

Food-specific immunotherapy: Past, present, and future

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Aside from a few anecdotal reports, until very recently we have had only a single, time-honored approach for the treatment of food allergy: avoidance of the offending food. In this case, however, time-honored signifies not an ideal or even an adequate approach but rather a complete absence of alternatives. In fact, for most common food allergens, avoidance is difficult to accomplish, and severe reactions from accidental exposures occur all too frequently.

A study of subcutaneous immunotherapy for peanut allergy conducted more than a decade ago was the first to investigate desensitization for food allergy in a placebo-controlled trial.^{1,2} Although it was exciting in that it demonstrated the potential to increase tolerance to oral peanut challenge, it was sobering in that the frequency of adverse reactions was unacceptably high. It was clear that this would be impractical for routine use and that a different approach, or combination of approaches, would be needed. To that end, a variety of potential strategies have been aggressively pursued in animal models. Now a few have undergone human study, including the use of humanized anti-IgE antibodies—the TNX-901 study³—as well as oral and sublingual immunotherapy.⁴⁻⁹

Although still very preliminary, the immunotherapy studies have all provided encouraging results, showing an undeniable signal toward increased tolerance to the food under study. These now include studies on milk allergy⁴⁻⁶ as well as egg,^{6,7} peanut,⁸ and hazelnut.⁹ Although encouraging, there still remain several major questions and concerns, most prominently regarding safety, the potential to induce long-term tolerance versus only transient desensitization, and whether these treatments will be safe and effective in those with the most severe forms of food allergy, arguably those who would need it most.

In this issue of the Journal, the paper by Longo et al¹⁰ represents a major contribution to this evolving field of investigation. This study was unique in that it included only children with a history of a severe reaction to milk, a cow's milk IgE level of at least 85 kU/L, and a positive baseline challenge to a low dose of milk, 8 mL or less. Of the 97 children age 5 and above who qualified on the basis of their clinical history and milk IgE level, 60 were eligible on the basis of their double-blind challenge at study entry. Those 60 children were randomly divided to either 1 year of

observation or treatment with oral milk immunotherapy, referred to in the article as *specific oral tolerance induction*. On rechallenge after 1 year, 36% of the children in the specific oral tolerance induction group achieved a daily intake of cow's milk equal to 150 mL or more and were on an "unrestricted diet," whereas 54% could take limited amounts of milk (5-150 mL), and 10% were not able to complete the protocol because of persistent respiratory or abdominal complaints. These results were very different from the untreated group who had essentially no change in reactivity.

Not surprisingly, especially given the highly allergic population being studied, adverse reactions occurred frequently in the treated children. In fact, all had allergic symptoms related to treatment. Oral pruritus was most common, followed by cutaneous and gastrointestinal symptoms, which occurred from a few minutes to 2 hours after milk ingestion. Adverse reactions were most common during the initial rush build-up, which was done with the children hospitalized for 10 days, but they also occurred in most children during home dosing as well. During the rush build-up, intramuscular epinephrine was administered to 4 children and nebulized epinephrine was given to 18 children, 7 on more than 1 occasion. With home dosing, 2 children required treatment in the emergency department. Of note, in the group that was not treated, 6 children (20%) had adverse reactions caused by accidental milk exposures, although none were severe and most were caused only by skin contact.

This study provides significant new information and at least begins to answer 2 of the unanswered questions noted. Although the study only included those children with the most severe variety of milk allergy, the overall outcome was similar to the other studies that have been published. In fact, the vast majority of treated patients achieved a significant increase in tolerance, with a subset appearing to be fully, or nearly fully, tolerant. This is in contrast to populations included in the previous studies, such as the hazelnut study in which some of the subjects had only a history of localized reactions, or the egg study by Buchanan et al,⁷ which specifically excluded children with a history of anaphylactic reactions.

The study also helps to provide a clearer picture regarding the risk of oral immunotherapy, which is also quite consistent with the previous studies. These studies teach us that local adverse reactions are extremely common and that most patients will have other reactions in the course of treatment, especially when a rush build-up is used. Severe reactions are possible and will almost certainly occur in some patients, as has been reported in the other trials as well. As these treatments progress through additional study and possibly more general use, it will be critical that the potential for adverse reactions be considered on an individual, case-by-case basis. For patients like those in the study by Longo et al,¹⁰ the odds of ever outgrowing the allergy are small and the risk of future severe reactions with accidental exposures is high, which makes the risk of treatment appear quite acceptable.

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This study was unfortunately not designed to answer the third question posed, which may well be the most important of all. It remains to be determined which of these children were merely desensitized in a transient fashion, or whether longer-term or permanent tolerance was truly induced. In the study by Staden et al⁶ that included oral immunotherapy for both milk and egg, it was clear that both outcomes are possible. Nine of 25 children (36%) were felt to have developed "permanent tolerance," whereas 3 children remained tolerant only with regular intake, 4 showed increased tolerance but were never able to achieve the full maintenance dose, and the remaining 9 were not able to tolerate the desensitization procedure. Similarly, in the oral egg immunotherapy study by Buchanan et al,⁷ 2 of 4 patients who were able to tolerate a full egg challenge at the end of treatment maintained that same level of tolerance 3 months off therapy, whereas the other 2 were once again reactive, 1 at a very low dose.

At this point, the future of oral and sublingual food immunotherapy is far from clear. Thankfully there are numerous trials underway, and many others in development, that will teach us a great deal in the next few years. However, there are so many unanswered questions that it is safe to say that this treatment will not be ready for general use for many years. It is also entirely possible that other approaches for the treatment of food allergy will emerge as safer, more effective, or both. For example, modified allergens may allow both greater efficacy and improved safety, and other possible therapies, such as the food allergy herbal formulas under development, might also have the advantage of treating multiple food allergies, which would be a distinct advantage for the many patients with numerous severe food allergies. It may also be that the eventual treatment for food allergy will rely on a combination of methods, such as oral immunotherapy plus omalizumab. The only thing that I can say with complete

confidence is that this will be an exciting 10 to 20 years as we have the opportunity to develop truly effective treatment for food allergy, and ideally replace the time-honored tradition of avoidance with real treatment for a serious, life-altering disease.

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