

Expert Opinion

Therapeutic approaches for the treatment of food allergy

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Food allergy is a life-changing and potentially life-threatening diagnosis, affecting approximately 6% of children and 4% of adults in the United States. A small number of foods account for the vast majority of food allergies, and the reactions after ingestion of a food to which a person is allergic are varied. At present, the standard of care for food-allergic patients is strict avoidance along with immediate access to self-injectable epinephrine and antihistamines. New treatment options are on the horizon. This review discusses the current research in the field of food allergy. Remarkable progress in the field of food allergy treatment demonstrates promise for disease-modifying therapies to be available clinically in the near future.

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Receiving a diagnosis of food allergy is a life-changing and potentially life-threatening experience. Food allergy affects approximately 6% of children and 4% of adults in the United States [1]. Recent data suggest that the prevalence of peanut allergy in particular has doubled in the last decade [2]. Reactions following the ingestion of a food to which a person is allergic include urticaria, angioedema, wheezing, vomiting and diarrhea. A small number of foods (cow's milk, egg, soy, wheat, seafood and nuts) account for the vast majority of food allergies; however, any food is capable of inducing hypersensitivity [1]. Typically, a patient is allergic to only one food but it is possible to be allergic to several at the same time. The current standard of care for food-allergic patients is strict avoidance along with immediate access to self-injectable epinephrine (adrenaline) and antihistamines. However, strict avoidance can be difficult, and nearly 50% of patients with food allergy report having an allergic reaction to a food during a given 2-year period [3]. The majority of milk-, egg-, soy-, and wheat-allergic patients go on to outgrow their allergies [4]; however, peanut, tree nut, and seafood allergies typically persist into adulthood. Only approximately 20% of children outgrow their peanut allergy [5].

Immunological tolerance is the norm following ingestion of a food. The gastrointestinal (GI) mucosal immune system has both innate and adaptive components that are proficient at inhibiting responses to harmless antigens such as food proteins and commensal bacteria of the gut [6,7]. Food allergy is the result of a breakdown in or lack of development of oral tolerance [4]. Therapeutic approaches for the treatment of food allergy attempt to restore that tolerance in either a specific or non-specific way.

Allergen-specific approaches change the immune response to a particular allergenic food protein to induce a state of desensitization or immune tolerance. Examples include subcutaneous, sublingual or oral immunotherapy; immunotherapy with engineered proteins; peptide immunotherapy; plasmid DNA immunotherapy; and immunotherapy using immune stimulatory sequences. Allergen non-specific approaches target various immune mediators to lower hypersensitivity responses

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to an allergenic food protein. Examples include cytokine treatments, anti-IgE therapy, and Chinese herbal medicine.

When discussing potential therapeutic approaches to the treatment of food allergy, two important definitions need to be clarified. The term 'desensitization' involves protection from life-threatening anaphylaxis; this can be short term or prolonged with ongoing therapy. The term 'tolerance' refers to active modulation of the immune response from a Th2 allergic phenotype to a Th1 phenotype or a down-regulation of a Th2 phenotype.

Subcutaneous immunotherapy (SCIT) is used to treat both environmental and insect allergies. This form of therapy is associated with allergen-specific immune changes, which include an initial increase in allergen-specific immunoglobulin E (IgE) followed by an eventual decrease, an increase in allergen-specific IgG, and a change from a Th2-driven phenotype to a Th1 phenotype. In the mid-1990s, a study was conducted using subcutaneous peanut immunotherapy in a rush protocol. Six patients received the extract and six received placebo. All patients treated demonstrated increased tolerance to higher peanut doses during food challenges and showed an increase in peanut-specific IgG; no change was noted in peanut-specific IgE. Although these results suggested clinical efficacy, significant adverse events were common, making this treatment unacceptable [8].

Both sublingual immunotherapy (SLIT) and oral immunotherapy (OIT) are used frequently outside of the United States to treat environmental allergies. The efficacy of these modalities is lower than SCIT for the treatment of allergic rhinitis; however, the safety profile is in general good [9]. Ongoing research in the field of food allergy involves using these forms of immunotherapy to treat specific food allergies. In a study of 23 patients using SLIT for hazelnut allergy (primarily patients with oral allergy syndrome to hazelnut), patients receiving the extract tolerated significantly higher hazelnut doses after treatment compared to those on placebo [10]. Another recent study investigated 58 patients who received OIT to cow's milk, egg, or fish. Seventy-seven percent of patients were desensitized, tolerating significantly higher doses of the known allergen after therapy. These patients demonstrated increased food-specific IgG and decreased specific IgE [11]. Other studies [12,13] suggested that desensitization to cow's milk in a majority of patients treated was achievable but did not necessarily result in tolerance over time. Meglio *et al.* [12] used OIT to treat 21 children with IgE-mediated cow's milk allergy. Desensitization was successful in 71.4% of patients. These patients were not followed off therapy to examine tolerance. A study of three patients [13] found that the two patients who completed the study were desensitized to milk but not tolerant upon re-exposure during challenge. Newer studies [14-16] demonstrate long-term tolerance in at least a subset of patients with cow's milk allergy. Staden *et al.* [14] found that nine of 25 children treated with milk or egg OIT showed permanent tolerance. Another report [15] found that eleven of 30 children

treated with a milk OIT protocol became tolerant after 1 year. Skripak *et al.* [16] demonstrated that twelve patients receiving milk OIT were able to tolerate significantly higher doses (5140 vs 40 mg) of milk compared to those receiving placebo.

Recent research has focused on OIT to peanuts. The safety of this treatment has been established, although the timing and nature of the allergic side effects are still somewhat unpredictable. The 20 patients in the study tolerated home dosing of oral peanut protein after initially starting and increasing their doses in a research setting. Treatment of symptoms related to home dosing was only required in 0.7% of the time [17]. Clinical studies of these same subjects showed that peanut OIT induced clinical desensitization to peanut in all 29 patients, with 27 tolerating 3.9 g peanut protein (~ 13 peanuts) and two tolerating 2.1 g protein. Laboratory data demonstrated increases in peanut-specific IgG, decreases in basophil activation, and decreases in peanut-specific IgE [18]. Ongoing studies are evaluating tolerance to the peanut allergen over time.

Other allergen-specific approaches include immunotherapy with mutated food proteins, overlapping peptide vaccines, plasmid DNA-encoded vaccines, and allergen-conjugated CpG immunostimulatory sequences. All of these studies show promise in murine models but few have human trials in place [19-22]. An interesting preventive study currently in clinical trials involves the use of high-dose peanut protein in young infants at risk of developing peanut allergy. This study is based on the observation that infants in Israel who regularly eat peanut snacks at a young age have a decreased incidence of peanut allergy compared to other infants that do not ingest these snacks. It is possible that early exposure to large amounts of peanut may induce oral tolerance and an induction of Th1 responses [23].

Allergen non-specific approaches include humanized monoclonal anti-IgE antibodies in an attempt to inactivate IgE, thereby preventing binding of IgE to its receptor and subsequent mast cell activation. This antibody, omalizumab, is effective for allergen-induced asthma. A double-blind, placebo-controlled trial evaluated the use of omalizumab for 84 patients with IgE-mediated peanut allergy. The majority of patients in the omalizumab arm were desensitized to peanuts, tolerating much higher doses of peanut protein on final peanut challenge. However, a minority of patients treated with the drug showed no response [24]. The results were inconsistent, making this treatment unreliable at this time. Further research is needed in this area to understand why a percentage of patients were non-responders.

Other non-specific strategies include Chinese herbal medicine and cytokine therapies. Two murine models studying Chinese herbal medicine show increased tolerance to milk or egg after manipulation of interleukin-10 (IL-10) or transforming growth factor- β (TGF- β) [25,26]. One study examined the effects of food allergy herbal formula 2 (FAHF-2) on peanut-allergic mice. Treated mice showed no signs of anaphylaxis, no changes in plasma histamine levels, and

decreased peanut specific IgE after a peanut challenge. All placebo-treated mice experienced anaphylaxis following the challenge [27]. The mechanism of action is poorly understood at this time, but the results are promising, and human studies are just beginning.

Our understanding of food allergens and oral tolerance has grown significantly over the past decade. Many different approaches show promise and need continued research to further understand the efficacy and safety of these potential treatments. Work also needs to be done to clarify which approaches lead to desensitization versus long-term tolerance. Larger-scale studies of OIT are ongoing to address these issues. Several of the promising prototypes in murine models

will likely soon move to human trials. Remarkable progress in the field of food allergy treatment demonstrates promise for disease-modifying therapies to be available clinically in the near future.

Declaration of interest

The author of this editorial is an ActoGeniX Consultant, an Allertein Minority Stockholder, is on the Dannon Co. Probiotics Advisory Board, is a Intelliject Consultant, is a Mast Cell, Inc. Minority Stockholder, is a McNeil Nutritionals Consultant, a Novartis Consultant and is on the Nutricia Expert Panel.

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