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Towards a Cure for Food Allergy

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Summary of recent advances

Over the past two decades, food allergies have become both more prevalent and long-lasting. This burgeoning problem has not been met with any therapeutic options to date, and patients must attempt to avoid known allergenic foods and treat any allergic reactions with “as-needed” medications. There are a number of promising emerging therapeutic modalities for food allergy, including allergen-specific and allergen non-specific immunotherapeutic approaches. Although the allergen-specific approaches have some distinct differences, they all attempt to induce tolerance by exposing the patient to an allergen via the mucosal route (oral tolerance induction). Allergen non-specific approaches include biologics to suppress free total IgE levels (e.g. anti-IgE antibody) or to induce more general immune suppression (Chinese Herbal medication).

Introduction

The burden on food-allergic patients and their families, as well as on the medical system, is significant and growing. There are an estimated 125,000 emergency department [ED] visits each year for food allergy and approximately 15,000 ED visits per year for food-induced anaphylaxis with 3,100 hospitalizations. [1] While some more recent retrospective studies have not found food-induced anaphylaxis-induced deaths to be extremely common, they unfortunately continue to occur [2,3], and remain the ultimate threat to all families dealing with food allergy.

Recently the administration of incremental amounts of a food allergen via the oral route has garnered considerable interest because of its ease of administration and potential efficacy based on recent information about the oral mucosa and its relation to tolerance induction, including a better understanding of the phenotype and trafficking of various cells of the immune system. Dendritic cell (DC) recruitment to the oral mucosa and subsequent presentation of antigen to T cells appears essential for successful oral immunization. [4] There appear to be differences in DC phenotype in the oral mucosa compared to those in the nasal mucosa, including relatively increased surface expression of CD14, CD207 and MHC I and II, and decreased expression of CD80, CD205, CD206 and CD11b. [5] A post-mortem analysis of multiple oral mucosal sites identified different ratios of Langerhans cells (LC) and mast cells at various sites within the oral mucosa. [6] This may be clinically relevant for optimizing the application of allergen-specific immunotherapeutic agents to antigen-presenting cell-rich sites in the oral cavity.

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Here we review several approaches being undertaken in attempts to establish safe and effective treatments for food allergy. A summary of the most significant therapeutic approaches is presented in Table I.

Prevention

The ideal goal in food allergy management would be to prevent the development of the condition. This year, the American Academy of Pediatrics published the following update on recommendations for infant and maternal nutrition options with respect to the development of allergies: [7] “1. There is insufficient evidence to support maternal dietary restrictions during pregnancy or lactation. 2. Breastfeeding (compared to cow milk formula) for at least 4 months can prevent or delay atopic dermatitis, cow milk allergy, and wheezing in childhood. 3. There is insufficient evidence to support any dietary restrictions beyond 4 to 6 months of age. The German Infant Nutritional Intervention Study (GINI) evaluated the use of cow milk formulas of varying degrees of hydrolysis. [8] Over 2,000 newborns at high risk for atopy based on family history were randomly assigned to receive either cow milk or one of three hydrolyzed formulas for the first 4 months of life as a supplement to breastfeeding. At 6 years of age, groups receiving the hydrolyzed formulas had a lower incidence (relative risk 0.82, 95% CI, 0.7-0.96) of all atopic disease compared to those supplemented with intact cow milk protein. Epidemiologic studies found that the incidence of peanut allergy is markedly lower in Israel (<0.1%) [9,10] than in several other westernized countries (~1%). [11] One potential explanation for this disparity is the early (6–7 months of age) introduction of peanut-containing snacks to Israeli infants. Lack et al. hypothesized that this early introduction of peanut protein may induce a form of high-dose tolerance and they have undertaken the Learning Early About Peanut Allergy (LEAP) study, which randomizes infants at high risk for peanut allergy to early introduction of peanut-containing foods versus strict elimination diets.

A number of recent experimental approaches for the prevention of food allergy in murine models have suggested other potential prophylactic approaches:

1. Administration of avirulent *S. typhimurium* to mice prior to allergen sensitization induced gut T cell IL-10 and IL-12 production, mitigated anaphylaxis on food challenge, and decreased antigen-specific IgE and IgG1. [12]
2. Pretreatment with a transfected IL-10-producing *L. lactis* prior to sensitization mitigated anaphylaxis to food challenge, decreased antigen-specific IgE and IgG1 production, and increased antigen-specific IgA production in the gut. [13]
3. Treatment prior to, or after sensitization, with a TLR-9 agonist resulted in inhibition of IL-5, IL-13, and antigen-specific IgE production, while IFN- γ and antigen-specific IgG2a production were enhanced. [14] Thus, some early studies in murine models utilizing treatments aimed at promoting Th1 skewing, or suppressing Th2 skewing, have demonstrated a significant clinical and serologic response.

Allergen-specific immunotherapy

Novel therapeutic approaches can be broadly categorized into allergen-specific and allergen non-specific immunotherapy. Allergen-specific immunotherapy has classically focused on delivering an antigen to the immune system via the subcutaneous route, but controlled human trials utilizing this approach in food allergy resulted in severe adverse reactions. [15,16] At the beginning of the 20th century and more recently, the gastrointestinal mucosa, usually the oral mucosa, has become the route of preferred antigen delivery.

Oral Immunotherapy (OIT)

OIT, where an allergen dose is immediately swallowed, is differentiated from sublingual immunotherapy (SLIT), where a dose is held under the tongue for one to two minutes before being swallowed. Scattered case reports have appeared in the literature since the early 1900's, but over the past decade, Patriarca and coworkers have published several reports of successful desensitization to specific foods in food-allergic patients by administering gradually increasing amounts of the offending food antigen over time. [17-20]

More recently, studies have involved treatment with milk, egg and peanut OIT utilizing various protocols. [19-26] In the first controlled trial of OIT, 25 milk or egg-allergic children underwent dose escalation and then were able to tolerate a maintenance dose of 3 – 8 gm of milk protein or 1.5 – 3 gm egg protein for 18 – 24 months. All treated subjects experienced adverse effects during the dose escalation phase and even while on maintenance therapy, but these reactions were considered mild (e.g. single hives, oral tingling, nausea, or worsening eczema) in most (84%) of the participants. [25] Various factors such as exercise, development of respiratory tract infections, or significant pollen exposure, were associated with increased adverse reactions. Overall 16 subjects (64%) were considered responders, i.e. able to tolerate the maintenance dose. After completion of OIT followed by a 2-month period of allergen avoidance, 9/25 (36%) children remained non-reactive [tolerant] to egg or milk as confirmed by oral food challenge. Food-specific IgE levels decreased significantly in the responder group compared to no change in the non-responders. Interestingly, 35% of the untreated control group also developed tolerance, i.e. were non-reactive to the food challenge, over the same time period. The similar outcomes in both the treatment and control groups suggested that OIT desensitizes the majority of patients during therapy but did not accelerate the natural rate of developing long-term tolerance. To date, no blinded, placebo-controlled trials have been published to answer this question.

Another study attempted to look at highly milk-allergic patients (30 treated with OIT; 30 controls on a milk elimination diet), all of whom reacted to 0.8 mL or less of milk at baseline challenge and who had a milk-specific IgE >85 kU_A/L. [22] Thirty children received an initial 10-day in-hospital rush dose escalation up to a maximum of 20 mL of milk (about 667 mg milk protein). They then gradually increased the dose at home over one year. Again, all experienced adverse reactions, with four requiring administration of self-injectable epinephrine. After one year, food challenges showed that 11 subjects (36%) in the OIT-treated group could consume at least 150 mL of milk with no adverse symptoms. Another 16 (54%) could consume 5 – 150mL of milk prior to reacting. All 30 untreated controls remained reactive to minimal amounts of milk on repeat challenge. Milk-specific IgE levels were unchanged over time, but 23 of 30 treated subjects had >100 kU_A/L and therefore, did not have a specific baseline level from which to measure changes. The investigators did not attempt to assess long-term tolerance.

Sublingual Immunotherapy (SLIT)

Although there is an extensive body of literature utilizing SLIT with environmental allergens, very few studies have been published on the use of SLIT with food allergens. In a recent double-blind, placebo-controlled trial, 23 hazel nut-allergic adults received SLIT with either hazelnut or placebo: 12 active treatment; 11 placebo. [27] Allergy was confirmed by blinded hazelnut challenge; about half were characterized as diagnosed with oral allergy syndrome. Oral pruritus occurred with 7.4% of all doses, while systemic reactions occurred with only 0.2% of all doses, occurred only during the build-up phase, and required only oral antihistamine for treatment. After 2-3 months of therapy, the mean quantity of hazelnut provoking an objective reaction was 2.3 g pre-treatment compared to 11.6 g post-treatment ($p = 0.02$) in the active group. There

was no significant change in the placebo group (3.5 g to 4.1 g). There was no change in hazelnut-IgE in either group, but in the active group, there were small but significant increases in hazelnut-IgG4 and serum IL-10. One other small study utilizing SLIT for milk allergy reported improved tolerance after 6 months of treatment, and also found no significant changes in casein-specific IgE. [28] The NIH-sponsored Consortium of Food Allergy Research (CoFAR) currently is conducting a clinical trial of peanut SLIT.

While no comparison studies of oral versus sublingual administration of a food-specific immunotherapy have been performed, such studies have been done with grass pollen immunotherapy. [29] While both groups ("sublingual" versus "supralingual" [oral]) exhibited improved symptom scores and decreased medication use compared to placebo, the effects were greater in the group receiving SLIT. In addition, only the SLIT group experienced a significant increase in allergen-specific IgG levels. However, both groups were treated with the same dose of allergen and it is possible that similar changes in IgG levels could have been achieved by utilizing higher allergen doses with OIT.

Heat-denatured Protein Exposure

Another variation on immunotherapy with whole food protein involves the use of baked (or, extensively heated) foods. It has been established that an allergic individual's antigen-specific IgE binding repertoire can include specificity to both sequential and conformational epitopes. [30] Frequently, extensively-heated food protein undergo sufficient alteration in the native tertiary structure (heat denaturation) to eliminate conformational epitopes. It has been demonstrated that there are egg-allergic individuals who react to raw egg protein but not heated. [31] In a recent study, 68 children who reacted to unheated cow milk but who tolerated milk in baked products were placed on a diet containing baked milk products for three months. [32] Milk-allergic children ingesting baked-milk products experienced no adverse reactions. A comparison of baseline and 3 months immunologic measures found a significant decrease in median milk skin prick test wheal size ($p = 0.001$) and a significant increase in median casein-specific IgG4 levels ($p = 0.005$). These findings are consistent with those seen in OIT and SLIT, and may represent a "natural" form of OIT.

Engineered Recombinant Food Protein

Several engineered [PCR mutagenesis] recombinant food proteins with immunologic activity have now been generated successfully. [33-35] These proteins can either be administered orally, rectally or by injection. This approach offers the potential to preserve an antigen's ability to stimulate antigen-specific T cells without binding IgE and triggering mast cell activation. Only one *in vivo* study done so far, in a murine system, evaluated clinical and immunologic effects of this type of treatment. [35] Peanut-sensitized mice treated with heat-killed *E. coli* containing modified Ara 1, 2 and 3 [EMP-123 administered rectally] exhibited significantly lower mean symptom scores and plasma histamine levels following peanut challenge than sham-treated mice. Treated mice also had significantly lower mean peanut-specific IgE levels and higher peanut-specific IgG2a. Clinical trials using EMP-123 are planned and expected to begin in the near future.

Allergen non-specific immunotherapy

The previously discussed therapeutic approaches all utilize a specific allergen to alter the immune response to that allergen. An alternative approach is to exert a more generally suppressive effect on all or some part of Th2-mediated immunity. This could provide greater benefit to individuals with multiple food allergies. On the other hand, it presents a potentially greater challenge to exert this broader effect in a clinically significant way.

Anti-IgE Immunotherapy

The concept of decreasing the amount of IgE available to bind an allergen and subsequently trigger an anaphylactic reaction is an attractive one. The ability of anti-IgE therapy to raise peanut-allergic individuals' thresholds for reaction has been studied. [36,37] A trial using the anti-IgE molecule, TNX-901, [36] showed in a double-blind, randomized trial, that thresholds for clinical reactivity can be increased in the majority of peanut-allergic individuals with treatment. However, 25% of participants in the study received no benefit from this form of treatment and no factors were identified to distinguish these non-responders. A second anti-IgE study utilizing omalizumab was discontinued prior to obtaining significant results because of safety concerns related to the pre-omalizumab peanut challenge. [37]

Chinese Herbal Medicine

A novel formulation of nine traditional Chinese herbs, called FAHF-2, has been studied by Li and colleagues for the treatment of food allergy and asthma. In a mouse model of peanut allergy, treatment with FAHF-2 daily for 6 weeks, initiated during the peanut sensitization phase, eliminated evidence of anaphylaxis up to 5 weeks post-therapy ($p < 0.001$ vs. placebo). On average, after active treatment, animals exhibited lower peanut-specific IgE ($p < 0.001$) and higher peanut-specific IgG2a ($p < 0.001$) compared to the placebo group. Additionally, splenocytes from treated mice stimulated with peanut protein in vitro produced lesser amounts of IL-4, IL-5 and IL-13, and greater amounts of IFN- γ on stimulation with peanut compared to sham-treated mice [38] Treatment initiated after completion of sensitization yielded the same complete abrogation of anaphylaxis. [39] Investigation of the activity of individual herbs is ongoing, [40] while the mechanism of activity for this formula remains to be determined. Phase I human trials are now underway.

Alternative Strategies

A number of novel strategies targeting specific immune system molecules or their receptors have been reported in preclinical studies utilizing rodent models of food-induced hypersensitivity. Strategies to block the interaction between TIM-4 and TIM-1 expressed on dendritic cells and T cells, respectively, reversed the Th2 response induced by cholera toxin and peanut extract in peanut-allergic mice. [41] In another study, injection of IL-21 was found to inhibit the development of anaphylaxis in peanut-allergic mice by activating the inhibitor of differentiation gene, Id2, which blocks B cell class switch recombination necessary for the production of IgE. [42] Administration of a peptide-based vaccine against three Fc ϵ RI binding sites on human IgE resulted in significant levels of IgG anti-human IgE titers, and decreased IgE antibody levels in rats when given either before or during sensitization protocols. [43] The oral administration of human recombinant TGF- β to mice undergoing sensitization to OVA resulted in increased serum levels of TGF- β , upregulation of intestinal Smad 7, decreased OVA-specific IgE and IgG1 levels and decreased T cell reactivity. [44] Studies have also targeted inhibition of Fc ϵ RI-induced mast cell degranulation by interfering with receptor cross-linking [45] or receptor signaling [46] in mouse and monkey models. Studies in murine models utilizing an immunotherapeutic protein delivered in conjunction with an immunostimulatory molecule have shown potential advantages in efficacy over immunotherapy alone. [47-50] Lastly, it is possible that immunotherapy can be better targeted to optimal mucosal sites. This has been demonstrated in mice by the addition of a mucoadhesive to the SLIT protein, resulting in enhancement of tolerance induction. [51]

Conclusions

Allergists continue to see an expanding number of patients with food allergy. At the same time, it appears that an increasing number of children are experiencing food allergies (aside from

nut allergies) that persist through school age. This has prompted the urgent need for developing safe and effective treatments for food allergy. It is encouraging that in light of this pressing need, one or more treatment modalities for food allergy appears within reach.

Prevention of disease should always be the first and foremost objective. In this area, much remains to be done. Whether early introduction of potential allergens (likely in forms with reduced allergenic potential) is helpful remains to be proven. Providing the immune system with a “second signal” to enhance tolerance induction has shown some promise in various rodent models.

Of the treatments reviewed above, it appears that some form of orally delivered, allergen-specific immunotherapy is likely to provide the first clinically applicable therapeutic option. It must be emphasized, however, that several issues need clarification before this form of therapy will be approved for clinical use. The route, frequency, and dose will need to be standardized and the safety profile improved, with identification of biomarkers indicating those at greatest risk for reactions. It also will be important to elucidate the underlying immunologic mechanisms for these strategies and determine whether long-term oral tolerance is established.

Allergen-non specific treatments also have shown promise, not only in mice, but also in limited human trials. These forms of therapy are particularly attractive for the treatment of those patients with multiple food allergies in whom allergen-specific treatment of multiple allergies could literally take decades. The combination of allergen-specific with allergen-non specific therapies could potentially yield the greatest benefits.

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Table I

Treatment Type	Key Features	Human Clinical Trials
Prevention		
Dietary allergen avoidance	May decrease atopy with: <ul style="list-style-type: none"> Breastfeeding $\geq$ 4 months[6] Hydrolyzed cow's milk[7] 	Yes
Early allergen introduction	Early peanut exposure maybe associated with decreased peanut allergy [8,9]	Ongoing
Allergen-specific		
Oral Immunotherapy	Incrementally increased swallowed allergen doses resulting in desensitization / ? tolerance	Yes [15-24]
Sublingual Immunotherapy	Incrementally increased allergen doses held under tongue, then swallowed, resulting in desensitization / ? tolerance	Yes [25,26]
Heat-denatured Protein	Extensively heated foods may be less allergenic allowing for administration in a subset of patients [29]	Yes [30]
Engineered Recombinant Food Protein	T cell interaction without IgE binding	No [31-33]
Allergen Non-specific		
Anti-IgE Immunotherapy	Decreases IgE available for allergen binding	Yes[34,35]
Chinese Herbal Medicine	General Th2 immune suppression, mechanism yet to be defined	Yes – Phase I trial underway