

Forecast for food allergen immunotherapy: partly desensitized or a chance of cure?

Expert Rev. Clin. Immunol. 6(2), 177–179 (2010)



Satya D Narisety, MD

*Post-Doctorate Fellow,
Division of Pediatric
Immunology & Allergy,
The Johns Hopkins
Hospital, School of
Medicine/CMSC 1102,
600 North Wolfe Street,
Baltimore,
MD 21287-3923, USA
Tel.: +1 410 955 5883
Fax: +1 410 955 0229
snarise1@jhmi.edu*



Robert A Wood, MD

*Author for correspondence
Professor of Pediatrics,
Division of Pediatric
Immunology & Allergy,
The Johns Hopkins
Hospital, School of
Medicine/CMSC 1102,
600 North Wolfe Street,
Baltimore,
MD 21287-3923, USA
Tel.: +1 410 955 5883
Fax: +1 410 955 0229
rwood1@jhmi.edu*

“If we are only able to achieve long-term tolerance in a subset of patients, then all others may be at considerable risk for future reactions if there are lapses in intake of the food allergen, and the eventual utility of this form of therapy may be limited.”

IgE-mediated food allergy is a common disorder that has been growing in prevalence in recent years. Currently, the standard of care is strict avoidance of the culprit food with ready access to injectable epinephrine. However, given that accidental reactions are common and often severe, there is great interest in the development of new therapeutic approaches for food allergy. While subcutaneous immunotherapy is currently used for the treatment of IgE-mediated respiratory disease and insect sting allergy, the use of subcutaneous immunotherapy in food allergy has been complicated by high rates of systemic reactions and cannot be recommended for general use [1,2]. However, newer strategies, including alternative routes of delivery as well as modification of the allergens to reduce IgE-mediated reactivity, are now being studied with encouraging results.

Recently, oral immunotherapy (OIT) has been studied for milk, egg and peanut allergies [3–13]. These studies have shown that many individuals with severe allergy to these foods can be successfully desensitized and, in some cases, can even introduce the food into their diets. A few studies have attempted to address the question of whether these OIT protocols confer long-term tolerance along with short-term desensitization. It appears that between a third and a half of children treated with OIT for milk or egg allergy are truly tolerant, in that they are able to eat the food after all exposure was stopped [3,12].

Another approach to immunotherapy involves the sublingual route (sublingual immunotherapy [SLIT]), which has been used with success for hazelnut allergy [14] and is currently being studied for milk and peanut allergy.

Most OIT and SLIT protocols involve rush or modified-rush desensitization followed by a longer period of gradual escalation and maintenance. These studies have varied with regard to participant age, dosing regimen, length of treatment, placebo control, and the use of baseline and follow-up food challenges. Side effects have been inconsistently reported but appear to be very common, ranging from local reactions to more severe systemic reactions, including anaphylaxis. SLIT has generated interest as it may be effective at lower doses, thereby potentially reducing the number and severity of side effects that have been seen with other forms of immunotherapy. It is also theorized that there are a plethora of cells that are part of the innate immune system in the oral mucosa that jump start the mechanism of desensitization and possibly augment the development of long-term tolerance.

Among the published food immunotherapy trials, adverse reactions have been common in all phases of the treatment regimen. Reactions most often have included hives, pruritis, and/or eczema flares of the skin, the upper and lower respiratory tract, and the GI tract with oropharyngeal pruritis and/or edema, nausea, vomiting

and/or diarrhea. Multisystem anaphylactic reactions have also been reported, necessitating rescue with injectable epinephrine. Of note, these more severe reactions have typically occurred at doses that were previously tolerated and appear to be more frequent when coupled with a viral illness or exercise [9].

Another important caveat regarding these therapies involves their potential to induce long-term tolerance versus short-term desensitization. If we are only able to achieve long-term tolerance in a subset of patients, then all others may be at considerable risk for future reactions if there are lapses in intake of the food allergen, and the eventual utility of this form of therapy may be limited. At present, the important message is that until clinical tolerance is documented, there is an ongoing need to be vigilant and to carry injectable epinephrine even though a therapy may be considered 'successful'.

While results so far are encouraging, it is important that other approaches also be pursued in an effort to maximize efficacy and minimize adverse reactions. Recent investigation into aeroallergen immunotherapy has utilized different modalities of administration, including oral tablets and allergen-impregnated oral mucosal adhesives, as well as a percutaneous approach. Several of these approaches are also in early investigation for the treatment of food allergy. Another approach under study involves OIT in combination with omalizumab, a recombinant DNA-derived humanized IgG monoclonal antibody that selectively binds to human IgE, in the hope that this will reduce IgE-mediated adverse reactions. Finally, we have recently initiated the first human trials studying the use of recombinant allergens that have been 'engineered' to reduce IgE binding, while still maintaining the effects on T cells necessary to induce desensitization and tolerance [15].

One final strategy of note involves two of the concepts introduced previously, those of oral introduction of allergenic foods as well as the modification of food proteins. It has long been recognized that the structure of food proteins and the immunologic responses they elicit may play important roles in the character and prognosis of food allergic individuals. For example, it has been found that heating reduces the allergenicity of some food

proteins [16], possibly by breaking down conformational epitopes into more linear forms. This clearly occurs with both milk and egg allergens, where it has been shown that specific IgE antibody-epitope binding patterns to milk and egg vary among different patients. Furthermore, it has been shown that children who have outgrown their milk and egg allergy tend to have specific IgE antibodies against conformational epitopes, while those with persistent allergy have IgE antibodies against linear epitopes [17–19], and that the former, less allergic populations, were often able to tolerate milk and egg in baked forms [20,21]. Even more importantly, early data suggests that the introduction of extensively heated milk and egg may help to induce complete tolerance earlier than would have otherwise been achieved.

"...until clinical tolerance is documented, there is an ongoing need to be vigilant and to carry injectable epinephrine even though the therapy was considered 'successful'."

In summary, research in immunotherapy for IgE-mediated food allergy has thus far produced exciting results. There are many innovative strategies that will be studied in the near future, as well as many others that are still in earlier phases of development. In fact, it remains to be seen whether what we will be doing 10 or 20 years from now even resembles what we are studying today. The good news, however, is that even with the many questions still to be answered, we can be optimistic that effective treatment for food allergy will eventually become a reality.

Financial & competing interests disclosure

Robert A Wood has received research funding from the National Institute of Health (grant NIH T32AI007007) and from Genentech, Inc. (CA, USA). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- 1 Oppenheimer JJ, Nelson HS, Bock SA *et al.* Treatment of peanut allergy with rush immunotherapy. *J. Allergy Clin. Immunol.* 90(2), 256–262 (1992).
- 2 Nelson HS, Lahr J, Rule R *et al.* Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J. Allergy Clin. Immunol.* 99(6 Pt 1), 744–751 (1997).
- 3 Buchanan A, Green T, Jones S *et al.* Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J. Allergy Clin. Immunol.* 119, 199–205 (2007).
- 4 Hofmann AM, Scurlock AM, Jones SM *et al.* Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J. Allergy Clin. Immunol.* 124, 286–291 (2009).
- 5 Jones SM, Pons L, Roberts JL *et al.* Clinical efficacy and immune regulation with peanut oral immunotherapy. *J. Allergy Clin. Immunol.* 124, 292–300 (2009).
- 6 Longo G, Barbi E, Berti I *et al.* Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J. Allergy Clin. Immunol.* 121, 343–347 (2008).
- 7 Meglio P, Bartone E, Plantamura M *et al.* A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 59, 980–987 (2004).
- 8 Morisset M, Moneret-Vautrin DA, Guenard L *et al.* Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. *Eur. Ann. Allergy Clin. Immunol.* 39, 12–19 (2007).
- 9 Narisety SD, Skripak JM, Steele P *et al.* Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J. Allergy Clin. Immunol.* 124, 610–612 (2009).
- 10 Patriarca G, Nucera E, Roncallo C *et al.* Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol. Ther.* 17, 459–465 (2003).
- 11 Skripak JM, Nash SD, Rowley H *et al.* A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J. Allergy Clin. Immunol.* 122, 1154–1160 (2008).

- 12 Staden U, Blumchen K, Blankenstein N *et al.* Rush oral immunotherapy in children with persistent cow's milk allergy. *J. Allergy Clin. Immunol.* 2, 418–419 (2008).
- 13 Staden U, Rolinck-Werninghaus C, Brewe F *et al.* Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 62, 1261–1269 (2007).
- 14 Enrique E, Pineda F, Malek T *et al.* Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo controlled study with a standardized hazelnut extract. *J. Allergy Clin. Immunol.* 116, 1073–1079 (2005).
- 15 Li XM, Srivastava K, Grishin A *et al.* Persistent protective effect of heat-killed *Escherichia coli* producing “engineered,” recombinant peanut proteins in a murine model of peanut allergy. *J. Allergy Clin. Immunol.* 112(1), 159–167 (2003).
- 16 Thomas K, Herouet-Guicheney C, Ladics G *et al.* Evaluating the effect of food processing on the potential human allergenicity of novel proteins: international workshop report. *Food Chem. Toxicol.* 45, 1116–1122 (2007).
- 17 Chatchatee P, Jarvinen KM, Bardina L *et al.* Identification of IgE- and IgG binding epitopes on α (s1)-casein: differences in patients with persistent and transient cow's milk allergy. *J. Allergy Clin. Immunol.* 107, 379–383 (2001).
- 18 Cooke SK, Sampson HA. Allergenic properties of ovomucoid in man. *J. Immunol.* 159, 2026–2032 (1997).
- 19 Jarvinen KM, Beyer K, Vila L *et al.* Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy. *Allergy* 62, 758–765 (2007).
- 20 Nowak-Wegrzyn A, Bloom KA, Sicherer SH *et al.* Tolerance to extensively heated milk in children with cow's milk allergy. *J. Allergy Clin. Immunol.* 122, 342–347 (2008).
- 21 Lemon-Mule H, Sampson HA, Sicherer SH *et al.* Immunologic changes in children with egg allergy ingesting extensively heated egg. *J. Allergy Clin. Immunol.* 122, 977–983 (2008).