

Food Allergy: Update on Clinical Interventions Leading to Desensitization and Tolerance

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Food allergy refers to an immune-mediated response to a food protein, and can be further divided into IgE-mediated, non-IgE-mediated, and mixed mechanisms. A significant proportion of Western society is affected, ranging from 1 to 2% but less than 10% of the population according to a recent systematic review. A breakdown in oral tolerance leads to the development of food allergy and is characterized by a heightened Th2 response in an allergic individual leading to an increase in the production of food-allergen specific IgE. Upon re-exposure to a food allergen, allergen-specific IgE bound to mast cells is cross-linked causing a release of inflammatory mediators manifesting symptomatically as an allergic reaction. The current standard treatment is avoidance of the provocative food allergen. Ongoing research is intensely studying novel ways of inducing desensitization and understanding which methods induce long-term tolerance. This review discusses our current understanding of the development of oral tolerance and takes a look at ongoing research investigating novel treatment modalities for IgE-mediated food allergies.

Introduction

ALLERGY IS A HYPERSENSITIVITY reaction initiated by specific immunologic mechanisms¹; thus, when this term is applied to a hypersensitivity reaction to a food, it implies the interaction between food and the immune system in producing the physical response. This definition is descriptive of a number of food-related diseases ranging from non-immunoglobulin E (IgE)-mediated diseases such as celiac disease to IgE-mediated reactions to foods resulting in anaphylaxis and includes diseases such as eosinophilic esophagitis, which involves both IgE and non-IgE-mediated mechanisms. This review will focus primarily on desensitization and tolerance development, as it relates to IgE-mediated food allergy.

Prevalence

A recent systematic review estimates that >1% to 2% but <10% of the population is affected by food allergies.² A cross-sectional survey of data on food allergy among children <18 years of age revealed the prevalence of reported food allergy increased 18% from 1997 through 2007.³ The same report states that ~1 in 25 children under the age of 18 have a food allergy, with a significantly higher proportion of children under the age of 5 years affected compared to those from 5 to 17 years. An increasing number of affected children is supported by self-reported surveys examining the incidence of peanut, tree nut, and sesame allergy in U.S. children.⁴ They report that tree nut allergies have increased from 0.2% in 1997

to 1.1% in 2008 in children <18 years, and peanut allergy increased from 0.2% to 1.4% in the same period.⁴

The underlying causes of the increased prevalence of food allergy are largely unknown. A comprehensive review of the various etiologies believed to contribute to the rise in food allergy prevalence was published in the *Journal of Allergy and Clinical Immunology* in 2008.⁵ Genetic predisposition in combination with various environmental factors is likely to play a large role. Picking out which environmental factors seem to have the largest influence is still largely unknown. Hypotheses include the following:

1. Timing of exposure to the most allergenic foods (eg, early introduction of highly allergenic foods versus avoidance early in life).⁵
2. Changes in dietary composition in the past 3 decades (eg, decreased consumption of animal fat and an increase in consumption of ω -6 polyunsaturated fatty acids,⁶ and both Vitamin D excess⁷ and deficiency⁸ have been postulated as potential contributors).
3. The hygiene hypothesis⁹ has been used to explain an overall increase in allergic disease though literature regarding its role in the development of food allergy in particular is lacking.
4. Environmental food exposure may sensitize an individual, particularly a child, with a compromised skin barrier such as patients with atopic dermatitis, bypassing allergen exposure through the oral route and thus preventing the development of oral tolerance.⁵

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The majority of IgE-mediated reactions secondary to food ingestion are caused by a limited number of foods. Milk, egg, and peanut are most common in children, followed by tree nuts as a group, wheat, soy, fish, shellfish, and sesame.¹⁰ The most common food allergens in adults are those that are least likely to be outgrown—shellfish, fish, peanuts, and tree nuts.¹⁰

Previous studies have shown that the majority of children will outgrow milk allergy by 3 years of life,^{11,12} and will outgrow egg allergy by early school-age years.^{13–15} Traditionally, it has been assumed that soy and wheat allergy are outgrown by preschool age years though few studies had been performed to establish that recommendation.¹⁶ Since 2007, data published from a major food allergy center suggests that food allergies to these foods may actually persist longer than originally believed.

In a series of publications, Dr. Robert Wood's group at Johns Hopkins University reported a later age of tolerance development than had been reported in other published reports. They showed that cow's milk allergy resolved in 64% of their population by 12 years of age,¹⁷ egg allergy resolved in 68% by 16 years of age,¹⁸ wheat allergy resolved in 62% by 10 years of age,¹⁹ and soy was outgrown by ~50% by 7 years of age.²⁰ These data must be interpreted in light of the fact that the population being studied was followed at a major food allergy center; thus, children with persistent allergy were more likely to follow-up and were included in the analysis.

Pathophysiology of Food Allergy and the Development of Oral Tolerance

For an IgE-mediated reaction to occur, an individual must first be sensitized. After ingestion, proteins are absorbed through the gut mucosa, taken up by specialized epithelial cells called M cells. Antigen presenting cells, such as dendritic cells, acquire the protein, and process the protein into peptide fragments. The peptides are then presented on the cell surface by class II MHC molecules. Antigen receptors on naïve helper T cells recognize the peptide. In a nonallergic individual, a Th1 response occurs, characterized by cytokines such as interferon γ (IFN- γ). Th2 cells are activated in an allergic individual releasing interleukins (ILs), including IL-4, IL-5, and IL-13. B cells are then stimulated to make IgE specific for the particular food to which the person is allergic. IgE binds to the high-affinity surface IgE receptor on mast cells and basophils, Fc ϵ RI. Upon re-exposure to the allergen, the IgE molecules are cross-linked by the allergen, and mast cells and basophils release their inflammatory contents, including histamine, cytokines, and leukotrienes, leading to symptoms typically associated with an allergic reaction.

Oral tolerance refers to a state of active inhibition of immune responses to an antigen by means of prior exposure through the oral route.²¹ Several reviews addressing this subject have been published in the past several years, and the reader is encouraged to read these reviews for more in-depth discussion of the mechanisms behind the development of oral tolerance.^{22–25} Briefly, murine research has shown that oral tolerance may be induced by either high-dose or prolonged low-dose exposure to an allergen. With high-dose exposure, tolerance is achieved via T-cell receptor ligation either in the absence of costimulatory molecules such as IL-2 or in the absence of interaction between costimulatory receptors on T-cells (CD28) and antigen presenting cells (CD80 and CD86), leading to anergy.²⁶ Alternatively, high-dose

exposure may also lead to clonal deletion of the effector T-cell via FAS-mediated apoptosis (Apo-1 or CD95).²⁷

Prolonged low-dose exposure leads to the development of tolerance primarily through the upregulation of regulatory T-cells (CD4+CD25+), which express the transcription factor forkhead box P3.²⁸ Forkhead box P3 is thought to inhibit Th1 and Th2 responses.²⁹ Immune responses are also suppressed through soluble or cell-surface-associated down-modulatory cytokines such as transforming growth factor β (TGF- β), IL-10, and IL-4. These antigen-specific regulatory cells migrate to lymphoid organs and inhibit the generation of effector T-cells, thus suppressing the immune response. They also migrate to target organs, suppressing disease by releasing antigen-nonspecific cytokines.²²

Recently, attention has turned to the influence of TGF- β in maternal breast milk, and its influence on the development of tolerance.³⁰ TGF- β acts to regulate Th1 and Th2 responses and promote regulatory T-cell development. It is believed that it is not the amount of TGF- β present in breast milk that determines whether or not allergy develops, but rather the strength of the signals from the cells to the nucleus.³¹ However, investigators have shown that orally administered TGF- β retains biological activity. The presence of TGF- β enhances oral tolerance development in ovalbumin-sensitized mice,³² and influences the development of a Th1 immune response profile in allergy-prone rats.³³ This evidence argues in favor of earlier introduction of food antigens, suggesting that early oral antigen exposure concomitant with breastfeeding or TGF- β supplementation may be beneficial for promoting tolerance development.³⁰

Food Allergy Research

Ongoing research for treatment of food allergies has centered around 2 major approaches, allergen-nonspecific immunotherapy and allergen-specific immunotherapy. Allergen-nonspecific immunotherapy focuses on suppressing the immune response rather than directly altering antigen-specific responses. Allergen-specific immunotherapy, on the other hand, deals predominately with the concepts of desensitization and tolerance. Desensitization refers to increasing the threshold of allergen needed to cause allergic symptoms and is dependent on regular allergen exposure. Tolerance, as mentioned above, implies a permanent loss of allergic reactivity independent of regular allergen exposure.

Anti-IgE Therapy

Nonspecific immunotherapy for peanut allergic subjects was investigated using an anti-IgE monoclonal antibody, TNX-901.³⁴ TNX-901 is a humanized IgG1 monoclonal antibody against IgE that recognizes and masks an epitope in the CH3 region of IgE responsible for binding to the high-affinity Fc ϵ receptor on mast cells and basophils. A double-blind, multicenter trial included 84 adolescent and adult subjects with a history of immediate hypersensitivity to peanut. Threshold doses of reactivity were confirmed by a double-blind, placebo-controlled food challenge at entry and then within 2–4 weeks of the fourth dose. Subjects were randomly assigned to receive 1 of 3 doses of TNX-901 or placebo every 4 weeks for 4 doses.

The study concluded that subjects receiving the highest dose of TNX-901 had a significantly increased threshold of

sensitivity to peanut on oral food challenge from 178 mg (equivalent to $\sim\frac{1}{2}$ of a peanut) at study entry to 2.8 g (equivalent to ~ 9 peanuts) at study end. However, $\sim 25\%$ of subjects in the highest-dose group tolerated the entire peanut challenge (10 g of peanut protein or >20 peanuts), and another 25% in the same group had no change in the amount of peanut flour required to induce a reaction. There were no identifiable characteristics, including peanut-specific IgE values or total serum IgE concentration, that differentiated reactors and nonreactors.

Although the study showed promise that TNX-901 would provide protection against accidental ingestion of peanut in the majority of those treated, drug development was discontinued. A trial using omalizumab (Xolair; Genentech, San Francisco, CA), an alternate anti-IgE monoclonal antibody, for the treatment of peanut allergy showed initial promise, but the trial was discontinued secondary to safety concerns from an external Data Monitoring Committee.³⁵

Chinese Herbal Medicine

Traditional Chinese Medicine has been used in Asia for centuries to treat numerous diseases. Over the past decade, Traditional Chinese Medicine has been investigated as a potential treatment for food allergies. Original studies were performed in mice delivering a combination of 11 herbs and labeled as Food Allergy Herbal Formula-1 (FAHF-1).³⁶ Mice sensitized to peanut were given FAHF-1 for a total of 7 weeks. Mice were then challenged to peanut, and peanut-induced anaphylaxis symptoms were completely abrogated, and mast cell degranulation and histamine release were significantly reduced. Peanut-specific serum IgE levels were also significantly reduced by 2 weeks of treatment and remained lower 4 weeks after discontinuation of treatment.

Secondary to concerns for potential toxicity in the original formulation, a second product, FAHF-2, was developed that contained the original ingredients except for 2 herbs.³⁷ In murine experiments, peanut-sensitized mice were given FAHF-2 daily for 6 weeks. Peanut challenges were performed monthly and FAHF-2-treated mice were found to have full protection >36 months after treatment. The long-lasting protection seen clinically is coupled with a shift in allergen-specific immune responses largely mediated by elevated CD8⁺T-cell IFN- γ production.³⁸ Peanut-specific IgE levels were reduced as much as 50%, and IgG_{2a} levels were increased as much as 60%.

More recently, FAHF-2 has entered into human trials. Phase 1 studies are complete and report that FAHF-2 appears to be safe and well-tolerated in food allergic subjects.³⁹ Phase 2 studies are underway.

Engineered Recombinant Proteins

By substituting amino acids on Ara h1, 2 and 3, the 3 major allergenic peanut proteins, the ability of IgE to bind to the protein is eliminated or drastically reduced.⁴⁰ Using site-directed mutagenesis, amino acids necessary for IgE binding were altered, but T-cell proliferation was not inhibited. Investigators were able to generate *Escherichia coli* clones expressing modified Ara h1, 2, and 3 and administer 3 different doses in a methylcellulose carrier to peanut allergic mice weekly for 3 doses. Mice were then challenged

to peanut from 2 to 10 weeks after therapy. Mice receiving the medium and high doses remained protected against anaphylaxis for up to 10 weeks after treatment. Investigators also noted a significant reduction in plasma histamine levels and IgE levels in all treated groups. The group receiving the highest doses showed depressed IL-4, IL-13, IL-5, and IL-10 production by splenocytes and increased IFN- γ and TGF- β production. Human studies are currently underway.

Effect of Heating on Food Protein Allergenicity

IgE binding to food proteins may be specific for either conformational or sequential epitopes within the protein itself. Conformational epitopes are formed by amino acid residues from different regions of the allergen and are dependent on protein folding.⁴¹ They may be affected by heating, enzymatic digestion, or low pH. Sequential epitopes, on the other hand, are comprised of sequential amino acids and, in general, are not affected by such factors. Reactivity to sequential epitopes rather than conformational epitopes is proposed to explain why some milk and egg allergic children are able to tolerate the baked forms of either milk or egg.

Investigators have examined both milk and egg allergic children and found that the majority of those labeled as milk and egg allergic are in fact able to eat the baked forms of milk and egg without having an allergic reaction.^{42,43} In the heated milk study,⁴² children with milk allergy were challenged with heated milk products and then subsequently challenged with unheated milk. Those who tolerated heated milk, but reacted to unheated milk, ingested heated milk products for 3 months and were then re-evaluated. At 3 months, investigators found significantly smaller skin prick test (SPT) wheal diameters and higher casein IgG₄ compared with baseline. Those who were able to tolerate heated milk had significantly smaller SPT wheal diameters and lower milk-specific and casein-specific IgE levels at entry than the reactive group.

Subjects with documented egg allergy were enrolled in a study looking at extensively heated egg tolerance with a similar design as that mentioned above for investigating heated milk tolerance.⁴³ Children who were reactive to regular egg but tolerant of heated egg (as confirmed by observed challenges) were told to incorporate heated egg into their diets. Similar to the findings in the heated milk study, children tolerant of heated egg had smaller SPT wheal diameters at baseline. They also had significantly lower egg white-specific, ovalbumin-specific, and ovomucoid-specific IgE levels compared to the reactive group. At 3 months, continued ingestion of heated egg showed that SPT wheal diameters and ovalbumin-specific IgE levels had decreased significantly and ovalbumin-specific and ovomucoid-specific IgG₄ levels had increased significantly.

The immunologic findings mentioned above are similar to what has been described in oral immunotherapy (OIT) trials and suggest that introduction of baked milk or baked egg may be an alternate route of attaining tolerance.⁴¹

Sublingual Immunotherapy

The first double-blind, placebo-controlled trial was published in 1986 looking at the use of sublingual immunotherapy

(SLIT) for the treatment of dust mite allergy.⁴⁴ Investigation into the use of SLIT for the treatment of food allergy has not been thoroughly investigated.

In 2005, Enrique et al. examined the utility of SLIT for hazelnut allergic subjects.⁴⁵ A double-blind, placebo-controlled trial was conducted in adults with hazelnut allergy, confirmed by a positive SPT as well as a positive oral food challenge. The active group was able to tolerate a significantly greater amount of hazelnut at the end of the study compared to entry and compared to the placebo group. Systemic and local reactions secondary to the SLIT drops were rare. However, the study was hampered by the fact that a large portion of those enrolled had oral allergy syndrome alone as their presenting complaint.

More recent work has been done examining the efficacy of SLIT for Class I food allergy (food-induced reactions characterized by the rapid onset of IgE-mediated symptoms that can progress to anaphylaxis). Studies looking at both milk SLIT⁴⁶ and peanut SLIT⁴⁷ are currently ongoing. Preliminary results from the milk SLIT study suggest that SLIT alone may be efficacious for desensitization of milk-allergic children.⁴⁶

Oral Immunotherapy

The concept of oral desensitization involves giving increasing amounts of a known allergenic food via the gastrointestinal tract. Several studies have examined the safety and efficacy of OIT, primarily focusing on milk, egg, and peanut desensitization.

Studies investigating the efficacy of milk OIT have used maintenance doses ranging from as little as 165 mg daily⁴⁸ to as much as 8,250 mg daily.^{49,50} The majority of participating subjects have been successfully desensitized. Few studies have tested whether or not tolerance develops, meaning that if daily exposure is stopped the subject is able to ingest milk after a period of milk avoidance without an allergic reaction.

Egg OIT has also been used successfully in several studies. Patriarca et al.⁵¹ desensitized 11 of 13 subjects after 3–8 months of therapy. Another group has reported successful desensitization in 7 children undergoing an egg OIT protocol,⁵² though on follow-up analysis 2 subjects out of 21 enrolled were unable to continue secondary to daily symptoms.⁵³ In a report by Staden et al.⁴⁹ 16 of 25 children with either cow's milk ($n = 14$) or hen's egg allergy ($n = 11$) were able to successfully complete an OIT protocol. Nine of the 25 subjects achieved permanent tolerance.

The challenges facing both egg and milk OIT trials include the fact that a significant number of children will outgrow their allergy to egg or milk by avoidance rather than through desensitization, and few studies have directly compared avoidance versus desensitization. In the study mentioned above by Staden et al.,⁴⁹ 35% of children in the control group were able to achieve tolerance by avoidance only. One study from France did show that children participating in an oral desensitization trial to either milk or egg were more likely to pass a food challenge than those who were strictly avoiding the allergenic food during the same period.⁵⁴ However, there were still a significant number of children able to pass a challenge at study completion through strict avoidance. Entry challenges were not performed in either group. Laboratory testing at this point is unable to predict which patients will eventually develop tolerance without intervention, thus

making it difficult to identify which patients will benefit most from intervention.

Unlike milk and egg allergy, peanut allergy is rarely outgrown.⁵⁵ Jones et al.⁵⁶ recently reported successful desensitization in 27 of 29 subjects enrolled in a peanut OIT desensitization protocol. The same group has shown that of 8 subjects who had completed from 32 to 61 months of desensitization, all 8 demonstrated clinical tolerance by passing an oral food challenge 4 weeks after stopping maintenance OIT.⁵⁷ Investigations, including placebo-controlled trials, into the safety and efficacy of peanut OIT are ongoing.

Conclusions

Over the past 20 years much progress has been made in understanding the natural development of oral tolerance, opening doors for investigators to more clearly examine methods of tolerance induction. Therapies such as Chinese herbal medicines may offer hope to families of children with multiple food allergies, and specific oral tolerance induction using either SLIT or OIT may provide an avenue for allowing protection against accidental ingestions and possibly the development of permanent tolerance. The risks of therapy versus avoidance, proper dosing, patient selection, reaction patterns, precautions after desensitization, and allocation of clinical resources must continue being investigated⁵⁸ before any specific therapy is ready for standard clinical practice, but there is certainly hope that a practical treatment for food allergy is in the near future.

Author Disclosure Statement

No competing financial interests exist.

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