

Will We Be Able to Desensitize Food Allergies by Either Injection or Oral Immunotherapy?

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Introduction

Food allergy is a complex immune response to food proteins. Recent data have suggested that the prevalence of food allergy has doubled over the past decade, and based on estimates from several studies using oral food challenges, approximately 5% of young children and 3% to 4% of adults are affected [1]. However, public perception of food allergy may be much higher [2]. Although any food can trigger an allergic reaction, most reactions are triggered by a limited number of foods. These include milk, eggs, wheat, soy, peanuts, tree nuts, shellfish, and fish. Anaphylaxis to foods can cause significant morbidity, and although fatal reactions are rare, they continue to occur [3]. Food allergy is also associated with a significant impact on quality of life and can adversely affect social well-being, including stress related to possible accidental reactions. The conventional wisdom was that 80% of children typically outgrow their food allergy to milk, egg, wheat, and soy by age 5 years. However, newer research suggests that it may take longer for certain foods, such as milk and eggs [4, 5]. On the other hand, peanuts are often considered a persistent allergen, with only 20% of children outgrowing this allergy [6].

Currently, the standard of care for managing the food allergic patient is recommending strict avoidance of the causative food along with immediate access to self-

injectable epinephrine and antihistamines, if appropriate. Avoidance of specific foods can be arduous for many reasons, including the ubiquitous nature of common food allergens and the risk of cross-contamination. This was illustrated in a study in which approximately 50% of patients with a food allergy reported having an accidental reaction to a food during a given 2-year period [7]. Food avoidance resulting in dietary limitations could lead to nutritional deficits, especially for children who must avoid multiple foods. In addition, the stress of always worrying about a possible accidental reaction can be significant for some. As a result, a clear need exists to develop an active treatment for food allergy. One approach that is currently in various stages of research is to desensitize patients to the causative food. This approach would be similar in theory to the more conventional immunotherapy currently being used for allergic rhinitis. The purpose of this commentary is to highlight some of the research that has been conducted in the various areas of food immunotherapy, particularly via the subcutaneous and mucosal route.

Subcutaneous Immunotherapy

Treatment of hay fever and hymenoptera sensitivity with subcutaneous immunotherapy has been used as a successful therapeutic approach for many years [8–10]. It is typically associated with specific immune changes, such as an initial increase in allergen-specific IgE, followed by an eventual decrease, an increase in allergen-specific IgG₄, and lastly a change from a T-helper type 2–driven phenotype to a T-helper type 1 phenotype. As a result, peanut immunotherapy was first studied using the more traditional subcutaneous route. In this study, six patients

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received aqueous peanut extracts and six received placebo. All the treated patients, compared with those receiving placebo, were able to tolerate more peanut protein upon a subsequent double-blinded, placebo-controlled peanut challenge. Peanut-specific IgG increased in the treatment group, but not specific IgE. No immunologic changes were observed in the placebo group. Although these results suggested a possible clinical effect, significant adverse events were recorded in the treatment group, making it an unfavorable treatment modality [11].

Sublingual and Oral Immunotherapy

Because subcutaneous immunotherapy was associated with unacceptable risks of severe anaphylaxis, sublingual immunotherapy (SLIT) and oral immunotherapy (OIT) have since been studied as possible safe alternatives. Both types of studies use similar protocols in which patients are given increasing amounts of antigen at regular intervals over time until a maintenance dose is achieved. SLIT involves the use of a liquid concentrate administered under the tongue, whereas OIT involves the use of a powdered food protein mixed with a food vehicle.

To date, three studies have examined the effectiveness of SLIT in the treatment of food allergy. In the first study, patients had primarily oral allergy symptoms to hazelnut. In this study, 23 patients received hazelnut extract or placebo for 8 to 12 weeks. Patients receiving the allergen extract tolerated significantly higher hazelnut doses after treatment compared with those on placebo [12]. In the second case study, a patient with life-threatening anaphylaxis to kiwi was successfully desensitized using sublingual kiwi extracts [13, 14]. In a more recent study investigating the efficacy of SLIT, Kim et al. were able to successfully demonstrate desensitization in a double blind placebo controlled trial in 18 peanut allergic children [15]. The patients receiving peanut treatment were able to tolerate 20 times more peanut protein than patients who received placebo. Moreover, the side effects in the treatment group were minor and the authors were able to show immunologic changes suggesting a change in the allergic response in the treatment group. Although these studies using SLIT have been encouraging, more research is required to determine whether SLIT can be used to effectively induce tolerance in patients with IgE-mediated food allergy and how it will compare to OIT in terms of safety and efficacy.

Studies evaluating OIT to definitively treat food allergy have been more extensive than those evaluating SLIT. In general, results from the various OIT studies have been encouraging. Patriarca et al. [16] were able to desensitize 77% of patients compared with age-matched controls to a variety of food allergens, including milk, eggs, and fish. In

another study, Meglio et al. [17] were able to desensitize a similar percentage of children allergic to milk protein. More recently, seven egg allergic patients completed a 24-month egg OIT protocol. All participants were able to tolerate significantly higher doses of egg during a double-blind, placebo-controlled food challenge than at the time of entry into study [18].

Although the results from these previous studies were promising, they lacked a proper control group to assess whether the positive outcomes could actually be a result of natural resolution of the allergy. This is particularly important, as mentioned above, for egg and milk allergies because these are frequently outgrown. To try to solve this issue, several studies compared their results with results of patients on an elimination diet to determine whether therapy outperformed the possible natural resolution of the food allergy. In one study, Longo et al. [19] compared children receiving milk OIT with those on an elimination diet at 6 and 12 months. In this study, all children failed the oral milk challenge, whereas 90% of children on treatment could tolerate 5 to 150 mL of milk. In a more recent double-blind, randomized, placebo-controlled trial of milk OIT, investigators treated 19 children with a modified rush immunotherapy protocol [20, 21]. At the end of the study, which included an open-label portion, patients on treatment tolerated significantly higher doses of milk protein compared with those receiving placebo. Some of the immunologic changes in the treatment group included decreases in end point titration skin prick testing and milk-specific IgE levels, as well as significant increases in milk-specific IgG₄. These studies demonstrate that desensitization to milk protein is effective; however, further study is needed to determine the safety of immunotherapy and possible tolerance induction.

In contrast to milk and egg allergy, peanut allergy persists in most cases. Peanut allergy is increasing in prevalence and can be associated with life-threatening anaphylaxis [22]. As a result, there is significant interest in developing an active therapy for this allergy. Results from preliminary studies have been encouraging. In a small study of peanut OIT, Clark et al. [23] reported a significant increase in the amount of peanuts and threshold levels that four patients could tolerate by the end of the study [23]. Reactions during the study were mild, and no patients needed epinephrine. In a larger open-label study, 27 of 29 (93%) children were able to tolerate the maximum amount of peanut protein while on maintenance therapy, resulting in clinical desensitization [24]. Immunologic parameters measured during this study demonstrated a significant decrease in titrated skin prick testing and basophil reactivity to peanut antigen. In addition, peanut-specific IgE levels initially increased but then decreased at 12 and 18 months, while peanut-specific IgG₄ increased through-

out the study. The safety of peanut OIT at all stages during this study was examined in a separate report [25]. Allergic reactions were most frequent on the initial dose escalation day, on which 20 of 28 patients needed some form of treatment. Most commonly, patients responded to antihistamines alone; however, 4 of 28 needed epinephrine in combination with antihistamines or albuterol. After the initial dose escalation day, the likelihood of adverse reactions decreased dramatically during both the build-up and home-dosing phases. It should be noted that two patients still required epinephrine during the home-dosing phase of the study. These two patients were able to continue on in the study to completion. Another follow-up report on this study suggested five patterns that may heighten the risk of reacting to a previously tolerated dose: concurrent illness, poorly controlled asthma, timing of dose after food ingestion, exercise after dosing, and dosing during menses [26]. Recognizing these factors likely will be important in improving the safety of future immunotherapy trials.

Conclusions

These studies suggest that the prospect of treating food allergies by mucosal immunotherapy may be possible in the near future. Although subcutaneous immunotherapy shows clinical and immunologic benefit, it is associated with significant undue reactions and is currently not recommended. OIT appears to be a safe and well-tolerated treatment when administered by experienced personnel in highly supervised research settings. Early studies suggest effective desensitization and immune modulation, but further studies are needed to address the issue of tolerance. Although SLIT is an attractive alternative to OIT because of its likely safety profile, more studies are needed to determine whether it will be as effective in inducing desensitization and eventual tolerance. Nevertheless, many unanswered questions remain surrounding OIT, particularly the risks of OIT compared with simple food avoidance. Other issues include associated dosing regimens, patient selection, and post-desensitization strategy. Although OIT represents a promising therapeutic intervention for food allergy, there is a high risk of systemic reactions, and because of the remaining unanswered questions, these therapies are not ready for broad implementation in clinical practice settings at this time.

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