

Update on Potential Therapies for IgE-Mediated Food Allergy

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Abstract

Purpose of Review Food allergy is common, affecting up to 8% of children in the USA. Currently, therapy is limited to avoidance of the implicated allergen and availability of self-injectable epinephrine. However, several new approaches to food allergy are under investigation. This article reviews the published data on these new approaches.

Recent Findings Oral immunotherapy, in which allergic subjects are exposed to increasing amounts of antigen, can be accomplished in the majority of allergic individuals. However, this approach is not a cure as most patients will react after cessation of regular intake. In addition, there is a high rate of side effects. Other approaches include epicutaneous immunotherapy, therapy with anti-IgE medications, and use of Chinese herbs.

Summary Several novel approaches on food allergy are under study. At the current time, these approaches show promise for preventing severe reactions to accidental exposures. However, there is little evidence that current approaches will represent a true cure for food allergy.

Keywords Food allergy · Desensitization · Immunotherapy

Introduction

IgE-mediated food allergy is present in up to 8% of children in the USA [1], and is the leading cause of anaphylaxis in children [2]; available data suggests the prevalence is increasing over time [3–5]. Current therapy for food allergy is limited to scrupulous avoidance and availability of self-injectable epinephrine. While recent work has demonstrated that early introduction of allergenic foods can decrease rates of allergy among high-risk patients [6, 7], this approach is less than 100% effective. New therapies for treatment of patients with food allergy are clearly needed and will be the focus of this review.

Goals of Food Allergy Treatment

The ultimate goal of research into treatments for existing food allergy would be to induce long-lasting tolerance to the antigen similar to that seen in individuals without allergy. That is, the treated individual could consume the allergen when (and only when) they wished and in whatever amount desired. While this ideal will remain the long-term goal, it is clear that current approaches are more limited, serving to decrease or eliminate reactions after accidental exposure or to use exposure to the specific food allergen to “desensitize” the patient such that exposure does not trigger an allergic reaction.

Allergen Independent Approaches

Allergen independent therapies for food allergy have the advantage that they are applicable to all food allergens and should work for patients with multiple food allergies. In

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addition, they do not require exposure to the allergen and may therefore present a lower risk of triggering a reaction.

IGE Blockade

Omalizumab is partially humanized, monoclonal antibody which binds to the Fc portion of human IgE and blocks binding to both the high and low affinity IgE receptor, including on mast cells and basophils [8]. It is approved for treatment of moderate to severe persistent asthma in patients 6 and above and also chronic urticaria unresponsive to antihistamines in those 12 and above. Its mechanism of action is thought to involve sequestering free IgE, leading to downregulation of FcεR1, and decrease reactivity of mast cells and basophils. However, it probably acts via additional mechanisms as evidenced by its activity in decreasing seasonal asthma exacerbations and improving the symptoms of chronic urticaria [9, 10].

Several trials have investigated the efficacy of omalizumab and other anti-IgE molecules in decreasing reactions in subjects with established food allergy. Leung et al. studied the efficacy of TNX-901 a very similar monoclonal antibody in a group of highly allergic patients with known peanut allergy [11]. Subjects received four doses of TNX-901 at 4-week intervals. At the highest studied dose, subjects treated with TNX-901 increased the amount of peanut which triggered a reaction from 178 to 2805 mg equivalent to approximate ½ and 9 peanuts, respectively. Lower doses showed significant but lesser increases in the amount of peanut tolerated. Further trials of this molecule were not pursued, however. Similarly, Sampson studied the efficacy of 24 weeks of omalizumab in increasing the amount of peanut required to trigger a reaction [12]. Unfortunately, this trial was stopped early due to safety concerns related to the peanut challenge conducted prior to randomization. Finally, in an open label study of adults with peanut allergy, 6 months of omalizumab treatment increased the reaction eliciting dose of peanut in a challenge from 80 to 6500 mg [13].

While promising, use of anti-IgE therapy as a treatment for food allergies has several important limitations. Most importantly, omalizumab is not currently approved for treatment of food allergies. While it could be used off label, insurance coverage is unlikely. Second, it is only effective while patients are receiving therapy. As omalizumab is very expensive and requires injections every 2–4 weeks, this represents a significant limitation. Finally, omalizumab therapy is only possible for patients with appropriate total IgE. At this time, omalizumab cannot be recommended for treatment of food allergies although it is likely that patients for whom this medicine is indicated for asthma (or urticaria) will derive some protection from accidental exposure. The combination of anti-IgE therapy and specific immunotherapy will be considered below.

A number of new molecules that prevent binding of IgE to its receptor on mast cells and basophils are in development. These include ligelizumab a fully humanized monoclonal antibody with higher affinity for IgE than omalizumab [14], quilizumab which recognizes membrane bound IgE and leads to B cell apoptosis [15], and designed ankyrin repeat proteins (DARPs) which disrupt established IgE: FcεR1 complexes [16•]. Finally, a recent report documents efficacy with a gene-therapy construct encoding an anti-IgE antibody in a mouse model of peanut allergy [17•]. While intriguing, data that these approaches will be effective in humans with established food allergy are not yet available.

Chinese Herbal Formula

Interest in non-traditional remedies, including Chinese herbal medicine, has been growing. Li et al. identified a mix of 11 Chinese herbs that prevented reactions in a mouse model of peanut allergy [18]. Further investigation revealed a subset of herbs that was as effective as larger initial formulation [19], but also demonstrated that efficacy could not be reduced to a single component. However, a recent double-blind randomized placebo controlled trial of this herbal formulation showed no efficacy [20•]. Whether alternative formulations might be more effective or the current formulation might be useful as an adjunct to immunotherapy is not known.

Allergen-Specific Immunotherapy

Nietzsche wrote that “that which does not kill us makes us stronger,” and the idea of inducing tolerance by graduated exposure is intuitively appealing. In fact, allergen-specific immunotherapy (IT) is an established therapy for environmental allergies, allergic asthma, and venom hypersensitivity. Closely related is the induction of a state of temporary unresponsiveness by graduated exposure to increasing amounts of allergen in the case of desensitization of patients with drug allergies.

As noted by Wood [21], the first case report of desensitization for food allergy was published in 1940 with sporadic interest thereafter. A Pubmed search for “Food Allergy” and “Immunotherapy” shows a rapid sustained increase in publications over the last 20 years (Fig. 1). As several excellent reviews of IT for food allergies have recently been published [21–23], this section will focus on highlights of published evidence and address the overall state of the field including obstacles to widespread implementation of this approach.

It is crucial to differentiate the different endpoints that can be achieved by various forms of IT. Most easily achievable is a state of temporary unresponsiveness to an antigen, analogous to that seen after drug desensitization. Such a state is

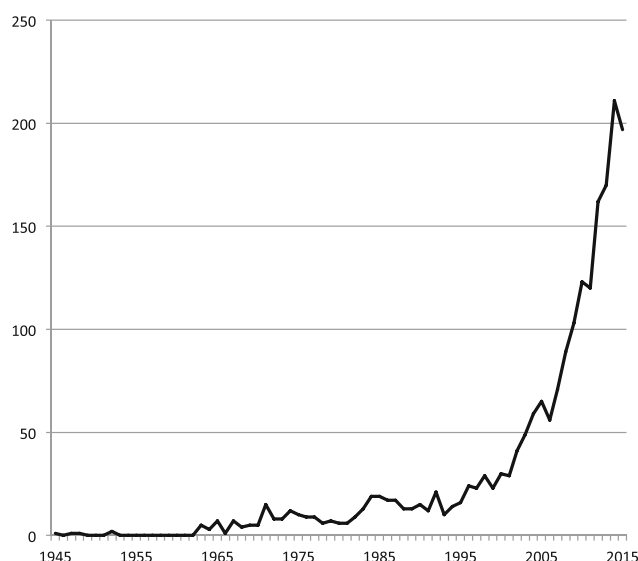


Fig. 1 Number of articles retrieved in Pubmed search of “Food allergy” and “Immunotherapy” by year

temporary, and typically, responsiveness is rapidly regained after cessation of exposure.

In contrast, the ideal endpoint for most IT is ongoing tolerance to the antigen, which might be defined as lack of reaction to exposure regardless of ongoing exposure. This is largely achieved for hymenoptera venom as patients who successfully complete venom IT have very low rates of systemic reactions, which remain low after cessation of therapy [24]. Of note, tolerance need not imply lack of specific IgE to an antigen, as evidenced, for example, by patients with serum-specific IgE to foods who are clinically tolerant.

There is little evidence that current approaches to food allergy IT lead to true tolerance, which is difficult to demonstrate empirically as patients typically retain evidence of specific IgE to the allergenic food as assessed by serum-specific IgE and skin testing. Instead, an intermediate endpoint, sustained unresponsiveness, has become the de facto standard. This can be defined as lack of response to ingestion of the implicated food after IT is stopped. It is likely that the interval from stopping IT along with the amount of allergen consumed will significantly influence the rate of unresponsiveness observed, but at this point there is no consensus on these items.

Forms of Food Allergy IT

Three primary forms of IT are currently being investigated for food allergy: oral (OIT), sublingual (SLIT), and epicutaneous (EPIT). Early studies of subcutaneous IT for peanut allergy showed some efficacy but high rates of adverse reactions [25]. A summary of the benefits and limitations of different routes of IT is shown in Table 1.

Oral Immunotherapy

OIT involves ingestion of gradually increasing amounts of the suspected allergen; a variety of protocols has been used with little data on which approach is optimal. Most commonly, an initial day of dose escalation is followed by periodic dose increases under supervision along with daily ingestion of the already tolerated dose at home. This build-up phase is followed by the maintenance phase where the dose level is maintained for a prolonged period. There is little consensus about the optimal maintenance dose.

OIT is generally well tolerated although most patients will have some reactions and up to 10–20% will experience anaphylaxis [26–30], particularly with peanut. Some evidence indicates that more allergic patients (those with the highest level of serum-specific IgE or the largest skin test response) are the most difficult to treat [31•, 32–34]. Up to 30% of patients are unable to be desensitized to the relevant allergen, often because of persistent GI symptoms [31•, 35•, 36]. Endoscopy of patients with ongoing GI symptoms has been performed rarely, but when done has revealed pathology consistent with eosinophilic esophagitis (EoE), which uniformly resolves upon discontinuation of OIT [36, 37]. The true incidence of this adverse effect will need to be clarified in future studies, including increased use of endoscopy to check for eosinophilia in symptomatic patients. Overall, reporting of adverse events in OIT trials is not standardized making comparison between studies difficult.

Oral IT has been described for a number of allergens, primarily peanut, milk, and egg but also wheat [38], with ongoing studies for tree nut and other foods. The vast majority of studies has focused on a single allergen, but approaches involving multiple foods have been described [39•]. This issue represents a significant disadvantage of allergen-specific approaches as many patients are sensitized to multiple allergens.

Various protocols for OIT have been described with wide variation, particularly in the highest antigen dose. Some studies have used high maintenance doses (e.g., 4000 mg of peanut, equivalent to about 17 peanuts) [27, 31•] with the hope that this level of exposure would promote sustained unresponsiveness. However, the recognition that many patients retain an aversion to implicated foods, especially for peanut, and worry about increased rate of reactions has led to alternative protocols examining use of lower doses (300 mg of peanut) which would be equally effective in protecting in the case of accidental exposure less likely to cause less adverse effects, and better tolerated. Lower dose protocols are likely to be more practical if multi-allergen OIT becomes more prevalent.

Results of OIT have shown that the majority of patients can tolerate significant doses of allergen, albeit with a fraction having persistent adverse effects. Results in relation to sustained unresponsiveness have been more mixed, with most studies showing only a minority of patients reaching this endpoint. In a rigorous study of peanut OIT [31•], after 5 years of therapy only 50% of

Table 1 Advantages and disadvantages of different routes of immunotherapy

	Subcutaneous	Oral	Sublingual	Epicutaneous
Protections against accidental exposure	+++	+++	++	Unknown
Long-term unresponsiveness	Unknown	+	Unknown	Unknown
Adverse effects	—	—	—	—

patients who achieved desensitization were unresponsive 4 weeks after stopping peanut intake. However, even those patients who did react did so at much higher doses (many 4000 mg of peanut) than were tolerated previously or would be encountered accidentally. Data from protocols of OIT for milk and egg show widely varying rates of sustained unresponsiveness, perhaps in part to differences in definition of this endpoint [40•, 41, 42•]. Likewise, rates of continued ingestion with longer follow-up are quite variable [29, 43]. As the majority of milk and egg allergic children see their allergy spontaneously resolves, rigorous studies examining long-term outcomes with OIT versus standard therapy for these allergens are necessary. Finally, recent data suggest that use of peanut OIT in younger children may increase rates of sustained unresponsiveness [44•].

A key unresolved issue is if and when to discontinue OIT. Some patients will likely prefer to continue regular ingestion feeling that this extends protection from accidental exposure. Whether the dosing interval could be extended (to every other day or even 1–2× weekly or less) is currently unknown but might be desirable. Of note, in trials, patients have been noted to miss occasional doses and even several consecutive doses without effect; however, others have had severe reactions after periods without ingestion [35•]. Of note, once maintenance dosing is reached in SCIT for venom and environmental allergens, dosing interval can be increased without loss of efficacy [24, 45].

Ingestion of well-cooked egg and milk in patients with these allergies can be seen as a form of OIT in wide use. Studies show that about 2/3 of patients with these allergies can tolerate some form of allergen [46]. Patients eating baked milk or baked egg outgrow the overall allergy sooner [46–48], but this finding must be interpreted with caution due to the possibility that patients unlikely to outgrow their allergy may experience mild symptoms after ingestion of the baked antigen and choose to avoid these items.

In summary, OIT is a promising therapy for food allergy, with the majority of subjects able to tolerate maintenance doses higher than would typically be ingested accidentally. Whether OIT is effective in promoting long-term unresponsiveness is less clear. A pharmaceutical-grade peanut flour is undergoing phase 3 trials (AImmune) and might be widely available in the next few years. While practiced clinically by some allergists [30, 49], at this time, OIT should be regarded as experimental and use confined to research protocols [50].

Sublingual IT

Several studies have examined the efficacy of sublingual IT. This route of IT has several theoretical advantages including the use of lower doses, potentially decreasing the risk of reactions, and the high concentration of tolerogenic antigen-presenting dendritic cells in the oral mucosa [51]. SLIT has been successfully used for patients with environmental allergies and allergic asthma with excellent efficacy and safety [52].

Studies of SLIT for food allergy have primarily focused on peanut and have demonstrated increases in the amount of peanut allergen tolerated without reaction [53, 54]. Current studies do not suggest that SLIT lead to sustained unresponsiveness, and in one head-to-head study, SLIT seemed to be somewhat less effective than OIT for peanut allergy [55•]. However, with its excellent safety profile, this remains a promising approach for patients who want to be protected from accidental exposure but do not wish to consume the implicated food. Multi-allergen SLIT for food allergies has not been examined, but limited data from studies of SLIT for environmental allergens along with limits on the physical volume of extracts that can be used suggest that this approach may be best suited for single allergen IT.

Epicutaneous IT

Epicutaneous IT represents a novel approach to IT and is not routinely used for other allergic diseases [56]. Only a single study of EPIT has been published, showing modest efficacy for milk allergy [57]. However, phase I and II studies of EPIT for food allergy have been conducted and promising results have been presented in an abstract form. These studies have studied peanut and other allergens applied to a patch using a proprietary technology (DBV Technologies). How dependent results are on this specific technology is unknown. EPIT for peanut allergy is currently in phase III studies and might be clinically available within the next few years. There is no human data on EPIT promoting sustained unresponsiveness when therapy is stopped.

One issue with EPIT as compared to OIT is establishing efficacy in individual patients. Patients actively receiving OIT consume a defined amount of peanut protein daily and can reasonably be assumed to have protection against accidental exposure from similar or lower doses. However, subjects receiving EPIT are not regularly exposed to the allergen orally. If efficacy rates are less than 100%, which is likely, they may be necessary to conduct food challenges to verify efficacy in each patient. This

could be a major drawback both because of patient hesitance and logistical considerations. Conducting low-dose challenges (e.g., maximal dose of 300 mg peanut protein) might obviate some of these concerns.

EPIT seems to be well tolerated without reports of anaphylaxis in the limited data published. Eczema at the patch site seems to be common, but manageable. No studies have addressed simultaneous EPIT for multiple allergens. Limits on the amount of protein that can be included in a single patch might make this approach impractical, at least with current technology.

Adjuncts to OIT

While OIT represents a promising approach to IgE-mediated food allergy, it has several limitations: not all patients tolerate it, reactions are frequent, and it does not result in sustained unresponsiveness for the majority of patients. Therefore, several approaches using adjuncts to OIT have been evaluated.

As discussed above, anti-IgE therapy serves to decrease reactions to food exposure in allergic patients. Several studies have addressed the use of omalizumab as an adjunct to OIT. Early studies showed efficacy in allowing desensitization with low rates of adverse effects for peanut, milk, and multiple allergens [39•, 58, 59].

Two recent double-blind placebo-controlled studies have advanced our knowledge about this strategy. In the first, Wood et al. used a prolonged course of omalizumab along with milk OIT [40••]. Omalizumab decreased the rate of reactions but did not increase the proportion of patients who successfully achieved desensitization nor sustained unresponsiveness. Second, MacGinnitie et al. showed that omalizumab versus placebo facilitated rapid desensitization to peanut with 75% of omalizumab-treated patients able to tolerate 250 mg on the first day of OIT and a similar proportion tolerating 2000 mg of peanut protein after 8 weeks of OIT versus just one of eight placebo patients [35••]. Rates of reaction were not significantly different, but omalizumab subjects were exposed to much higher doses of peanut protein. Of note of 27 patients in this study who received omalizumab and peanut OIT, all but two met the endpoint of tolerating 2000 mg of peanut protein [35••]. The two failures both suffered chronic GI symptoms consistent with EoE.

The role of omalizumab as an adjunct to OIT remains to be established given it is expensive and requires injections every 2–4 weeks. It might be of benefit in patients with high serum-specific IgE values or those with a history of life-threatening reactions. The possibility that a shorter course of this medicine might facilitate rapid desensitization is also worthy of study.

A single study examined use of the probiotic *Lactobacillus* as an adjunct to peanut OIT [60]. While desensitization was attained in 90% of those receiving *Lactobacillus* plus peanut OIT (versus 7% in the placebo group), the lack of a group

receiving OIT alone makes it impossible to judge the contribution of the probiotic.

Conclusion

The current standard for treatment of IgE-mediated food allergies is strict avoidance and availability of self-injectable epinephrine. However, this paradigm seems certain to shift in the near future if OIT and EPIT for peanut allergy are FDA approved and become widely available. Use of these and similar approaches for other allergens and patients with multiple food allergies should follow. However, a number of issues remain to be addressed. These include optimal selection of patients, optimum duration of maintenance therapy, minimizing reactions, and optimizing adjunctive therapies.

Compliance with Ethical Standards

Conflict of Interest Dr. MacGinnitie declares grants from Genentech and from FARE.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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