



Managing food allergy in childhood

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Purpose of review

This study reviews the newest developments on experimental therapies for the treatment of food allergy.

Recent findings

Epitope studies and microarray technology promise to improve the accuracy of diagnostic testing and may allow the prediction of reaction severity and the likelihood of allergy resolution. The regular ingestion of small amounts of food in oral immunotherapy (OIT) has been shown to dramatically increase reaction thresholds. However, a subset of patients have developed significant gastrointestinal symptoms requiring discontinuation of the treatment. A similar treatment given sublingually has appeared safer than OIT, but has also shown a less robust effect. Ingestion of extensively heated foods seems to accelerate the natural resolution of milk and egg allergy. The injectable anti-IgE therapy omalizumab has been shown to benefit in conjunction with OIT and preliminary data has suggested that it may also be effective as monotherapy. The Chinese herbal formula FAHF-2 has been shown to suppress anaphylaxis from single and multiple food allergies in mice, and early human studies have shown that it is well tolerated.

Summary

Improved testing should allow more accurate diagnosis of food allergy. For these patients, treatments are on the horizon, but further studies are needed to determine long-term safety and efficacy.

Keywords

anaphylaxis, food allergy, immunotherapy

INTRODUCTION

Food allergy has become an epidemic in developed countries and has particularly affected children. Among children in the United States, the prevalence was recently estimated to be 3.9%, affecting approximately 3 million school age children. This represented an 18% increase in prevalence from 1997 to 2007. Similar increases were seen for specific food allergies, including a more than three-fold increase in the prevalence of peanut and tree nut allergies [1]. Despite these growing numbers, there continues to be no active treatment for food allergy.

Practice guidelines published in December 2010 by a National Institute of Allergy and Infectious Diseases expert panel maintained the standard of care for food allergy to include proper diagnosis, strict avoidance, and ready access to emergency medications for accidental ingestions, in particular self-injectable epinephrine [2]. Despite improved public awareness, improved food labeling practices, and parental vigilance, accidental ingestions have remained common, with annual ingestion rates for peanut estimated to be 14–20% [3–5]. This has left millions of parents and children in a state of constant fear of life-threatening reactions from unseen exposures. Hope appears to be on the horizon as

significant advances have been made over the past few years toward a treatment for food allergy. The first part of this study will focus on the advances related to the current standard of care. The latter part of the study will then highlight progress made over the past 18 months on future therapies for food allergy.

STANDARD OF CARE FOR FOOD ALLERGY

The most important and often most difficult step in the management of food allergy remains making the correct diagnosis; however, this is often taken for granted. Over the past year alone, more than 25 published studies focused on the diagnosis of food allergy, supporting the argument that making the diagnosis is far from straightforward. The increase in

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KEY POINTS

- Advanced diagnostic testing using epitope and microarray technology will enable more accurate testing.
- Oral immunotherapy and sublingual immunotherapy can increase the reaction thresholds to foods, but questions about safety and long-term efficacy remain.
- Extensively heated milk and egg products accelerate the natural resolution of milk and egg allergy compared with strict avoidance.
- Anti-IgE therapy with omalizumab improves the safety and efficacy of OIT and may provide benefit in monotherapy.
- The Chinese herbal formula FAHF-2 is safe in humans and may protect against multiple food allergens simultaneously.

food allergy prevalence has led primary care providers to become increasingly involved in the diagnosis of food allergy and many have taken advantage of the widespread availability of serum IgE testing. Unfortunately, this has helped to bring out some of the inherent shortcomings and pitfalls of current food-specific IgE testing. Sampson [6] developed predictive values for food-specific IgE testing to confirm suggestive histories of food allergy. However, without a strong history suggestive of food allergy, the low pretest probability of food allergy makes the testing no better than flipping a coin for ruling in disease. Despite this poor positive predictive value, broad screening panels continue to be used regularly. This has resulted in innumerable patients avoiding foods unnecessarily with resultant increases in anxiety and decreases in quality of life. On the other side of the spectrum, reports of these 'false positives' have led some patients not to trust the testing, resulting in inadequate avoidance and increased risk for potentially dangerous allergic reactions.

ADVANCES IN DIAGNOSTIC TESTING

Efforts have been ongoing to increase the accuracy of available testing as well as to develop new modalities for diagnosing food allergy. Some of these advances may also allow practitioners to predict the severity of disease, a vital characteristic of food allergy that cannot be determined with available testing. Ito *et al.* [7] compared currently used serum IgE testing to whole milk extract versus IgE specific for the milk protein components casein, beta-lactoglobulin, and alpha-lactalbumin in detecting

challenge-proven allergy. They showed that casein-specific IgE was superior to whole milk extract as well as the other proteins, and that using a cutoff of 6.6 kU/l resulted in 100% specificity. This seems to be in agreement with the previous work that showed that casein-specific IgE was more prevalent in persistent milk allergy [8]. Advances in microarray technology allowed Nicolaou *et al.* [9] to look beyond whole proteins and to investigate the use of epitope-specific IgE testing for peanut allergy. They showed that levels of IgE specific for Ara h 2 that were greater than 0.35 kU/l conferred 100% sensitivity and 96.1% specificity. This decision point also correctly identified 97.5% of their peanut-allergic patients. Two reviews by Sanz *et al.* and Caubet and Sampson provide further details about the recent advances in allergy testing [10,11].

Once the correct diagnosis has been made, the guidelines recommend strict avoidance of the food allergen. Unfortunately, many food-allergic patients, especially those allergic to peanut, tree nuts, fish, and shellfish, do not outgrow their disease naturally. Considering the propensity of these allergens to cause severe reactions together with the high accidental ingestion rate emphasizes the need for an active treatment for food allergy.

ADVANCES IN ALLERGEN-SPECIFIC THERAPY

Oral immunotherapy (OIT) involves the ingestion of small, increasing amounts of food allergen on a regular basis to desensitize and potentially permanently tolerize patients to the implicated food. Of all the treatments for food allergy that have been studied over the past decade, the most progress has been made with OIT. Most protocols for OIT have involved an initial day of multiple dose increases called a rush escalation day. This is followed by a more gradual biweekly dose escalation period. Because the majority of adverse events with OIT occurred during this rush escalation day, Anagnostou *et al.* [12] treated 22 challenge-confirmed, peanut-allergic children with an open peanut OIT protocol that omitted this rush escalation day. Treatment instead began with gradual biweekly dose escalation to a maintenance dose of 800 mg of peanut protein, with one peanut being equivalent to about 300 mg. After 6 weeks of maintenance, 12 out of 22 (54%) passed a food challenge to 2600 mg of peanut protein and after 30 weeks of maintenance, 14 out of 22 (64%) passed a food challenge to 6600 mg of peanut protein. The median 30-week food challenge threshold was 6459 mg (range 800–7510 mg), which represented a greater than 1000 times increase in tolerated dose compared

with baseline challenges. Considering the potential benefits of omitting a rush desensitization period, one out of 22 patients dropped out during the dosing phase and two of the remaining patients were unable to reach the 800 mg maintenance dose.

Also in the last year, the results of the first double-blind, placebo-controlled study of peanut OIT were published by Varshney *et al.* [13[¶]]. Twenty-eight children were enrolled and underwent a rush escalation day, gradual dose escalation, and maintenance dosing with 4000 mg of peanut protein, a significantly higher dose than used by Anagnostou. Like the open studies before it, this study showed that OIT could be impressively effective, with 100% of the patients reaching maintenance going on to successfully pass a blinded food challenge to 5000 mg after 12 months of treatment. Mechanistic studies showed decreases in skin prick testing, a transient rise then fall in peanut-specific IgE, an increase in peanut-specific IgG4, a decrease in T_H2 cytokines [interleukin (IL) 5 and IL-13], and an increase in regulatory T cells. These changes paralleled the response to allergy shots for environmental allergies and suggested the modulation of the allergic response and the possibility of long-lasting immune tolerance. Looking at the safety of the protocol, two out of 19 failed the rush escalation day and one out of 19 dropped out after the first gradual escalation. This resulted in a similar percentage of patients reaching the maintenance dose as with the Anagnostou protocol.

The good news from these studies has been tempered somewhat by reports of the approximately 10–20% of patients from various studies who were unable to reach maintenance because of gastrointestinal symptoms and concerns for eosinophilic esophagitis [14–17].

In an attempt to improve the safety of OIT and to allow more rapid dose escalation, Nadeau *et al.* [18] investigated the addition of anti-IgE therapy with omalizumab in conjunction with OIT for milk allergy. Eleven children were enrolled and started on omalizumab ranging from 150 mg every 4 weeks up to 300 mg every 2 weeks based on their total IgE level. After 9 weeks, the patients underwent a rush escalation day followed by weekly escalations to a maintenance dose of 2000 mg of milk protein. Omalizumab was discontinued after 16 weeks and a blinded food challenge was performed after 24 weeks. One patient dropped out during the rush escalation and another did not achieve the maintenance dose during the allotted time. The remaining nine out of 11 patients who reached maintenance were able to pass a 7250-mg (220 ml) challenge to milk and reintroduce milk into their diets. Omalizumab caused no adverse events and

symptoms with OIT were similar to other protocols despite the rapid up dosing involved in this protocol. A follow-up report on this cohort by Bedoret *et al.* [19[¶]] provided fascinating insights into the potential mechanism of OIT. A dramatic decrease in the proliferation of milk-specific CD4⁺ T-cells was seen 1 week after desensitization but, contrary to current thinking, this appeared to be independent of regulatory T-cells. Instead, their results suggested that this may have been a result of anergy, a state of immunological nonresponsiveness. As the T-cell response returned, the cytokine profile changed from primarily IL-4 to interferon (IFN) gamma, demonstrating a shift from a proallergic T_H2 to a proinflammatory T_H1 phenotype. Basophil reactivity was also diminished shortly after initiating omalizumab and persisted on milk OIT therapy, suggesting initial desensitization by omalizumab and maintenance of this state by OIT.

A similar modality to OIT called sublingual immunotherapy (SLIT) also utilizes small, increasing amounts of food allergen for treatment but involves administration under the tongue rather than by ingestion. The typical dosage amounts are about 1000 times less with SLIT than with OIT. The results of the first double-blind study of SLIT for peanut allergy were recently published by Kim *et al.* [20[¶]]. Eighteen peanut-allergic children were enrolled and underwent dose escalation to a maintenance dose of 2 mg of peanut protein, a significantly smaller dose than the 4000 mg maintenance dose used by Varshney for peanut OIT. After 12 months of treatment, the median amount of peanut tolerated on food challenge was 1710 mg for those on treatment versus 85 mg for those on placebo with no dropouts from dosing adverse events. In addition, similarly to OIT, mechanistic studies demonstrated decreases in basophil reactivity and skin prick testing, a transient increase then decrease in peanut-specific IgE, an increase in peanut-specific IgG4, and decreases in IL-5 and IL-13 without a change in IFN-gamma. Increasing regulatory T cells showed a trend toward significance that was later confirmed with additional subjects [21]. In a follow-up study investigating potential mechanisms of SLIT, Kulis *et al.* [22] demonstrated that persistent mucosal exposure of peanut SLIT resulted in an increase in peanut-specific salivary IgA that has been hypothesized to block antigen uptake. This was supported by the finding that the increase in peanut-specific IgA correlated well with food challenge results ($R^2=0.52$, $P=0.0011$).

The efficacy of SLIT was compared with OIT in a study of milk-allergic children by Keet *et al.* [23]. Thirty children were enrolled and started on SLIT to

reduce the number of dropouts from the initial rush escalation seen in other OIT protocols. All children were escalated to 3.7 mg of milk protein and then randomized to receive 7 mg of milk SLIT, 1000 mg of milk OIT, or 2000 mg of milk OIT. Only one out of 10 patients on SLIT passed the 8000-mg food challenge after 60 weeks of maintenance dosing compared with six out of 10 and eight out of 10 for the 1000-mg milk OIT and 2000-mg milk OIT groups, respectively. Similarly to the results presented at the 2012 American Academy of Allergy, Asthma, and Immunology annual conference comparing peanut OIT and peanut SLIT [24], this study showed that OIT was likely more efficacious than SLIT but also carried a higher risk of serious adverse events.

In a shift from these standard immunotherapy protocols, molecular studies of epitope binding have paved the way for a new type of ingested therapy. Studies have shown that most children who eventually outgrow milk allergy form IgE antibodies against conformational epitopes rather than linear epitopes within milk proteins [25]. Extensive heating denatures conformational epitopes and, correspondingly, the majority of milk-allergic patients have recently been found to be tolerant of baked milk [26]. With this background, Kim *et al.* [27] compared the frequency of milk allergy resolution after the regular ingestion of baked milk products versus strict avoidance. Of the 89 milk-allergic children who were enrolled, 74% tolerated a challenge to baked milk at study entry. Of these, 60% became unheated milk tolerant within the 5-year follow-up time frame compared with 22% of the controls who strictly avoided all milk products. Of those who did not tolerate baked milk at study entry, only 9% of these children became tolerant to unheated milk after 5 years. Mechanistically, those who tolerated baked milk demonstrated significant decreases in casein-specific IgE and increases in casein-specific IgG4. These results suggest that avoidance may not be the best recommendation and that regular ingestion of baked milk products may speed the induction of tolerance and the resolution of milk allergy.

ADVANCES IN ALLERGEN NONSPECIFIC THERAPY

Two of the most promising allergen nonspecific therapies are the monoclonal anti-IgE antibody omalizumab and the food allergy herbal formula-2 (FAHF-2). Anti-IgE therapy was first reported in the treatment of food allergy by Leung *et al.* [28] in 2003. A 450-mg dose of the experimental anti-IgE drug talizumab (TNX-901), given monthly for 4 months, increased the reaction threshold to peanut from 178 up to 2805 mg. Unfortunately, legal concerns over

patenting resulted in discontinuation of the development of talizumab. A phase 2 study of omalizumab was initiated with similar results expected because of omalizumab's similar binding properties to talizumab, but the study was prematurely terminated because of two serious adverse events during entry food challenge prior to omalizumab initiation. Preliminary results from the 14 patients who reached the primary endpoint of food challenge after 24 weeks of therapy were recently published by Sampson *et al.* [29]. Although the results did not reach significance, likely due to the small sample size, the nine patients on therapy had an 80-fold increase in peanut tolerated compared with a four-fold increase for the five patients on placebo and represented an improvement from the 16-fold increase found with talizumab. With its favorable safety profile and potential benefits for multiple food allergies, omalizumab is a therapy that clearly warrants further study.

The second allergen nonspecific therapy in development for food allergy is the Chinese herbal formula, FAHF-2, that is being investigated at Mt Sinai Medical Center. In early studies, the formulation seemed to suppress anaphylaxis in mouse models of peanut allergy [30]. Three papers dedicated to this treatment were published in the past year. Patil *et al.* [31] reported on the safety of FAHF-2 in an extended phase 1 study and showed that daily dosing for 6 months was safe and well tolerated. However, the standard dose, consisting of 12 tablets taken three times daily, was found to be burdensome for adults and prohibitive for children. To address this concern, Srivastava *et al.* [32] reported on the efficacy of a butanol-extracted version of FAHF-2 in mice. The procedure reduced the dose volume by almost five-fold while maintaining its efficacy and safety. Finally, Srivastava *et al.* [33] addressed one of the potential advantages of an allergen nonspecific therapy by investigating the efficacy of FAHF-2 in a mouse model of multiple food allergies. Mice were sensitized to three unrelated food allergens, peanut, codfish, and egg, and then treated with FAHF-2 for 7 weeks. Upon challenge, FAHF-2 blocked anaphylaxis from all three food allergens. In the opinion of this author, the ability to treat multiple allergies with one therapy is one of the most exciting recent advances in food allergy, considering that most OIT and SLIT protocols involve several years of therapy to treat a single allergy.

CONCLUSION

There have been many advances in potential therapies for food allergy, but the most important step in

the management of food allergy remains making the correct diagnosis. Advances in molecular biology have allowed improved diagnostic testing and hold the promise of predicting severity of reactions and the likelihood of outgrowing the allergy. OIT remains the most researched treatment for food allergy and the last year saw several reports further confirming its efficacy and providing insights into its mechanisms. Two other studies showed that SLIT could also have a role in food allergy treatment because of its ease of administration and superior safety profile. For food allergies caused by IgE binding to conformational epitopes, such as with milk and egg, the use of extensively heated food offers the promise of broadening the diet in the short term and speeding up the resolution of the allergy in the long term. On the basis of positive results of the experimental drug talizumab (TNX-901) and the preliminary results from its phase 2 trial, omalizumab continues to hold significant promise as monotherapy, in addition to having a role in combination therapy with allergen-specific therapies such as OIT. Most compelling is the Chinese herbal formula, FAHF-2, which seems to be able to suppress multiple food allergies simultaneously. Despite these promising results, it should be stressed that there are no treatments that are ready for everyday use, as further studies are needed to evaluate the long-term safety of these treatments and the ability of these treatments to induce permanent immune tolerance.

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Conflicts of interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 661).

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