th2 cytokines over the course of the treatment, with data suggesting an increase in T regulatory cells producing IL-10.

Designing molecules that have reduced or abolished IgE binding, while preserving their ability to stimulate T cells, have been shown to be effective treatments in the case of inhaled allergens and are expected to result in the availability of safe and effective therapeutics for the treatment of food allergy. Genetically modified birch pollen allergens were effective in patients with oral allergy syndrome (Niederberger V et al. J Allergy Clin Immunol 2007; 119: 1013). Alteration of such molecules in foods theoretically could substantially reduce the incidence of food-induced anaphylactic reactions in sensitized patients. If this technique would be viable, allergic patients might be able to ingest the less allergenic foods. However, this approach currently is very unlikely because of the large numbers of allergens in some of the most prevalent allergenic foods such as egg, milk, peanut, tree nuts etc.

DNA Immunization: Another novel approach to the treatment of food allergy currently under investigation is DNA immunization ^(32;33). DNA immunization employs the subcutaneous injection of a plasmid DNA (pDNA) vector encoding a specific allergenic protein. The pDNA sequence is taken up by antigen presenting cells (APC). Once inside the cell, the DNA encoding allergen is transcribed and translated. The allergen is then presumably presented on the surface of the APC, in the context of the major histocompatibility complex (MHC), to T cells. This endogenously produced allergenic protein or protein fragment induces a T_H1 phenotypic response with up-regulation of IFN- γ , an increase in IgG₂, and suppression of allergen-specific IgE production ^(34;35). Oral delivery of DNA immunizations has also been described. It has been utilized as an immunoprophylactic strategy to modulate peanut antigen-induced anaphylaxis ⁽³⁴⁾. In this model, the oral delivery of DNA complexed to chitosan, a

biocompatible polysaccharide, also favored a T_h1 response and suppressed the T_h2 allergic immune response.

Immunization with Immunostimulatory Sequences: Another DNA immunization technique under investigation is immunization with pDNA conjugated to immunostimulatory sequences (ISS). These ISS contain unmethylated cytosine and guanine dinucleotide repeat motifs. These CpG motifs stimulate APCs and natural killer cells to secrete IFN- γ and IL-12, cytokines that promote immune deviation with TLR-9 toward the T_h1 phenotype and away from the allergic T_h2 phenotype ⁽³⁵⁾. These ISS stimulate immune deviation to the T_h1 phenotype when administered in several ways. They can be administered with DNA encoding the allergen (DNA immunization), ⁽³⁶⁾ given alone, ⁽³⁷⁾ or conjugated with allergen. Although the majority of these DNA immunization techniques have been studied in the mouse model, a recent report describes enhanced immune deviation to the T_h1 phenotype and reduced allergenicity after injection immunotherapy with the major ragweed allergen, Amb a 1, conjugated to ISS in mice and rabbits, as well as in primates ⁽³⁸⁾.

SLIT and food allergy: Because subcutaneous immunotherapy is associated with a relatively high prevalence of adverse events, sublingual immunotherapy (SLIT) has been proposed as a potential alternative. While virtually all published controlled studies with SLIT have been directed against sensitivity to inhalant allergens, there was a recent publication on SLIT use for hazelnut food allergy by Enrique and co-workers ⁽³⁹⁾. In that study, 23 adult subjects, divided into 2 treatment groups (12 hazelnut SLIT and 11 placebo SLIT) with sensitivity to hazelnut confirmed by double-blind, placebo-controlled food challenge, received a four day buildup in the clinic followed by 3 months

of home administration of hazelnut extract by the sublingual-discharge technique. On repeat DBPCFC, the tolerated dose of hazelnut increased from 2.29 grams to 11.56 grams in the active treatment group ($p=0.02$), and from 3.49 to 4.14 in the placebo group ($p = \text{NS}$). The authors theorized that the increase in the threshold of sensitivity to hazelnut in the active group should translate into at least partial protection against most accidental ingestions of hazelnuts. In addition, laboratory data showed an increase in IgG₄ and IL-10 levels after immunotherapy in the actively treated group.

As for safety, systemic reactions were observed in 0.2% (3 reactions in 1466 doses), and all appeared only during the rapid 4-day buildup phase. Only antihistamines were required for treatment of adverse events. Local reactions, mainly in the form of immediate oral pruritus, were observed in 7.4% (109 reactions in 1466 doses) and did not require treatment.

Another published report using SLIT to treat food allergy involved a 29-year-old patient with a history of severe anaphylaxis associated with shock and loss of consciousness to kiwi fruit ingestion ⁽⁴⁰⁾. The patient was started on gradually increasing amounts of kiwi protein via SLIT until maintenance therapy was reached after 5 weeks. After 6 weeks of maintenance therapy, there was a marked increase in kiwi-specific IgG₄ levels compared with pre-therapy values (82.2 mcg/L before therapy to 774 mcg/L after therapy). In a follow-up report almost 5 years later, the patient's kiwi-specific IgE levels had dropped, kiwi-specific IgG₄ levels remained substantially elevated, and Western blots with kiwi extract demonstrated diminished IgE-reactivity to the dominant kiwi allergen. However, no food challenges to kiwi were performed to

demonstrate increased or complete tolerance to kiwi. Besides the study by Enrique there are other works showing that SLIT was not effective in patients with OAS {989}

Currently, a pilot study using the Greer Laboratory peanut extract is being conducted at Duke University (present authors) exploring low dose peanut SLIT in peanut allergic subjects. Entry is ongoing, and escalations have occurred in all subjects enrolled to date as planned. Minimal allergic side effects from SLIT have occurred to date in the Duke pilot study including oral pruritis, sneeze, cough, skin pruritis, hives, abdominal pain, flair in atopic dermatitis, rhinorrhea and throat tightness, skin erythema and nausea.. Only one subject has required any treatment for symptoms (an isolated hive) and only Benadryl was required.

OIT and food allergy: Other somewhat similar studies to SLIT include the use of specific oral tolerance induction (SOTI) or oral immunotherapy (OIT) have recently been conducted ⁽⁴¹⁾. Although somewhat promising, these studies hope to induce initial desensitization (not unlike an antibiotic desensitization) and in the longer term clinical tolerance. In a standardized OIT protocol for treatment of various food allergies, desensitization occurred in 77% of treatments. ⁽⁴²⁾ The most common food allergy among subjects was milk, followed by egg and fish. In comparison to age-matched food allergic controls, subjects receiving OIT experienced a significant decrease in food-specific IgE and an increase in specific IgG₄. Meglio and colleagues ⁽⁴³⁾ employed an OIT protocol in children with proven IgE-mediated sensitivity to milk. In 6 months, 15 of 21 children were fully desensitized; 3 children were partially so. Even partial desensitization dramatically reduced the risk of severe reactions after accidental or unnoticed ingestion of cow's milk at low quantities. More recently, 7 subjects with egg

allergy completed a 24-month protocol for egg oral immunotherapy.⁽⁴⁴⁾ Four of the 7 subjects passed a double blind, placebo controlled food challenge to 10 g of egg at the conclusion of the therapy. The remaining 3 subjects had significantly increased tolerance to egg.

While both SLIT and OIT have shown positive results, most of the studies reported to date have lacked control groups, and it has been suggested that success of the therapy may be due to spontaneous desensitization that can occur with age. In 2005, Rolinck-Werninghaus et al⁽⁴⁵⁾ reported initial results for 3 patients enrolled in a randomized, placebo-controlled study of oral tolerance induction therapy for cow's milk or egg allergy. Home daily dosing was conducted until patients achieved tolerance to 250 mL milk or 4.5 g egg protein, which happened after 37 to 52 weeks. Daily dosing was followed by an elimination diet for 2 months and then a double blind, placebo controlled food challenge. Of the 2 patients who underwent the final food challenge, both experienced moderate systemic allergic reactions, similar to their symptoms prior to therapy.

Results from the larger study of 45 patients, which followed the same protocol, have recently been published.⁽⁴⁶⁾ At the follow-up food challenge, 9 of 25 children (36%) showed permanent tolerance in the tolerance induction group, versus 7 of 20 (35%) in the elimination diet control group. The results suggest that oral tolerance induction therapy may not alter the natural course of tolerance development. However, in the tolerance induction group, 7 children were considered either partial responders or responders when receiving regular antigen intake, boosting the rate of any response to 64%. Allergen-specific IgE decreased significantly in children who developed natural

tolerance during the elimination diet and those who received induction therapy. Even though partially tolerant patients would need a regular intake of allergen to maintain desensitization, this could protect patients against severe reactions or those resulting from accidental exposure to antigen. Cow's milk and egg allergies are commonly outgrown, which may explain the similar values in the treatment induction and control groups.

For allergies that are rarely outgrown—such as peanut—the spontaneous development of tolerance is less likely. On ongoing work, we are studying whether peanut OIT is safe and can induce desensitization and clinical tolerance in peanut-allergic children. Twenty-four patients have been enrolled in a 24-month protocol that ends with an open food challenge to 3.9 g peanut protein. To date, 20 subjects have completed the study, and 18 of them (90%) ingested 3.9 g peanut protein during the challenge. During the study, subjects experienced typical allergic symptoms, primarily in the initial phases of therapy. Peanut-specific IgE increased initially but then decreased at 12 and 18 months, whereas peanut-specific IgG4 increased significantly throughout the study. The initial results suggest peanut OIT can safely establish desensitization in peanut-allergic children but it remains to be seen whether clinical tolerance will develop after this treatment.

Expert Opinion

Food allergy affects approximately 6% of children and 3.5% of adults ⁽⁴⁷⁾. For those patients, and the families of patients, who have anaphylactic reactions, food allergy can be devastating. Reactions can range from mild urticarial reactions to severe

anaphylactic shock and death from allergenic foods consumed unknowingly. The only preventative measure currently available for food allergy is strict avoidance of the incriminating food, which is often very difficult. It is likely immunotherapy will be available in the near future as a safe and potentially effective therapy for the treatment of food allergy. New therapies currently under investigation should help the physician greatly improve care for food-induced allergic reactions while reducing the risk of anaphylaxis in these patients.

Peptide immunotherapy and allergen DNA immunization are likely years away from practical use, even in preliminary pilot studies.

Anti-IgE therapy holds some promise but several studies need to be completed before FDA approval would be obtained. It is likely though the best use of anti-IgE would be as an adjunct with another type of food allergen immunotherapy to help induce less side effects of the new treatment. Traditional Chinese Medicine is a fascinating concept and as the investigators are able to make progress to identify the active ingredients, then clinical trials should begin soon. Mutated allergen immunotherapy is likely to begin the initial pilot studies in humans with the next year and should yield interesting results. Lastly, SLIT and OIT has shown much promise in the initial studies and with the studies in the next two to three years, if positive, should help with an active form of therapy for food allergy.

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Table 1: Potential immunotherapeutic strategies for the treatment of food allergy.

Therapy	Type of Allergy	Route	Immunologic Mechanism	Risks
Traditional Injection Immunotherapy	Oral Allergy Syndrome	Subcutaneous	Increased IgG-blocking antibodies, decreases specific-IgE	Safe when performed properly
Sublingual Immunotherapy	IgE-mediated food allergy	Sublingually	Increased IgG-blocking antibodies, decreases specific-IgE	Generally safe, few reported significant systemic effects
Oral Immunotherapy (OIT) (Specific Oral Tolerance Induction-SOTI)	IgE-mediated food allergy	Orally	Increased IgG-blocking antibodies, decreases specific-IgE	Expected allergic side effects, systemic symptoms observed
Peptide Immunotherapy	IgE-mediated food allergy	Subcutaneous	Immune deviation from T_H2 to T_H1	Has both immediate and delayed allergic reactions
Traditional Chinese Medicine	IgE-mediated food allergy (asthma)	Subcutaneous	Immune deviation from T_H2 to T_H1	Appears safe
Fusion proteins	IgE-mediated (all types)	Subcutaneous	Blocks IgE-mediated signaling	Unknown now
Mutated protein immunotherapy	IgE-mediated food allergy	Subcutaneous, intranasal and oral	Immune deviation from T_H2 to T_H1 (?)	Appears safe, normal allergic side effects expected
DNA Immunization	IgE-mediated food allergy	Subcutaneous and oral	(Subcutaneous) Immune deviation from T_H2 to T_H1 , (Oral) increase levels of allergen specific secretory IgA in gut, and increase systemic IgG	Unknown long-term
Immunostimulatory Sequences (ISS)	IgE-mediated food allergy	Subcutaneous	Immune deviation from T_H2 to T_H1	Appears safe
Anti-IgE Therapy	IgE-mediated food allergy	Subcutaneous	Depletes IgE, Blocks IgE from binding to high affinity IgE-receptor ($FC\epsilon RI$), Down regulates IgE receptor production	Appears safe

